Acid-catalysed Cyclization of 1-Aryl-2-thienylmethyl- and 1-Aryl-2-furfuryl-aminoethanols *via* Spiro Intermediates

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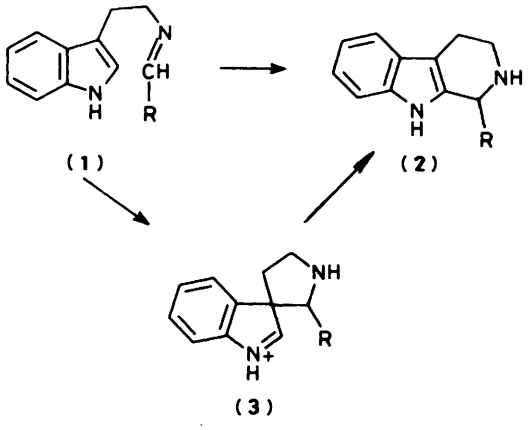
1-(4-Chlorophenyl)-2-(5-chloro-2-thienylmethyl)methylaminoethanol (**7**) reacts in trifluoroacetic acid to give the spirothiolenone (**10**) and the two isomeric tetrahydrothieno[2,3-*c*]- and [3,2-*c*]-pyridines (**8**) and (**9**). Treatment of 1-aryl-2-furfurylaminoethanols (**12a—d**) with trifluoroacetic acid gives 7-aryl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridines (**13a—d**) as the major products. The corresponding reaction of 1-(3,4-dimethoxyphenyl)-2-furfuryl(methyl)aminoethanol (**12e**) yields the polycyclic spirodihydrofuran (**23**). For the formation of the tetrahydrofuro- and tetrahydrothieno-[3,2-*c*]pyridines a mechanistic pathway is discussed in which a spirocyclic intermediate is involved followed by a rearrangement reaction. The isolated spiro compounds support this mechanism.

It is well established that cyclization of alkylidenetryptamines (**1**) to tetrahydro-β-carbolines (**2**),[1] as well as *N*-acyltryptamines to dihydro-β-carbolines[2] and intramolecular electrophilic substitution of 4-indol-3-ylbutanol to the corresponding tetrahydrocarbazole[3] involves initial intramolecular cyclization at the 3-position followed by rearrangement of the intermediate spirocycle (**3**)[4] (Scheme 1). Recently, it has been found that



Scheme 1.

1-phenyl-2-(2-thienylmethyl)aminoethanols (**4**)[5–7] yield 4-phenyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines (**5**) in polyphosphoric acid (PPA), aluminium chloride, or methanesulphonic acid and 7-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]-pyridines (**6**) in trifluoroacetic acid (TFA). The authors[7] assumed that the latter is formed by a spirocyclic rearrangement (Scheme 2). The mechanism of the overall process thus closely parallels that of the intramolecular cyclization of 3-substituted indole derivatives.

During our studies on the syntheses of biologically active compounds related to tetrahydrothienopyridines[8] based on the cyclization of 1-aryl-2-thienylmethyl- and 1-aryl-2-furfuryl-aminoethanols, we observed the formation of the hitherto unknown spirothiolenone (**10**) and 8,9-dimethoxy-2-methyl-3a,6-epoxy-1,2,3,3a,6,10b-hexahydrobenzo[3,4]cyclohepta-

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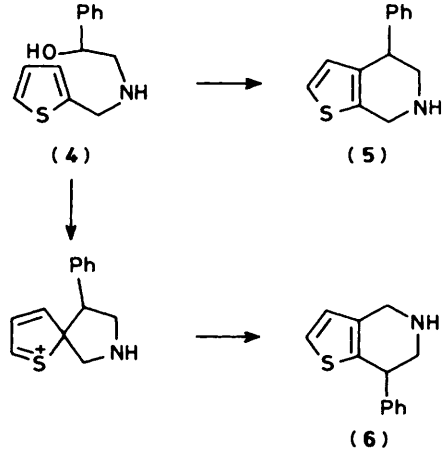


Scheme 2.

[1,2-*c*]pyrrole (**23**) which strongly supports the proposed spirocyclic rearrangement. The details are reported here.

Results and Discussion

Recently we have shown that 1-(4-chlorophenyl)-2-(5-chloro-2-thienylmethyl)methylaminoethanol (**7**) undergoes cyclization in the presence of aluminium chloride in 1,2-dichloroethane at 10 °C producing only 2-chloro-4-(4-chlorophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (**8**) in 56% yield.[8] Treatment of compound (**7**) with TFA at 50 °C for 8 h furnished 98% of cyclized material. H.p.l.c. indicated the formation of four products. Chromatographic isolation allowed the identification of the peaks as the isomers (**8**) (5.1%) and (**9**) (33.9%), and the diastereoisomeric spirothiolenones (**10a**) (24.8%) and (**10b**) (33.8%).

The isomeric tetrahydrothienopyridines (**8**) and (**9**) were distinguished on the basis of their ^{1}H n.m.r. spectra. Complete data are summarized in Table 1. A characteristic upfield shift is observed for the thiophene proton 3-H in compound (**8**) compared with (**9**) (Δδ 0.5 p.p.m.) due to the effect of the aryl ring. This is in agreement with the results of Mackay and Waigh,[7] obtained from analogous compounds. As seen from Table 1, the benzylic protons 4-H in compound (**8**) and 7-H in (**9**) are also diagnostic for the isomeric structure (Δδ = 0.3 p.p.m.).

Table 1. N.m.r. spectral data of the compounds (**8**)–(**10a,b**), (**13a**), (**14a**), (**23**), and (**24**)

Compd.	δ_H(p.p.m.)	δ_C(p.p.m.)[c]
(**8**)·HCl[a]	6.42 (1 H, s, 3-H), 4.35 (1 H, m, 4-H), 3.45 and 3.90 (each 1 H, dd, *J* 12 Hz, 5 Hz and 12 Hz, 12 Hz, 5-CH_2), 4.54 (2 H, brs, 7-CH_2), 3.09 (3 H, s, NMe), and 7.51–7.15 (4 H, m, Ph)	
(**9**)·HCl[a]	6.91 (1 H, s, 3-H), 4.66 (1 H, m, 7-H), 3.55 and 3.90 (each 1 H, dd, *J* 11 Hz, 5 Hz and 11 Hz, 11 Hz, 6-CH_2), 4.47 (2 H, s, 4-CH_2), 3.10 (3 H, s, NMe), and 7.54–7.22 (4 H, m, Ph)	
(**10a**)[b]	6.09 (1 H, d, *J* 6.2 Hz, 3-H), 7.41 (1 H, d, *J* 6.2 Hz, 4-H), 3.74 (1 H, t, *J* 8.2, Hz, 9–H), 3.17 and 3.12 (each 1 H, dd, *J* 8.2 Hz, 9.4 Hz and 8.5 Hz, 9.4 Hz, 8–CH_2), 3.23 and 3.20 (2 H, AB, *J* 10.0 Hz, 6–CH_2), 2.49 (3 H, s, NMe), and 7.05 and 7.22 (each 2 H, d, *J* 8 Hz, Ph)	181.8 (C-2), 130.8 (C-3), 159.3 (C-4), 72.4 (C-5), 60.5 (C-6), 52.9 (C-8), 67.1 (C-9), 41.9 (NMe) 136.4 (C-10), 129.7 (C-11), 128.1 (C-12), and 133.1 (C-13)
(**10b**)[b]	5.84 (1 H, d, *J* 6.2 Hz, 3-H), 7.15 (1 H, d, *J* 6.2 Hz, 4-H), 3.98 (1 H, m, 9-H), 3.20 and 3.10 (each 1 H, dd, *J* 9.7 Hz, 6.4 Hz, and 9.7 Hz, 8.4 Hz, 8-CH_2), 3.12 and 3.09 (2 H, AB, *J* 10.1 Hz, 6-CH_2), 3.19 (3 H, s, NMe), 7.22 (4 H, m, *sym*-ArH)	182.1 (C-2), 129.8 (C-3), 159.6 (C-4), 69.3 (C-5), 60.7 (C-6), 53.5 (C-8), 66.5 (C-9), 41.8 (NMe), 136.6 (C-10), 129.0 (C-11), 128.6 (C-12), and 133.2 (C-13)
(**13a**)·HCl[a]	7.50 (1 H, d, *J* 1.6 Hz, 2-H), 6.47 (1 H, d, *J* 1.6 Hz, 3-H), 4.65 (1 H, m, 7-H), 3.45 and 3.90 (each 1 H, dd, *J* 12, 6, and 12, 12 Hz, 6-CH_2), 4.93 (2 H, m, 4-CH_2), 3.06 (3 H, s, NMe), and 7.47—7.10 (5 H, m, Ph)	
(**14a**)·HCl[a]	7.57 (1 H, d, *J* 1.7 Hz, 2-H), 6.30 (1 H, d, *J* 1.7 Hz, 3-H), 4.33 (1 H, m, 4-H), 3.33 and 3.80 (each 1 H, dd, *J* 11, 5, and 11, 11 Hz, 5-CH_2), 4.43 (2 H, br s, 7-CH_2), 3.08 (3 H, s, NMe), and 7.52—7.28 (5 H, m, Ph)	
(**23**)[b]	6.62 (1 H, s, 7-H), 6.63 (1 H, s, 10-H), 6.42 (1 H, dd, *J* 5.7 and 1.7 Hz, 5-H), 6.03 (1 H, d, *J* 5.7 Hz, 4-H), 5.20 (1 H, d, *J* 1.7 Hz, 6-H), 3.80 (3 H, s, 8-OMe), 3.83 (3 H, s, 9-OMe), 2.86 (1 H, dd, *J* 7.7, 7.0 Hz, 10b-H), 2.57 and 3.44 (each 1 H, dd, *J* 10.7, 8.2, and 8.5, 7.0 Hz, 1-CH_2), 2.68 and 3.68 (2 H, Ab, *J* 11.6 Hz, 3-CH_2), and 2.50 (3 H, s, NMe)	60.3 (C-1), 62.1 (C-3), 92.1 (C-3a), 130.2 (C-4), 136.8 (C-5), 80.2 (C-6), 129.9 (C-6a), 113.4 (C-7), 148.8 (C-8), 146.9 (C-9), 107.7 (C-10), 125.9 (C-10a), 43.3 (C-10b), 42.2 (NMe), and 56.0 (2-OMe)
(**24**)[b]	6.60 (1 H, s, 7-H), 6.57 (1 H, s, 10-H), 4.95 (1 H, d, *J* 7.0 Hz, 6-H), 3.85 (3 H, s, 8-OMe), 3.84 (3 H, s, 9-OMe), 2.94 (1 H, dd, *J* 10.5, 7.2 Hz, 10b-H), 2.60 and 3.27 (each 1 H, dd, *J* 8.5, 7.2, and 10.5, 8.5 Hz, 1-CH_2), 2.77 and 4.42 (2 H, AB, *J* 11.6 Hz, 3-CH_2), 2.46 (3 H, s, NMe), 1.98 and 2.34 (each 1 H, m, 4-CH_2), and 2.01 (2 H, m, 5-CH_2)	62.0 (C-1), 64.0 (C-3), 88.1 (C-3a), 32.7 (C-4), 34.7 (C-5), 77.2 (C-6), 124.3 (C-6a), 107.5 (C-7), 148.3 (C-8), 147.6 (C-9), 112.0 (C-10), 134.2 (C-10a), 49.1 (C-10b), 42.6 (NMe), and 56.2 and 56.0 (2-OMe)

[a] Spectrum recorded in CD_3OD at 90 MHz. [b] Spectrum recorded in $CDCl_3$ at 400.13 MHz. [c] ^{13}C Spectra recorded in $CDCl_3$ at 100.62 MHz.

The structural assignments of (**10a**) and (**10b**) as diastereoisomeric spirothiolenones was based upon elemental analysis, i.r. and mass spectra (see the Experimental section), and ^1H and ^{13}C n.m.r. data (see Table 1). The i.r. absorption at 1 695 and 1 700 cm^{-1} for compounds (**10a**) and (**10b**) indicates the presence of an unsaturated thiolactone structure,[9] whilst the ^1H n.m.r. spectra exhibited a pattern typical of a cyclic CO–CH=CH moiety with a vicinal coupling of 6.2 Hz; the latter is in full agreement with the findings of Hörnfeldt and Gronowitz for 3-thiolen-2-one.[9] The $CHCH_2NMeCH_2$ portion reveals regular ABX and AB patterns. Evidence for the chiral spiro carbon C-5 came from the ^{13}C n.m.r. resonances at 72.4 and 69.3 p.p.m. for compounds (**10a**) and (**10b**) respectively.

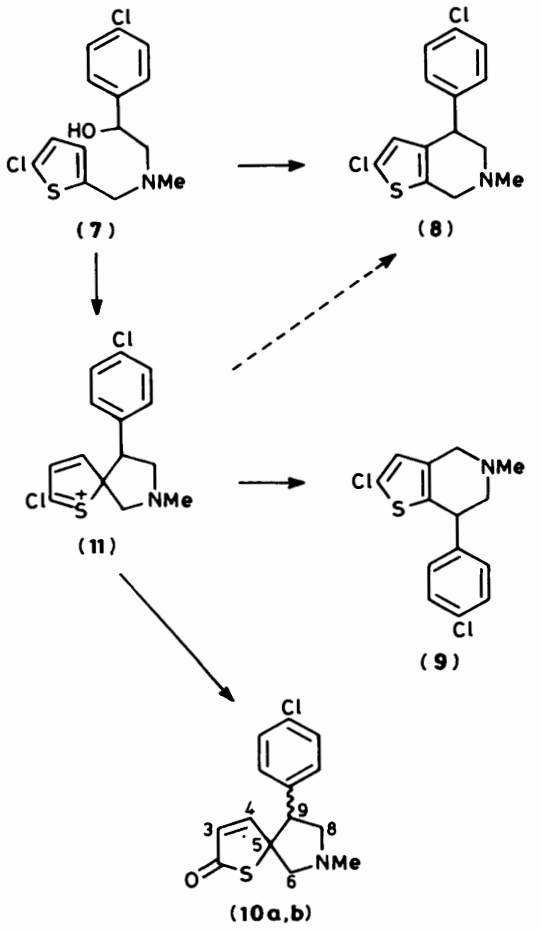
The mechanistic pathway which has been proposed[7] to account for the formation of the isomer (**9**) involves electrophilic attack by the carbonium ion, generated in TFA from compound (**7**), on the thiophene 2-position to give the spiro intermediate (**11**) with subsequent ring opening and reclosure to give the isomer (**9**) (Scheme 3). Trapping of the spiro-cation (**11**) by hydrolysis to give the spirothiolen-2-one (**10**) supports this mechanistic pathway.

Attention was then turned to the analogous series in which a furan ring takes the place of the thiophene residue. 1-Aryl-2-furfurylaminoethanols (**12a**—**e**) were readily prepared in high yield as described for the thiophene compound (**7**), starting from furaldehyde. Treatment of the compounds (**12a**—**e**) with PPA, aluminium chloride, or methanesulphonic acid largely gave polymeric material from which no identifiable product could be isolated.

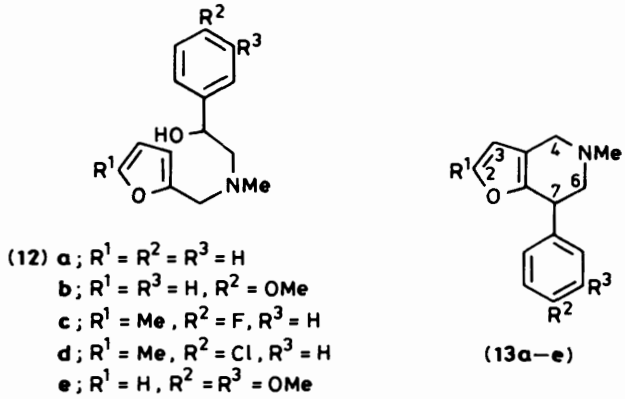
When a solution of (**12a**) in TFA was refluxed for 2 h, the 5-methyl-7-phenyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (**13a**) was obtained in 30% yield together with a small amount (3%) of the isomeric compound (**14a**). Similar treatment of the furfurylaminoethanols (**12b**—**d**) gave tetrahydrofuro[3,2-*c*]-pyridines (**13b**—**d**) in moderate yield. In these cases, the corresponding isomeric tetrahydrofuro[2,3-*c*]pyridines (**14b**—**d**) could not be isolated, although they were detected in the reaction mixture by t.l.c. and ^1H n.m.r. spectroscopy.

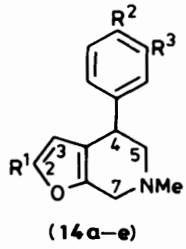
An alternative synthesis was devised for compounds (**14a**—**e**). Furfurylamine (**15**) was alkylated with ethyl chloroacetate in toluene to give the 2-furfurylglycine ethyl ester (**16**) which, on treatment with ethyl chloroformate, furnished compound (**17**). The ester group of (**17**) was hydrolysed to the corresponding carboxylic acid and then converted into the carboxylic acid chloride which, without purification, was treated with aluminium chloride in dichloromethane to give the cyclic ketone (**18**). The *N*-tosyl derivative of (**18a**) was previously prepared in 15% yield.[10] Reduction of compound (**18a**) with lithium aluminium hydride afforded compound (**19a**), thus the 4-oxo group was converted into a hydroxy group and the 6-ethoxycarbonyl group reduced to the methyl substituent in one step. The 2-methyl derivative (**19b**) was synthesized in an analogous manner. Treatment of compound (**19**) with benzene, fluoro-, and chloro-benzene in the presence of aluminium chloride gave compounds (**14a,c**, and **d**) and with anisole and veratrole in methanesulphonic acid gave (**14b** and **e**).

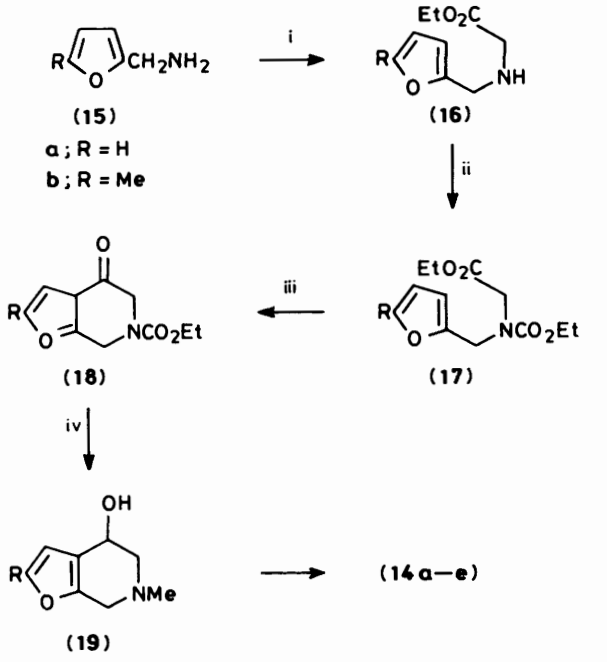
The structures of the new tetrahydrofuropyridines were determined from their chemical and spectroscopic data. As observed for compounds (**8**) and (**9**) the ^1H n.m.r. spectra of the isomers (**14a**—**e**) showed the furan 3-H in an upfield position as compared with the 3-H in (**13a**—**e**) ($\Delta\delta$ 0.17—0.37 p.p.m.). Complete data for one pair of isomers (**14a**), (**13a**) are given in Table 1. The structure of (**14a**) was confirmed as tetrahydrofuro[2,3-*c*]pyridine by the independent synthesis of authentic material from the reaction of compound (**19**) with benzene (Scheme 4).



Scheme 3.



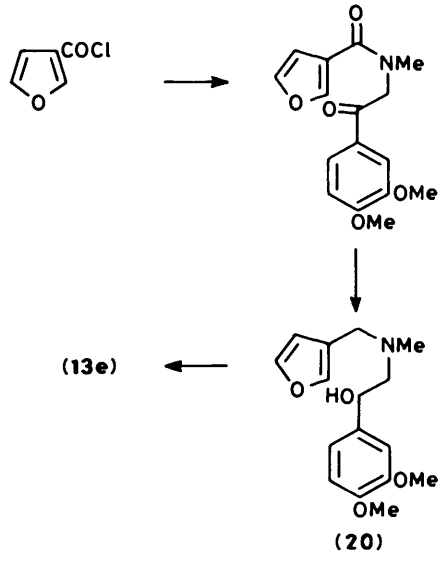




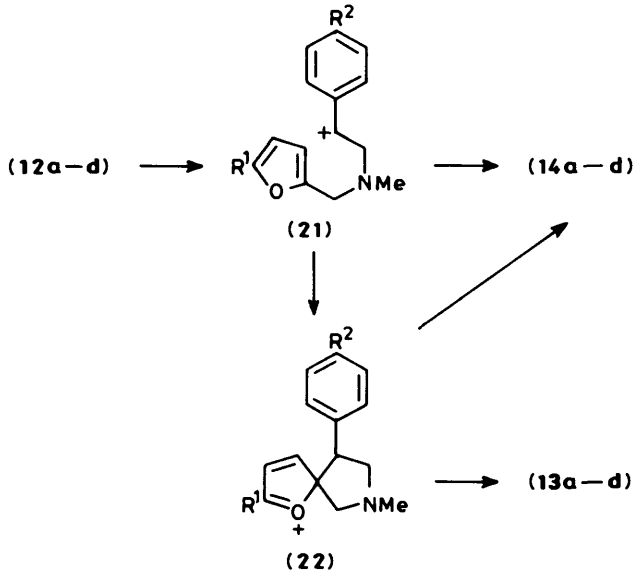
Scheme 4. *Reagents:* i, $ClCH_2CO_2Et$; ii, $ClCO_2Et$; iii, $KOH–SOCl_2–AlCl_3$; iv, $LiAlH_4$

Treatment of the 1-(3,4-dimethoxyphenyl)-2-furfurylmethylaminoethanol (**12e**) with TFA for 30 min at 40 °C led to the formation of a new product in 90% yield, which was shown to have the molecular formula $C_{16}H_{19}NO_3$. This proved to be neither the expected tetrahydrofuro[3,2-*c*]pyridine (**13e**) which was unambiguously synthesized in three steps from 3-furylcarboxylic acid chloride (Scheme 5), nor the tetrahydrofuro[2,3-*c*]pyridine (**14e**). On the basis of the evidence described below structure (**23**) was assigned to it. Hydrogenation of the dihydrofuran (**23**) led to the tetrahydrofuran (**24**). On the basis of the above results, a reaction sequence for the transformation of the furfurylaminoethanols (**12**) to the tetrahydrofuro[3,2-*c*]pyridines (**13**) and the spirodihydrofuran (**23**) can be explained by analogy with the mechanism for the formation of the tetrahydrothieno[3,2-*c*]pyridine (**9**) (Scheme 6). The initial attack of the cationic intermediate (**21**) at the 2-position of the furan ring is followed by a ring contraction to the spiro intermediate (**22**) and a subsequent ring-opening ring-closure sequence to form (**13**). However, in the case of the dimethoxy derivative (**12e**), the C-2 of the furan ring of the spiro intermediate (**12**) intramolecularly attacks the phenyl *ortho*-position to give compound (**23**) (Scheme 7). This electrophilic attack only happens with (**12e**), presumably because only in this case does the aryl ring bear an activating substituent in the 3-position. The formation of the spirodihydrofuran (**23**) as the only product from (**12e**) is a significant result. The former can arise from the cationic intermediate (**21**) only *via* the spiro intermediate (**22**).

Structure proof of the new polycyclic spirodihydrofuran (**23**) was obtained using normal and advanced n.m.r. techniques in a complementary way. In the first step 1D-^1H n.m.r. spectra served to determine distinct patterns for the CH(6)–CH(5)=CH(4), CH(10b)–CH_2(1)–NMe–CH_2(4), and the aryl moiety (see Table 1). Secondly, a mutual $^1H–^{13}C$ assignment was routinely done for all CH_n units by means of the $^1H–^{13}C$ 2D-shift correlations.[11] Assignment of the quaternary carbon had then to be accomplished in such a way as to demonstrate the linkages between the units given above. This was attempted using a specific $^1H–^{13}C$ long-range two-dimensional correlation



Scheme 5.



Scheme 6.

Table 2. ^{1}H–^{13}C Long-range correlations for (**23**)[a] from the COLOC-experiment[12,13]

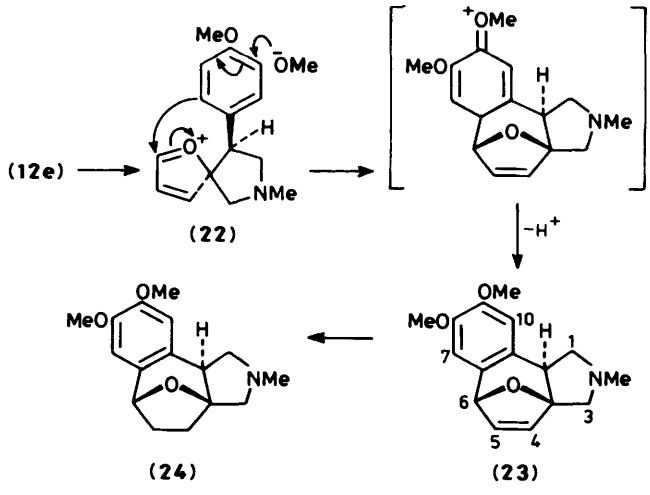
Proton	Carbon	Pathway
4-H	C-3a	^{2}J
5-H	C-3a	^{3}J
5-H	C-6	^{2}J
4-H	C-6	^{3}J
6-H	C-4	^{3}J
C-H	C-1	^{3}J
3-H	C-3a	^{2}J
10b-H	C-1	^{2}J
1-H	C-3	^{3}J
6-H	C-3a	^{3}J

[a] Obtained in $CDCl_3$ (60 mg in 0.6 ml) at 400.13/100.62 MHz.

Table 3. Correlations; HCC–COSY experiment[14] for compound (**23**)[a]

Quaternary carbon	Connected C	Connected H	$J^{13}C/^{13}C$
6a	6	6	C-6/C-6a 45.3 Hz
6a	7	7	C-7/C-6a 61.5 Hz
10a	10	10	C-10/C-10a 61.5 Hz

[a] Obtained in $CDCl_3$ (240 mg in 2.4 ml) at 400.13/100.62 MHz



Scheme 7.

technique, COLOC, which was recently developed by Kessler *et al.*[12,13] This technique enables mainly ^{2}J and ^{3}J H–C correlations. The unambiguous connectivities obtained for compound (**23**) which completely confirm the spiro moiety are given in Table 2.

Within the 6a-, 10a-, 7-, and 10-positions the correlations were not conclusive, because the C(6a)–C(10a) aryl bond activates ^{4}J magnetization transfer.[14] In order to relay C-6a directly to HC-6 and HC-7 (and so detect the point of ring attachment according to Scheme 6) the HCC-COSY experiment recently introduced by Kessler *et al.*[14] was employed. The direct ^{1}H–^{13}C–^{13}C transfer performed therein rules out any alternative pathway. As seen from Table 3, clear correlations were obtained including ^{13}C–^{13}C couplings. The missing 10b-H/C-10a correlation is due to a non-coplanar geometry in the 10b-10a-10 unit. In addition, the hydrogenation product (**24**) (see Scheme 6) was examined using all the techniques mentioned; the data (see Table 1) are fully consistent with structure (**23**).

All n.m.r. details and extended applications (COLOC and HCC) will be published elsewhere.

Experimental

Melting points are uncorrected. The ^{1}H and ^{13}C n.m.r. spectra were recorded on a Bruker WH 90 or a Bruker AM 400 n.m.r. spectrometer. Chemical shifts are reported in p.p.m. downfield from internal tetramethylsilane. I.r. spectra were recorded as Nujol mulls on a Perkin-Elmer 287 spectrophotometer. H.p.l.c. was carried out with a home built chromatograph consisting of a Waters M 6000 A pump, a Rheodyne 7125 valve, and a Waters 440 spectrophotometric detector (λ = 254 nm), using an ODS-Hypersil 5 μ reverse-phase column.

Column chromatography was performed with 0.063—0.020

mm mesh Merck silica gel adsorbant. TFA refers to trifluoroacetic acid. Methyl(5-methylfurfuryl)amine (b.p. 55—57 °C at 10 mmHg) was prepared according to the method of Beck.[15]

Reaction of 1-(4-*Chlorophenyl*)-2-(5-*chloro*-2-*thienylmethyl*)-*methylaminoethanol* (**7**) with TFA..—A solution of compound (**7**) (17.6 g) in TFA (350 ml) was heated under reflux for 8 h. The reaction was monitored by t.l.c. [cyclohexane–ethyl acetate (1:1); R_F values: 0.4, 0.29, 0.15, and 0.05 for compounds (**8**), (**9**), (**10a**), and (**10b**), respectively]. Most of the solvent was then removed under reduced pressure. To the residue was added crushed ice (100 g) and the mixture was neutralized with ammonia (*d* 880) and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Reverse-phase h.p.l.c. analysis [mobile phase: acetonitrile–0.01M-ammonium carbonate–diethylamine (650 + 350 + 0.1 ml, respectively)] demonstrated the presence of 97.6% cyclized material in the ratio 5.1, 33.9, 33.8, and 24.8% for compounds (**8**), (**9**), (**10a**), and (**10b**), respectively. The reaction mixture was separated by column chromatography [silica gel; cyclohexane–ethyl acetate (1:1)] to yield compound (**8**) (650 mg, 3.7%), m.p. 60—61 °C, the HCl salt, m.p. 226—228 °C, *m/z* 297 and 299 (M^+), 254 and 256 ($M^+ - C_2H_5N$); *compound* (**9**) (4.7 g, 27%) as an oil, the HCl salt, m.p. 274—275 °C (Found: C, 50.1; H, 4.15; N, 4.3. $C_{14}H_{14}Cl_3NS$ requires C, 50.24; H, 4.22; N, 4.81%); *m/z* 297 and 299 (M^+), 254 and 256 ($M^+ - C_2H_5N$); the diastereoisomers (**10a**) (4.5 g, 25.5%), m.p. 85—86 °C, the HCl salt 228—230 °C (Found: C, 53.05; H, 4.55; N, 4.55. $C_{14}H_{15}Cl_2NOS$ requires C, 53.17; H, 4.78; N, 4.43%); ν_{CO} 1 695 cm^{-1}; *m/z* 279 (M^+, 35%), 281 (15); and (**10b**) (3.4 g, 19.3%), m.p. 104—105 °C, the HCl salt, m.p. 224—225 °C (Found: C, 53.05; H, 4.75; N, 4.3%); ν_{CO} 1 700 cm^{-1}; *m/z* 279 (M^+, 32%), 281 (14). N.m.r. data are given in Table 1.

1-*Phenyl*-2-(*furfurylmethylamino*)*ethanol* (**12a**) *Oxalate*.—To a stirred solution of furfurylmethylamine[15] (16.6 g, 0.15 ml) in dry ethanol (200 ml) were added potassium carbonate (20.7 g) and phenacyl bromide (29.85 g, 0.15 mol). Stirring of the mixture was continued at room temperature for 2 h, whilst $NaBH_4$ (7.5 g) was added in small portions at 5 °C. The mixture was stirred at room temperature for a further 2 h and then poured into ice–water (500 ml). The organic material was extracted from the aqueous layer with dichloromethane and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was chromatographed on a silica gel column with cyclohexane–ethyl acetate (1:1) as the eluant. The colourless, oily base was converted into the oxalate salt, to yield pure (**12a**) oxalate (32.8 g, 68%), m.p. 146—147 °C (Found: C, 59.8; H, 6.0; N, 4.5. $C_{16}H_{19}NO_6$ requires C, 59.81; H, 5.96; N, 4.36%); δ (90 MHz; CD_3OD) 7.68 (1 H, m), 6.78 (1 H, m), 6.54 (1 H, m), 7.61—7.24 (5 H, m), 5.16 (1 H, q), 4.54 (2 H, s), 3.22 (2 H, m), and 2.96 (1 H, s).

The following compounds were similarly prepared by using the appropriately substituted furfurylamines and phenacylbromides.

2-*Furfuryl*(*methyl*)*amino*-1-(4-*methoxyphenyl*)*ethanol* (**12b**) *oxalate*: 48% yield, m.p. 114—115 °C (Found: C, 57.8; H, 6.05; N, 3.9. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.02; N, 3.99%); δ (90 MHz; CD_3OD) 7.69 (1 H, m), 6.78 (1 H, m), 6.54 (1 H, m), 7.50—6.84 (4 H, m), 5.08 (1 H, m), 4.53 (2 H, s), 3.79 (3 H, s), 3.06—3.49 (2 H, m), and 2.94 (3 H, s).

1-(4-*Fluorophenyl*)-2-(5-*methylfurfuryl*)*methylaminoethanol* (**12c**) *oxalate*: 44.5% yield, m.p. 119—120 °C (Found: C, 57.6; H, 5.7; N, 3.95. $C_{17}H_{20}FNO_6$ requires C, 57.78; H, 5.71; N, 3.96%); δ (90 MHz; CD_3OD) 7.50 (2 H, m), 7.16 (2 H, m), 6.68 (1 H, d), 6.16 (1 H, d), 5.18 (1 H, q), 4.50 (2 H, s), 3.30—3.16 (2 H, m), 2.96 (3 H, s), and 2.33 (3 H, s).

1-(4-*Chlorophenyl*)-2-(5-*methylfurfuryl*)*methylaminoethanol* (**12d**) *oxalate*: 56% yield, m.p. 147—148 °C (Found: C, 55.15; H, 5.45; N, 3.8. $C_{17}H_{20}ClNO_6$ requires C, 55.21; H, 5.45; N, 3.79%); δ (90 MHz; CD_3OD) 7.40 (4 H, s), 6.61 (1 H, d, *J* 3 Hz), 6.11 (1 H, m), 5.13 (1 H, t, *J* 7 Hz), 4.56 (2 H, s), 3.22 (2 H, d, *J* 7 Hz), 2.93 (3 H, s), and 2.31 (3 H, s).

1-(3,4-*Dimethoxyphenyl*)-2-*furfuryl*(*methyl*)*aminoethanol* (**12e**) *hydrochloride*: 65% yield, m.p. 163—164 °C (Found: C, 58.7; H, 6.85; N, 4.05. $C_{16}H_{22}ClNO_4$ requires C, 58.62; H, 6.76; N, 4.27%); δ (90 MHz; CD_3OD) 7.75 (1 H, m), 6.83 (1 H, m), 6.58 (1 H, m), 7.15—5.94 (3 H, m), 5.08 (1 H, m), 4.57 (2 H, s), 3.85 (3 H, s), 3.83 (3 H, s), 3.29 (2 H, m), and 2.97 (3 H, s).

General Procedure for the Cyclization of the Furfurylaminoethanol Derivatives (**12a**—**d**).—The furfurylaminoethanol derivatives (**12a**—**d**) were heated in TFA under reflux for 5 h, 2 h, 3 h, and 2.5 h, respectively, after which most of the TFA was removed under reduced pressure. Ice–water was added to the residue and the mixture was neutralized with aqueous ammonia (*d* 880) and extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel; cyclohexane–ethyl acetate (1:1)]. The oily bases were dissolved in acetone and a saturated ethereal solution of hydrochloric acid was added to give the HCl salt.

5-*Methyl*-7-*phenyl*-4,5,6,7-*tetrahydrofuro*[3,2-c]*pyridine* (**13a**) *hydrochloride*: 28% yield, m.p. 237—238 °C (Found: C, 67.25; H, 6.5; N, 5.5. $C_{14}H_{16}ClNO$ requires C, 67.33; H, 6.46; N, 5.61%). From the first eluate 5-methyl-4-phenyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (**14a**) was obtained, which was then converted into the maleate (200 mg, 1%), m.p. 174—175 °C (Found: C, 65.8; H, 5.9; N, 4.2. $C_{18}H_{19}NO_5$ requires C, 65.64; H, 5.81; N, 4.25%). N.m.r. data for compounds (**13a**) and (**14a**) are given in Table 1.

7-(4-*Methoxyphenyl*)-5-*methyl*-4,5,6,7-*tetrahydrofuro*[3,2-c]-*pyridine* (**13b**) *hydrochloride*: 22.5% yield, m.p. 221—222 °C (Found: C, 64.0; H, 6.45; N, 4.95. $C_{15}H_{18}ClNO_2$ requires C, 64.39; H, 6.48; N, 5.00%); δ (90 MHz; CD_3OD) 3.07 (3 H, s), 3.75 (3 H, s), 4.00—3.31 (2 H, m), 4.68—4.24 (3 H, m), 6.45 (1 H, d, *J* 2 Hz), 7.23—6.48 (4 H, m), and 7.49 (1 H, d, *J* 2 Hz).

7-(4-*Fluorophenyl*)-2,5-*dimethyl*-4,5,6,7-*tetrahydrofuro*-[3,2-c]*pyridine* (**13c**) *hydrochloride*: 27% yield, m.p. 202—203 °C (Found: C, 63.95; H, 6.05; N, 4.95. $C_{15}H_{17}ClFNO$ requires C, 63.94; H, 6.08; N, 4.97%); δ (90 MHz; CD_3OD) 2.21 (3 H, s), 3.05 (3 H, s), 3.49—3.88 (2 H, m), 4.34 (2 H, d), 4.58 (1 H, m), 6.07 (1 H, s), and 7.42—7.0 (4 H, m).

7-(4-*Chlorophenyl*)-2,5-*dimethyl*-4,5,6,7-*tetrahydrofuro*-[3,2-c]*pyridine* (**13d**) *hydrochloride*: 21% yield, m.p. 177—178 °C (Found: C, 58.75; H, 5.65; N, 4.6. $C_{15}H_{18}Cl_2NO$ requires C, 58.64; H, 5.90; N, 4.55%); δ (90 MHz; CD_3OD) 2.22 (3 H, s), 3.05 (3 H, s), 4.01—3.34 (2 H, m), 4.33 (2 H, d), 4.76—4.43 (1 H, m), 6.09 (1 H, s), and 7.50—7.10 (4 H, m).

Ethyl Furfurylaminoacetate (**16a**).—A solution of furfurylamine (20 g, 0.206 mol), triethylamine (20 g), and ethyl chloroacetate (24.5 g, 0.23 mol) in toluene (100 ml) was heated under reflux for 2 h. It was then diluted with water and extracted with diethyl ether. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with cyclohexane–ethyl acetate (1:1) gave ethyl 2-furylaminoacetate (**16a**) (25.6 g, 68%) as a colourless oil which was suitable for use as described below. A sample was converted into the oxalate salt, m.p. 204—205 °C (decomp.) (Found: C, 48.15; H, 5.6; N, 5.4. $C_{11}H_{15}NO_7$ requires C, 48.35; H, 5.53; N, 5.13%); δ (90 MHz; CD_3OD–D_2O) 7.67 (1 H, m), 6.72 (1 H, m), 6.53 (1 H, m), 4.42 (2 H, s), 4.31 (2 H, q, *J* 6.8 Hz), 4.00 (2 H, s), and 1.32 (3 H, t).

The following compound was similarly prepared: *ethyl* 5-

methylfurfurylaminoacetate (**16b**) *oxalate*, yield 71%, m.p. 193—194 °C (Found: C, 50.15; H, 5.95; N, 4.9. $C_{12}H_{17}NO_7$ requires C, 50.11; H, 6.0; N, 4.87%); δ (90 MHz; CD_3OD–D_2O), 6.50 (1 H, d, *J* 3 Hz), 6.06 (1 H, m), 4.28 (2 H, s), 4.27 (2 H, q, *J* 7 Hz), 3.91 (2 H, s), 2.30 (3 H, s), and 1.31 (3 H, t).

Ethyl Furfuryl(ethoxycarbonyl)aminoacetate (**17a**).—Ethyl chloroformate (10.6 g, 97 mmol) was added dropwise with stirring to a solution of ethyl furfurylaminoacetate (16.2 g, 0.088 mol) and triethylamine (9.9 g) in dichloromethane (120 ml) and triethylamine (9.9 g) in dichloromethane (120 ml) which was cooled in an ice–water bath. The mixture was stirred at room temperature for 1 h, diluted with water, acidified with hydrochloric acid, and extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with cyclohexane–ethyl acetate (3:1) gave (**17a**) (18 g, 79.8%) as an oil (Found: C, 56.45; H, 6.95; N, 5.6. $C_{12}H_{17}NO_5$ requires C, 56.46; H, 6.71; N, 5.49%); δ (90 MHz; $CDCl_3$) 7.37 (1 H, m), 6.42—6.17 (2 H, m), 4.56 (2 H, m), 4.18 (4 H, q, *J* 6.8 Hz), 3.99 (2 H, m), and 1.27 (6 H, t, *J* 6.8 Hz).

The following compound was similarly prepared: *ethyl* (5-*methylfurfuryl*)*ethoxycarbonylaminoacetate* (**17b**), yield 83%, colourless oil *m/z* 269 (M^+), 196 ($M^+ - CO_2C_2H_5$); δ (90 MHz; $CDCl_3$) 6.14 (1 H, m), 5.92 (1 H, m), 4.50 (2 H, m), 4.20 (4 H, q, *J* 6.8 Hz), 4.00 (2 H, m), 2.27 (3 H, s), and 1.27 (6 H, t, *J* 6.8 Hz).

6-*Ethoxycarbonyl*-6,7-*dihydrofuro*[2,3-c]*pyridine*-4(5H)-*one* (**18a**).—A mixture of ethyl fufuryl(ethoxycarbonyl)amino acetate (**17a**) (18 g, 70 mmol) and potassium hydroxide (4.5 g), in methanol was stirred and heated at 50 °C for 3 h and then concentrated under reduced pressure. Diethyl ether was added and the potassium salt filtered off (15 g, 81%), m.p. 169—170 °C. The potassium salt was converted into the acid and a solution of this (12.7 g, 0.056 mol), thionyl chloride (10 g), and dimethylformamide (0.5 ml) in dichloromethane (250 ml) was heated under reflux for 3 h. The mixture was then diluted with dichloromethane (500 ml) and aluminium chloride (15 g) was added. The mixture was stirred for 10 min and then poured into ice–water. The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with ammonia (*d* 880) and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue crystallized in diethyl ether to give (**18a**) (5 g, 43%), m.p. 65—66 °C (Found: C, 57.55; H, 5.3; N, 6.75. $C_{10}H_{11}NO_4$ requires C, 57.41; H, 5.30; N, 6.70%); δ (90 MHz; $CDCl_3$) 7.43 (1 H, d, *J* 2 Hz), 6.72 (1 H, d, *J* 2 Hz), 4.81 (2 H, s), 4.24 (2 H, s), 4.21 (2 H, q, *J* 7 Hz), and 1.30 (3 H, t, *J* 7 Hz).

The following compound was similarly prepared: 6-*ethoxycarbonyl*-2-*methyl*-6,7-*dihydrofuro*[2,3-c]*pyridine*-4(5H)-*one* (**18b**), yield 46%, m.p. 66—67 °C (Found: C, 59.3; H, 5.8; N, 6.3. $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27%); δ (90 MHz; $CDCl_3$) 6.28 (1 H, q, *J* 1 Hz), 4.74 (2 H, s), 4.20 (2 H, s), 4.19 (2 H, q, *J* 7 Hz), 2.33 (3 H, d, *J* 1 Hz), and 1.30 (3 H, t, *J* 7 Hz).

6-*Methyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]*pyridin*-4-*ol* (**19a**).—A solution of the keto ester (**18a**) (5.3 g, 25 mmol) in dry tetrahydrofuran (60 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.3 g) in dry tetrahydrofuran (60 ml) with ice cooling. The mixture was then heated under reflux for 30 min. Excess of hydride was destroyed by the addition of ice–water and aqueous 40% diammonium tartrate was added. The organic phase was separated and the aqueous layer was washed with ethyl acetate. The combined organic phases were dried and concentrated under reduced pressure. The residue was purified by chromatography [silica gel; dichloromethane–methanol (90:10)] to give compound (**19a**) as a colourless oil (3.1 g, 81%). A sample was converted to the HCl salt, m.p. 167—168 °C (Found: C, 50.8; H, 6.25; N, 7.4. $C_8H_{12}ClNO_2$ requires C, 50.67; H, 6.38; N, 7.39%); δ (90 MHz; CD_3OD) 7.58 (1 H, d, *J* 2 Hz), 6.59 (1 H, d, *J* 2 Hz), 4.95 (1 H, m), 4.43 (2 H, m), 3.64 (2 H, m), and 3.13 (3 H, s).

The following compound was similarly prepared. 2,6-*Dimethyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]*pyridin*-4-*ol* (**19b**) *hydrochloride*, yield 52%, m.p. 200—201 °C (Found: C, 53.0; H, 7.0; N, 6.8. $C_9H_{14}ClNO_2$ requires C, 53.08; H, 6.93; N, 6.88%); δ (90 MHz; CD_3OD) 6.20 (1 H, s), 4.85 (1 H, m), 4.36 (2 H, m), 3.58 (2 H, m), 3.10 (3 H, s), and 2.29 (3 H, s).

6-*Methyl*-4-*phenyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]*pyridine* (**14a**) *Maleate*.—To a solution of compound (**19a**) (7.65 g, 50 mmol) and benzene (5 ml) in 1,2-dichloroethane (100 ml) was added anhydrous aluminium chloride (13.3 g). The reaction mixture was stirred at room temperature for 15 min and then poured into ice–water. The acid solution was made alkaline and the phases were separated. The organic layer was dried ($MgSO_4$) and concentrated and the crude oil obtained was chromatographed [silica gel; cyclohexane–ethyl acetate (3:1)] and converted into the maleate salt (8.5 g, 56%) identical with the product obtained above. The following compounds were similarly prepared.

4-(4-*Fluorophenyl*)-2,6-*dimethyl*-4,5,6,7-*tetrahydrofuro*-[2,3-c]*pyridine* (**14c**) *hydrochloride*: yield 38.5%, m.p. 209—210 °C (Found: C, 63.8; H, 6.35; N, 4.85. $C_{15}H_{17}ClFNO$ requires C, 63.94; H, 6.08; N, 4.97%); δ (90 MHz; CD_3OD) 7.43—6.98 (4 H, m), 5.79 (1 H, s), 4.45 (2 H s,), 4.33 (1 H, m), 3.40—3.85 (2 H, m), 3.10 (3 H, s), and 2.29 (3 H, s). From the first eluate, a small amount of the *o*-isomer 4-(2-*fluorophenyl*)-2,6-*dimethyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]*pyridine* was recovered and converted into its HCl salt, m.p. 242—243 °C (Found: C, 64.0; H, 6.3; N, 4.8%); δ (90 MHz; CD_3OD), 7.52—7.02 (4 H, m), 5.79 (1 H, s), 4.64 (1 H, m), 4.45 (2 H, m), 3.99—3.26 (2 H, m), 3.09 (3 H, s), and 2.26 (3 H s,).

4-(4-*Chlorophenyl*)-2,6-*dimethyl*-4,5,6,7-*tetrahydrofuro*-[2,3-c]*pyridine* (**14d**) *hydrochloride*: yield 33.5%, m.p. 241—242 °C (Found: C, 60.2; H, 6.1; N, 4.55. $C_{15}H_{17}Cl_2NO$ requires C, 60.41; H, 5.75; N, 4.70%); δ (90 MHz, CD_3OD) 7.14—7.45 (4 H, m), 5.72 (1 H, s), 5.47—4.17 (3 H, m), 3.95—3.38 (2 H, m), 3.07 (3 H, s), and 2.25 (3 H, s). From the first eluate, a small amount of the *o*-isomer 4-(2-*chlorophenyl*)2,6-*dimethyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]*pyridine* was recovered and converted into its HCl salt, m.p. 223—224 °C (Found: C, 60.45; H, 6.0; N, 4.6%); δ (90 MHz; CD_3OD) 7.61—7.12 (4 H, m), 6.79 (1 H, s), 4.94 (1 H, m), 4.84 (2 H, s), 3.87—3.37 (2 H, m), 3.08 (3 H, s), and 2.28 (3 H, s).

4-(4-*Methoxyphenyl*)-6-*methyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]-*pyridine* (**14b**) *Hydrochloride*.—A solution of compound (**19a**) (11.6 g, 76 mmol) and anisole (30 g) in methanesulphonic acid (90 g) was stirred at 10 °C for 1 h and then poured into ice–water. The acid solution was made alkaline and extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated. The crude oil was chromatographed [silica gel; cyclohexane–ethyl acetate (3:1)] and converted into its HCl salt (11 g, 56%), m.p. 199—200 °C (Found: C, 64.7; H, 6.6; N, 5.0. $C_{15}H_{18}ClNO_2$ requires C, 64.40; H, 6.48; N, 5.01%); δ (90 MHz; CD_3OD) 7.52 (1 H d, *J* 2 Hz), 7.32—6.77 (4 H, m), 6.13 (1 H, d, *J* 2 Hz), 4.49 (2 H, s), 4.49—4.24 (1 H, m), 3.92—3.14 (2 H, m), 3.75 (3 H, s), and 3.07 (3 H, s). From the first eluate, a small amount of the *o*-isomer 4-(2-*methoxyphenyl*)-6-*methyl*-4,5,6,7-*tetrahydrofuro*-[2,3-c]*pyridine* (m.p. 116—117 °C) was recovered (Found: C, 73.8; H, 6.85; N, 5.65. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%); δ (90 MHz; $CDCl_3$) 7.28 (1 H d, *J* 2 Hz), 6.12 (1 H, d,

J 2 Hz), 7.26—6.17 (4 H, m), 4.51 (1 H, m), 3.86 (3 H, s), 3.55 (2 H, m), 3.02—2.38 (2 H, m), and 2.45 (3 H, s).

The following compound was similarly prepared. 4-(3,4-*Dimethoxyphenyl*)-6-*methyl*-4,5,6,7-*tetrahydrofuro*[2,3-c]*pyridine* (**14e**) *hydrochloride*, yield 51%, m.p. 205—206 °C (decomp.); δ (90 MHz; CD_3OD) 3.10 (3 H, s), 4.0—3.23 (2 H, m), 3.82 (3 H, s), 3.80 (3 H, s), 4.48—4.22 (1 H, m), 4.51 (2 H, s), 7.08—6.74 (3 H, m), 6.20 (1 H, d, *J* 2 Hz), and 7.58 (1 H, d, *J* 2 Hz).

1-(3,4-*Dimethoxyphenyl*)-2-[(3-*furylmethyl*)*methylamino*]-*ethanol* (**20**) *Hydrochloride*.—To a solution of 1-dimethoxyphenyl-2-methylaminoethanol (21.1 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol) in dichloromethane (250 ml) was added dropwise a solution of 3-furoyl chloride (13 g, 0.1 ml) in dichloromethane (100 ml) at −10 °C. After being stirred for 1 h, the reaction mixture was poured into water. The organic phase was separated and washed consecutively with dilute hydrochloric acid, saturated aqueous sodium carbonate, and water, and then dried. Evaporation of the solvent left 1-(3,4-dimethoxyphenyl)-2-[(3-furoyl)methylamino]ethanol (28.7 g, 94%) as a yellow oil, which was used in the next step without further purification.

The 3-furamide (28.7 g, 0.094 mol) was dissolved in dry THF (150 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (6 g) in dry THF (150 ml) at 10 °C. Then the mixture was stirred for 3 h at room temperature. Excess of hydride was destroyed by the addition of ice–water, and aqueous 40% diammonium tartrate (600 ml) was added. The organic phase was separated and the aqueous layer was washed with ethyl acetate. The combined organic phases were dried and concentrated under reduced pressure and the residue was dissolved in acetone and a saturated ethereal solution of hydrochloric acid was added, to give compound (**20**) hydrochloride (22.2 g, 72%), m.p. 167—168 °C (Found: C, 58.8; H, 6.9; N, 4.1. $C_{16}H_{22}ClNO_4$ requires C, 58.62; H, 6.76; N, 4.27%); δ (90 MHz; CD_3OD) 7.83 (1 H, m), 7.64 (1 H, m), 6.67 (1 H, m), 7.15—6.87 (3 H, m), 5.09 (1 H, m), 4.36 (2 H, m), 3.84 (3 H, s), 3.82 (3 H, s), 3.28 (2 H, m), and 2.98 (3 H, s).

7-(3,4-*Dimethoxyphenyl*)-5-*methyl*-4,5,6,7-*tetrahydrofuro*-[3,2-c]*pyridine* (**13e**) *Hydrochloride*.—A solution of the aminoethanol (**20**) hydrochloride (22 g, 67 mmol) in methanesulphonic acid (150 ml) was stirred for 30 min at 35 °C and then poured into ice–water. The acidic solution was neutralized with aqueous ammonia (*d* 0.880) and extracted with diethyl ether. The organic phase was washed with water, dried, and concentrated. The residue was chromatographed [silica gel; dichloromethane–ethyl acetate–methanol (70:20:10)], and treated with an ethereal solution of hydrochloric acid to give (**13e**) hydrochloride (13.2 g, 63.5%), m.p. 212—213 °C (Found: C, 62.0; H, 6.5; N, 4.45. $C_{16}H_{20}ClNO_3$ requires C, 62.03; H, 6.51; N, 4.52%); δ (90 MHz; CD_3OD) 3.40—4.03 (2 H, m), 3.79 (3 H, s), 3.82 (3 H, s), 4.76—4.35 (3 H, m), 6.49 (1 H, d, *J* 1.8 Hz), 7.05—6.70 (3 H, m), and 7.51 (1 H, d, *J* 1.8 Hz).

8,9-*Dimethoxy*-2-*methyl*-3a,6-*epoxy*-1,2,3,3a,6,10b-*hexahydrobenzo*[3,4]*cyclohepta*[1,2-c]*pyrrole* (**23**).—A solution of compound (**12e**) (5.8 g, 20 mmol) in TFA was stirred at 40 °C for 30 min and then poured into ice–water. The acid solution was neutralized (K_2CO_3) and extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated. The residue crystallized from di-isopropyl ether, to give the product (**23**) (4.8 g, 89%), m.p. 130—131 °C (Found: C, 70.25; H, 7.05; N, 5.05. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.12%); *m*/*z* 273 (M^+, 34%), 201 (36). N.m.r. data are given in Table 1.

8,9-*Dimethoxy*-2-*methyl*-3a,6-*epoxy*-1,2,3,3a,4,5,6,10b-*octahydrobenzo*[3,4]*cyclohepta*[1,2-c]*pyrrole* (**24**) *Hydrochloride*.—A solution of compound (**23**) (1.6 g, 5.8 mmol) in methanol (20 ml) in a Parr hydrogenation bottle was deoxygenated with nitrogen and 10% Pd–C (200 mg) was added to the vessel. This was placed onto a Parr hydrogenator at 5 bar for 2 h. The solution was filtered and the solvent removed under reduced pressure. The crude product was dissolved in acetone and treated with an ethereal solution of hydrochloric acid to give the HCl salt of (**24**) (1.6 g, 88%), m.p. 246—247 °C (Found: C, 61.35; H, 7.3; N, 4.55. $C_{16}H_{22}ClNO_3$ requires C, 61.63; H, 7.11; N, 4.49%). N.m.r. data are given in Table 1.

Acknowledgements

We thank H. Baltes for his enthusiastic experimental assistance and W. Pryss for his n.m.r. spectroscopy expertise.

References

1 (*a*) A. H. Jackson and A. E. Smith, *Tetrahedron*, 1967, **24**, 404; (*b*) A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc. C*, 1969, 1193; (*c*) J. R. Williams and L. R. Unger, *Chem. Commun.*, 1970, 1605.
2 (*a*) K. M. Biswas, A. H. Jackson, and M. Tehrani, *J. Chem. Soc., Chem. Commun.*, 1982, 765; (*b*) K. Blau, G. S. King, and M. Sandler, *Biomed. Mass Spectrom.*, 1977, **4**, 232.
3 D. W. Clack, A. H. Jackson, N. Prasitpan, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 2*, 1982, 909.
4 For a review see F. Ungemach and J. M. Cook, *Heterocycles*, 1978, **9**, 1089.
5 C. S. Schneider, K. H. Weber, A. Langbein, W. D. Bechtel, and K. Boeke, G.P. Appl. 2746443, 1979 (*Chem. Abstr.*, 1979, **91**, 56978w).
6 J.-P. Maffrand, R. Boigegrain, J. Courregelongue, G. Ferrand, and D. Frehel, *J. Heterocycl. Chem.*, 1981, **18**, 727.
7 C. Mackay and R. D. Waigh, *J. Chem. Soc., Chem. Commun.*, 1982, 793.
8 C. S. Schneider, K. H. Weber, H. Daniel, W. D. Bechtel, and K. Boeke-Kuhn, *J. Med. Chem.*, 1984, **27**, 1150.
9 A.-B. Hörnfeldt and S. Gronowitz, *Arkiv. för Kemi*, 1963, **21**, 239.
10 M. P. Mertes, R. F. Borne, and L. E. Hare, *J. Org. Chem.*, 1968, **33**, 133.
11 A. Bax. 'Two-Dimensional Nuclear Magnetic Resonance in Liquids,' Delft University Press, D. Reidel Publishing Co., Dordrecht, Boston, 1982, p. 51.
12 H. Kessler, C. Griesinger, J. Zarbock, and H. R. Looslie, *J. Magn. Reson.*, 1984, **57**, 331.
13 H. Kessler, C. Griesinger, and J. Lautz, *Angew. Chem.*, 1985, **96**, 434.
14 H. Kessler, W. Bermel, and C. Griesinger, *J. Magn. Reson.*, 1985, **62**, 573.
15 W. Beck, J. A. Kaye, J. C. Kogon, H. C. Klein, and W. J. Burlant, *J. Org. Chem.*, 1951, **16**, 1434.

Received 22*nd July* 1985; *Paper* 5/1237