8. The Synthesis of Spiro[tetrahydroisoquinoline-piperidines] and related compounds

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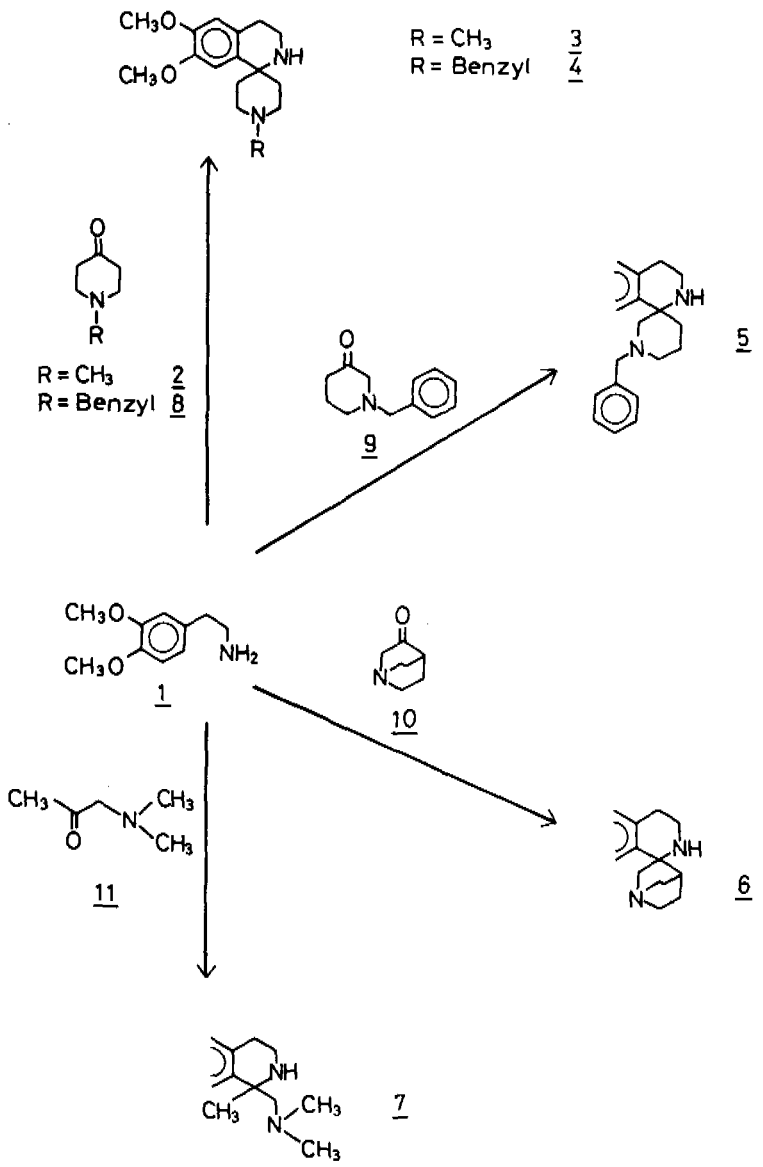
Summary. The reaction of 3,4-dimethoxyphenethylamine with some cyclic aminoketones in the presence of polyphosphoric acid afforded 1-spiro-tetrahydroisoquinolines. A two-step procedure starting from veratrylamine and amino-ketones gave 3-spiro-tetrahydroisoquinolin-4-ones. The *Schmidt* rearrangement of 5,6-dimethoxy-3-spiro-indan-1-ones yielded 4-spiro-tetrahydroisoquinolin-1-ones.

1-Spiro-tetrahydroisoquinolines. In contrast to aldehydes, ketones do not easily react with phenylethylamines to yield tetrahydroisoquinolines. The literature indicates that attempts to condense cyclic ketones with 3,4-alkoxy-phenethylamines in strongly acidic media were largely unsuccessful [1] [2]. *Belleau* [3] suggested that phenylacetamides might be more reactive than phenethylamines, and he successfully condensed cyclopentanone with 3,4-dimethoxyphenylacetamide to the corresponding 1-spiro-tetrahydroisoquinolin-3-one. *Crundwell* [4] described similar results with 4-piperidones. We wish to report a few examples of condensations between 3,4-dimethoxyphenethylamine (**1**) and amino-ketones in the presence of polyphosphoric acid (PPA), leading to tetrahydroisoquinolines. It is worth noting that such cyclization occurred only when the phenethylamine was first mixed with the amino-ketone, thus forming the intermediate imine, PPA was then added and the mixture heated to achieve cyclization.

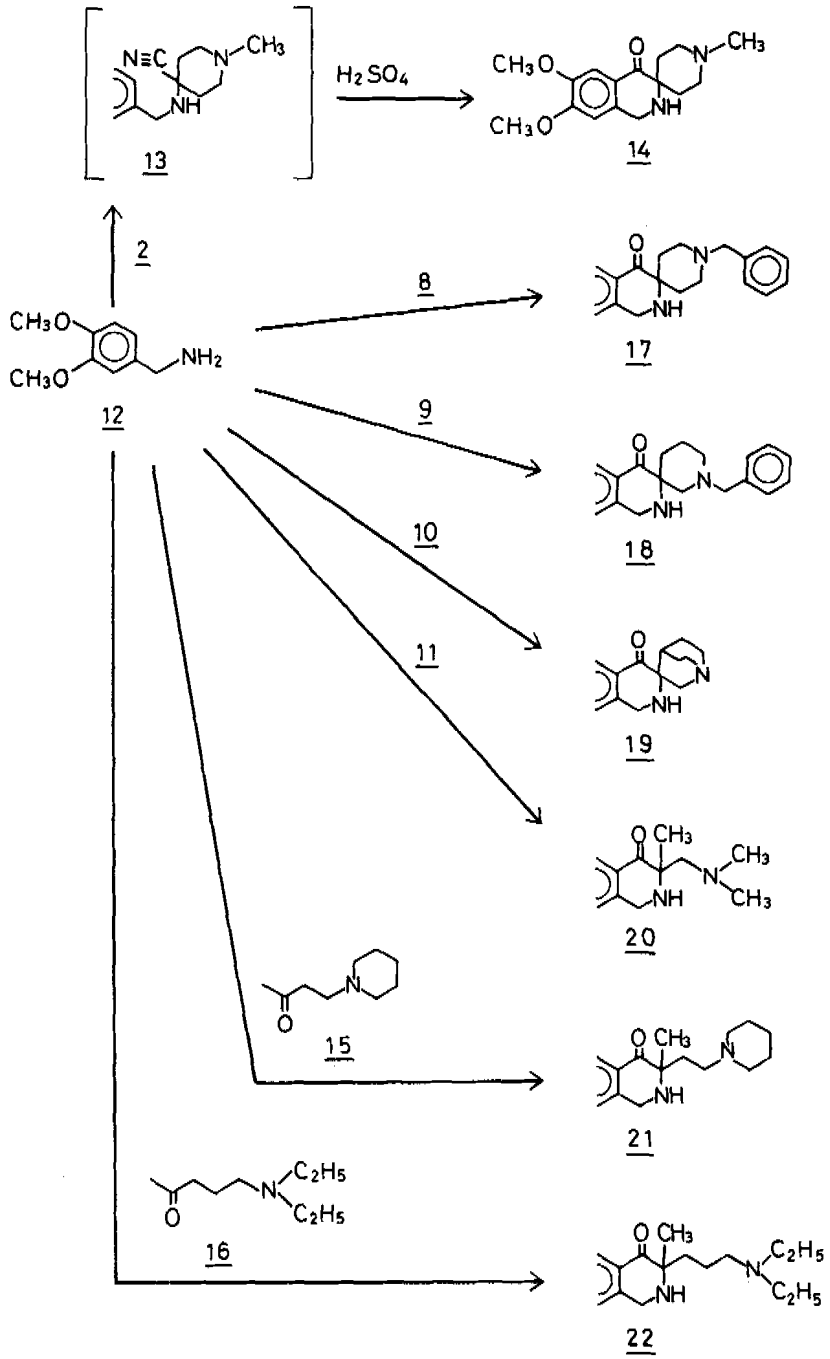
When 3,4-dimethoxyphenethylamine (**1**) was allowed to react with N-methyl-4-piperidone (**2**) and was then thoroughly mixed with PPA, spiro compound **3** was obtained in 46% yield. Similarly the spiro products **4**, **5**, **6** and the 1,1-disubstituted compound **7** were prepared by treating **1** with the corresponding amino-ketones **8**, **9**, **10** and **11**.

3-Spiro-tetrahydroisoquinolines. Recently *Harcourt & Waigh* [5] reported a simple procedure for synthetising 3,3-disubstituted tetrahydroisoquinolin-4-ones. We have found this method to be successful for the synthesis of 3-spiro-tetrahydroisoquinolin-4-ones as well for 3,3-disubstituted tetrahydroisoquinolin-4-ones, where one of the substituents contained a nitrogen atom. When 3,4-dimethoxybenzylamine **12** was treated with the amino-ketone **2** in the presence of KCN and HCl, the intermediate **13** was formed, which cyclised when mixed with conc. H_2SO_4. On hydrolysis the spiro product **14** was obtained. Similar results were recorded when the same benzylamine **12** was treated with amino-ketones **8**, **9**, **10**, **11**, **15** or **16** thus yielding **17**, **18**, **19**, **20**, **21** and **22**, respectively. The cyclic aromatic ketone **14** was reduced with sodium borohydride to the alcohol **23** which was dehydrated with PPA to the dihydroisoquinoline **24**; no *Wagner-Meerwein* rearrangement was observed. The sodium borohydride reduction of **24** gave the tetrahydroisoquinoline **25**.



4-Spiro-tetrahydroisoquinolines. The synthesis of several 3-spiro-5,6-dimethoxy-indan-1-ones with a nitrogen-containing cycle has been reported previously [6]. These compounds on treatment with sodium azide in conc. H_2SO_4, followed by *Red-al*[1]) reduction of the intermediate lactams, gave 4-spiro-tetrahydroisoquinolines. Indanones **26** and **27** subjected to the *Schmidt* reaction yielded lactams **28** and **29** which were reduced to the tetrahydroisoquinolines **30** and **31**. NMR. spectra of

[1]) 70% solution of sodium-bis(2-methoxyethoxy)-aluminum hydride in benzene (*Aldrich*).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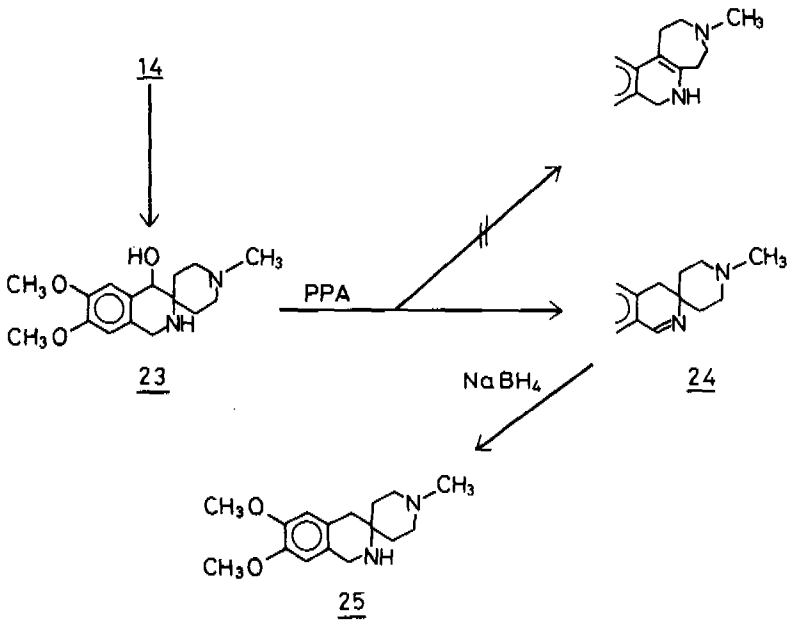
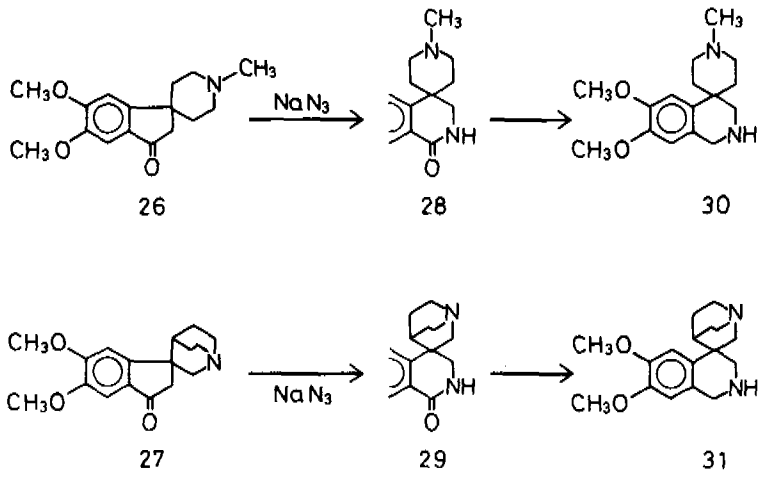


compounds **28** and **29** showed a coupling between the NH and the CH_2N protons, which clearly indicated that the *Schmidt* reaction had given the isoquinoline rather than the quinoline-type of products.



Experimental Part

General. NMR. spectra were taken at 60 MHz with tetramethylsilane as an internal standard, using a *Varian* T-60 high resolution NMR. spectrometer. In the case of salts, a sample of the free base was prepared and used in $CDCl_3$. Abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet; chemical shifts in δ-values (ppm). Analytical results obtained for the indicated elements were within $\pm$ 0.4% of the theoretical values.

6,7-Dimethoxy-1'-methyl-spiro[1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine] (**3**) *dihydrochloride.* In a conical flask, 18.1 g (0.1 mol) β-(3,4-dimethoxyphenyl)ethylamine (**1**) and 13.6 g (0.12 mol) N-methyl-4-piperidone were mixed and heated at 80° for 15 min, 350 g of polyphosphoric acid (*Fluka*) were then added. The mixture was thoroughly stirred by hand and heated at 130° for 20 min. The dark viscous solution was poured into water, ice was added, and the solution made alkaline with a 30% NaOH solution. The product was extracted with $CHCl_3$ and the extract was washed twice with water, dried over Na_2SO_4 and evaporated. The residual oil was dissolved in a small amount of abs. ethanol and treated with an HCl gas/ether solution to yield, after recrystallisation from alcohol/ether, 16.1 g (46%) of **3**, m.p. 310° (dec.). Known compound, m.p. not reported [7]. – NMR. ($CDCl_3$): 6.6 (*s*, 1H, arom); 6.9 (*s*, 1H, arom); 3.9 (*s*, 6 H, 2 OCH_3); 2.4 (*s*, 3 H, NCH_3). – $C_{16}H_{26}Cl_2N_2$: C, H, N.

The following compounds were similarly prepared:

1'-Benzyl-6,7-dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine] (**4**) *dihydrochloride.* β-(3,4-Dimethoxyphenyl)ethylamine (**1**) 18.1 g (0.1 mol), N-benzyl-4-piperidone (**8**) 22.7 g (0.12 mol), PPA 350 g. Yield 19.2 g of **4** (45%), m.p. 298–304° (dec.). Known compound, m.p. not reported [7]. – $C_{22}H_{30}Cl_2N_2O_2$: C, H, N.

1'-Benzyl-6,7-dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-1,3'-piperidine] (**5**) *dihydrochloride.* β-(3,4-Dimethoxyphenyl)ethylamine (**1**) 18.1 g (0.1 mol), N-benzyl-3-piperidone (**9**) 22.7 g (0.12 mol), PPA 350 g. Yield 18.9 g (44.5%) of **5**, m.p. 229–235° (dec.). – NMR. ($CDCl_3$): 7.2 (*s*, 5 H, phenyl); 6.75 (*s*, 1H, arom); 6.55 (*s*, 1H, arom); 3.8 (*s*, 3 H, OCH_3); 3.75 (*s*, 3 H, OCH_3); 3.7 and 3.4 ($d \times d$, J = 14 Hz, $PhCH_2N$). – $C_{22}H_{30}Cl_2N_2O_2$; C, H, N.

6,7-Dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-1,3'-quinuclidine] (**6**) *dihydrochloride.* β-(3,4-Dimethoxyphenyl)ethylamine (**1**) 18.1 g (0.1 mol), 3-quinuclidinone (**10**) 15.0 g (0.12 mol), PPA 350 g. Yield 18 g (41.5%), m.p. 250–276° (dec.). – NMR. ($CDCl_3$): 6.95 (*s*, 1H, arom); 6.65 (*s*, 1H, arom); 3.90 (*s*, 3 H, OCH_3); 3.95 (*s*, 3 H, OCH_3). – $C_{17}H_{26}Cl_2N_2O_2$: C, H, N.

6,7-Dimethoxy-1-(N,N-dimethylaminomethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (**7**) *dihydrochloride.* β-(3,4-Dimethoxyphenyl)ethylamine (**1**) 18.1 g (0.1 mol), N,N-dimethylaminoacetone 12.1 g (0.12 mol), PPA 350 g. Yield 14.5 g (44%), m.p. 210–225° (dec). – NMR. ($CDCl_3$): 6.85 (*s*, 1H, arom); 6.55 (*s*, 1H, arom); 3.90 (*s*, 6 H, OCH_3); 2.80 (*m*, 4 H, CH_2CH_2); 2.45 (*s*, 2 H, CCH_2N); 2.10 (*s*, 6 H, $N(CH_3)_2$); 1.25 (*s*, 3 H, CH_3). – $C_{15}H_{26}Cl_2N_2O_2$: C, H, N.

6,7-Dimethoxy-1'-methyl-spiro[1,2,3,4-tetrahydroisoquinoline-1,4'-piperidin]-4-one (**14**). In a conical flask, 16.7 g (0.1 mol) veratrylamine (**12**) and 13.6 g (0.12 mol) N-methyl-4-piperidone (**2**) were added to 200 ml 1N HCl with stirring. A solution of 10 g KCN in 50 ml H_2O was then added. The mixture was stirred overnight at room temperature and for 2 h at 60°, and was then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried and evaporated. The residual oil or crystalline mass, dissolved in 200 ml $CHCl_3$, was added slowly to 200 ml of concentrated H_2SO_4 contained in a 500-ml-flask equipped with a reflux condenser and magnetic stirrer. The temperature rose to the boiling point of $CHCl_3$ and was maintained at that temperature for a further 15 min. The red solution was then cooled and poured into ice. After being made alkaline with a 30% NaOH solution, the mixture was then extracted with $CHCl_3$, and the chloroform extract was washed with water, dried and evaporated to dryness. Compound **14** was recrystallised from $CHCl_3$/ether, yielding 24 g (82.5%), m.p. 170–174°. – NMR. ($CDCl_3$): 7.55 (*s*, 1H, arom); 6.65 (*s*, 1H, arom); 4.15 (*s*, 2 H, benzylic); 4.0 (*s*, 3 H, OCH_3); 3.95 (*s*, 3 H, OCH_3); 2.3 (*s*, 3 H, NCH_3). – $C_{18}H_{22}N_2O_3$: C, H, N.

A similar procedure was used for the following compounds.

1'-Benzyl-6,7-dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-3,4'-piperidin]-4-one (**17**). Veratrylamine 16.7 g (0.1 mol), N-benzyl-4-piperidone 18.9 g (0.1 mol), 200 ml 1N HCl and 10 g KCN in 50 ml H_2O were mixed together. Ethanol was then added in order to keep the amines in solution. The intermediate product was treated with conc. H_2SO_4 yielding 21 g (57%) of **17**, m.p. 180–181°. – NMR ($CDCl_3$): 7.55 (*s*, 1H, arom); 7.35 (*s*, 5 H, phenyl); 6.55 (*s*, 1H, arom); 4.05 (*s*, 2 H, benzylic); 3.90 (*s*, 6 H, 2 OCH_3); 3.60 (*s*, 2 H, benzylic). – $C_{22}H_{26}N_2O_3$: C, H, N.

1'-Benzyl-6,7-dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline3,3'-piperidin]-4-one (**18**). Veratrylamine 16.7 g (0.1 mol) with 22.5 g (0.1 mol) N-benzyl-3-piperidone hydrochloride, 0.5N HCl 200 ml and 10 g KCN in 50 ml H_2O were mixed, ethanol being added until the solution was clear.

The intermediate product was treated with *200 ml of* conc. H_2SO_4. Since the residual oil did not crystallise, the dihydrochloride was prepared by dissolving the residue in a small amount of abs. ethanol and adding a solution of HCl gas in ether. Compound **18** was recrystallised from alcohol/ether. Yield 18.2 g (49.5%), m.p. 174–177°. – NMR. ($CDCl_3$): 7.55 (*s*, 1 H, arom); 7.35 (*s*, 5 H, phenyl); 6.65 (*s*, 1 H, arom); 4.05 (*s*, 2 H, benzylic); 3.30 (*s*, 6 H, 2 OCH_3); 3.55 (*s*, 2 H, benzylic); 2.9 and 2.4 (*d* × *d*, J = 12 Hz, 2 H, CCH_2N). – $C_{22}H_{28}Cl_2N_2O_8$: C, H, N.

6,7-Dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-3,3'-quinuclidin]-4-one (**19**). Veratrylamine 16.7 g (0.1 *mol*), *3*-quinuclidone hydrochloride 16.2 g (0.1 mol), 0.5 N HCl 200 ml and 10 g KCN dissolved in 50 ml H_2O were mixed together. Ethanol was added until the solution was clear and the intermediate product was then treated with conc. H_2SO_4 yielding 19.2 g (65.5%), m.p. 190–195°. – NMR. ($CDCl_3$): 7.6 (*s*, 1 H, arom); 4.5 and 3.85 (*d* × *d*, J = 8 Hz, 2 H, $ArCH_2N$); 3.95 (*s*, 6 H, 2 OCH_3). – $C_{17}H_{22}N_2O_3$: C, H, N.

6,7-Dimethoxy-3-(N,N-dimethyl-aminomethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-4-one (**20**). Veratrylamine 16.7 g (0.1 mol), N,N-dimethylaminoacetone 10.1 g (0.1 mol), 200 ml 1 N HCl and 10 g KCN in 50 ml H_2O were mixed together. Ethanol was then added until the solution was clear. The intermediate product was treated with conc. H_2SO_4 to yield 15.3 g (55%), m.p. 105–108° (dec.). – NMR. ($CDCl_3$): 7.6 (*s*, 1 H, arom); 6.7 (*s*, 1 H, arom); 4.4 and 5.0 (*d* × *d*, J = 18 Hz, 2 H, $ArCH_2N$); 4.0 (*s*, 1 H, OCH_3); 3.99 (*s*, 1 H, OCH_3); 3.25 and 2.35 (*d* × *d*, J = 14 Hz, 2 H, CCH_2N); 2.25 (*s*, 6 H, $-N(CH_3)_2$); 1.25 (*s*, 3 H, CH_3). – $C_{15}H_{22}N_2O_5$: C, H, N.

6,7-Dimethoxy-3-methyl-3-(piperidinoethyl)-1,2,3,4-tetrahydroisoquinolin-4-one (**21**) *dihydrochloride hydrate*. Veratrylamine 16.7 g (0.1 mol), 4-piperidino-2-butanone hydrochloride 19.3 g (0.1 mol), 0.5 N HCl 200 ml and 10 g KCN in 50 ml H_2O were mixed together. Ethanol was then added until the solution was clear. The intermediate was treated with conc. H_2SO_4, and the free base of **21** was converted to the dihydrochloride as for compound **18**. Recrystallisation from H_2O/ethanol/ether yielded the dihydrochloride hydrate, 19.5 g (45.5%), m.p. 205–208°. – NMR. ($CDCl_3$): 7.6 (*s*, 1 H, arom); 6.65 (*s*, 1 H, arom); 4.1 (broad *s*, 2 H, $ArCH_2N$); 3.95 (*s*, 6 H, 2 OCH_3); 1.3 (*s*, 3 H, CH_3). – $C_{19}H_{32}Cl_2N_2O_4$: C, H, N.

3(N,N-Diethylamino-propyl)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinolin-4-one (**22**) *dihydrochloride hydrate*. Veratrylamine 16.7 g (0.1 mol), 5-diethylamino-2-pentanone 15.7 g (0.1 mol), 1 N HCl 200 ml and 10 g KCN in 50 ml H_2O were mixed together. Ethanol was then added until the solution was clear. The intermediate was treated with conc. H_2SO_4. The free base obtained after working up was converted to the dihydrochloride hydrate as that of compound **21** yielding 19 g (44.5%), m.p. 195–215° (dec.). – NMR. ($CDCl_3$): 7.6 (*s*, 1 H, arom); 6.65 (*s*, 1 H, arom); 4.1 (*s*, 2 H, $ArCH_2N$); 3.96 (*s*, 3 H, OCH_3); 3.95 (*s*, 3 H, OCH_3); 1.3 (*s*, 3 H, CH_3); 1.0 (*t*, J = 8 Hz, 6 H, CH_3 ethyl). – $C_{19}H_{34}Cl_2N_2O_4$: C, H, N.

6,7-Dimethoxy-1'-methyl-spiro[1,2,3,4-tetrahydroisoquinoline-3,4'-piperidin]-4-ol (**23**) *dihydrochloride*. A solution of 2.92 g (0.01 mol) of ketone **14** in 50 ml methanol maintained at 10° and 1.5 g $NaBH_4$ was added over a period of 15 min. When the reduction was complete 300 ml H_2O was added and the product was extracted with several portions of CH_2Cl_2. The organic layers were combined and washed with H_2O, dried and evaporated to dryness. The residue was dissolved in a small amount of abs. ethanol and an ethereal solution of HCl gas was added. Recrystallisation from ethanol/ether afforded 2.7 g (80.5% of **23**, m.p. 225° (dec.). – NMR. ($CDCl_3$): 6.9 (*s*, 1 H, arom); 6.5 (*s*, 1 H, arom); 4.05 (*s*, 1 H, ArCH—O); 3.90 (*s*, 3 H, OCH_3); 3.85 (*s*, 3 H, OCH_3); 3.8 (*s*, 2 H, $ArCH_2N$); 2.95 (*s*, 3 H, CH_3). – $NC_{16}H_{26}Cl_2N_2O_3$: C, H, N.

6,7-Dimethoxy-1'-methyl-spiro[3,4-dihydroisoquinoline-3,4'-piperidine] (**24**) *dihydrochloride*. In a conical flask 2.9 g (0.01 mol) of **23** free base, were thoroughly mixed with 30 g of PPA and heated to 100° until the orange mixture changed to a fluorescent green-yellow color. It was then poured into water, ice was added, and the resulting solution was made strongly alkaline. The product was extracted with $CHCl_3$. The organic layer was washed with water, dried and evaporated to dryness. The dihydrochloride was prepared in the same manner as that of **23**. Recrystallisation from ethanol/ether yielded 2.1 g (60.5%) of **24** as a yellow crystalline powder, m.p. 240° (dec.). – NMR. ($CDCl_3$): 8.3; 6.9 and 6.7 (3 *s*, 3 H, arom and —CH=N—); 3.95 (*s*, 3 H, OCH_3); 2.65 (*s*, 2 H, $ArCH_2$); 2.35 (*s*, 3 H, NCH_3). – $C_{16}H_{24}Cl_2N_2O_2$: C, H, N.

6,7-Dimethoxy-1'-methyl-spiro[1,2,3,4-tetrahydroisoquinoline-3,4'-piperidine] (**25**) *dihydrochloride*. When 2.74 g (0.01 mol) of **24**, free base, was reduced with $NaBH_4$ by a procedure similar to that used for reduction of **14** to **23**, 2.6 g (74.5%) of the tetrahydroisoquinoline **25** dihydrochloride were obtained, m.p. 260–266° (dec.). – NMR ($CDCl_3$): 6.55 (*s*, 1H, arom); 6.5 (*s*, 1H, arom); 3.85 (*s*, 2H, $ArCH_2N$); 3.8 (*s*, 6H, 2 OCH_3); 2.55 (*s*, 2H, $ArCH_2C$); 2.25 (*s*, 3H, NCH_3). – $C_{16}H_{26}Cl_2N_2O_2$: C, H, N.

6,7-Dimethoxy-1'-methyl-spiro[1,2,3,4-tetrahydroisoquinoline-4,4'-piperidin]-1-one (**28**). The indanone **26**, 3.1 g (0.01 mol) was added to 50 ml conc. H_2SO_4. The solution was then heated to 60° and 3 g sodium azide was added in small portions over a period of 30 min. After a further 15 min heating, the solution was poured on ice, made alkaline with a 30% NaOH solution and extracted with chloroform. The organic layer was washed with water, dried and evaporated to dryness. The residue was recrystallised from chloroform/ether yielding 2.3 g (79%) of the lactam **28**, m.p. 200–208°. – NMR. ($CDCl_3$): 7.7 (*s*, 1H, arom); 7.05 (broad signal, 1H, NH); 7.0 (*s*, 1H, arom); 3.95 (*s*, 6H, OCH_3); 3.55 (broad signal which colapses to a singlet after deuterium exchange, 2H, NCH_2). – $C_{16}H_{22}N_2O_3$: C, H, N.

6,7-Dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-4,3'-quinuclidin]-1-one (**29**). The procedure was similar to that used for the preparation of **28**. Spiro-indanone hydrochloride **27** 3.23 g (0.01 mol), 50 ml conc. H_2SO_4 and 3 g NaN_3 were used, yielding 2.7 g (90%) of the lactam **29**, m.p. 232–234°. – $C_{17}H_{22}N_2O_3$: C, H, N.

6,7-Dimethoxy-1'-methyl-spiro[1,2,3,4-tetrahydroisoquinoline-4,4'-piperidine] (**30**) *dihydrochloride*. The lactam **28** 2.9 g (0.01 mol) was suspended in 40 ml of dried dimethoxyethane, 6 ml of *Red-al* were added, and the mixture was refluxed for 6 h. After cooling, water was added dropwise until no more reaction occurred. Chloroform was added and the suspension filtered, washed with water, dried and evaporated to dryness. The dihydrochloride was prepared and recrystallised as for the dihydrochloride of **3**, yielding 1.9 g of **30** (54%), m.p. 215–230° (dec.). – NMR ($CDCl_3$): 7,0 (*s*, 1H, arom); 6.5 (*s*, 1H, arom); 3.95 (*s*, 2H, $ArCH_2N$); 3.85 (*s*, 6H, 2 OCH_3); 3.05 (*s*, 2H, CCH_2N); 2.35 (*s*, 3H, NCH_3). – $C_{16}H_{26}Cl_2N_2O_2$: C, H, N.

6,7-Dimethoxy-spiro[1,2,3,4-tetrahydroisoquinoline-4,3'-quinuclidine] (**31**) *dihydrochloride*. Similar conditions as those for reduction of **28**. Lactam **29** 2.9 g (0.01 mol), dimethoxyethane 40 ml, *Red-al* 3 ml, yielding 1.8 g of **31** dihydrochloride (50%), m.p. 230° (dec.). – NMR. ($CDCl_3$): 7.0 (*s*, 1H, arom); 6.6 (*s*, 1H, arom); 4.1 (*s*, 2H, $ArCH_2N$); 3.90 (*s*, 3H, OCH_3); 3.85 (*s*, 3H, OCH_3); 3.4 and 2.7 ($d \times d$, J = 14 Hz, 2H, CCH_2N). – $C_{17}H_{26}Cl_2N_2O_2$: C, H, N.

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