# A Novel Synthesis of 2-Aryl-4-Piperidones By Mannich Cyclization of Iminoketals (1)



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2-Aryl-4-piperidones have been synthesized by condensation between an aromatic aldehyde and a β-aminoketone ethylene ketal, and further cyclization of the resulting iminoketal with dry hydrogen chloride or anhydrous *p*-toluenesulfonic acid. Alternatively, reaction of the above iminoketals with methyl fluorosulfonate followed by dry hydrogen chloride treatment and acid hydrolysis gives directly *N*-methyl-4-piperidones. The application of these reactions to the synthesis of some 2-aryl-3-acetylpyrrolidine systems is also described.

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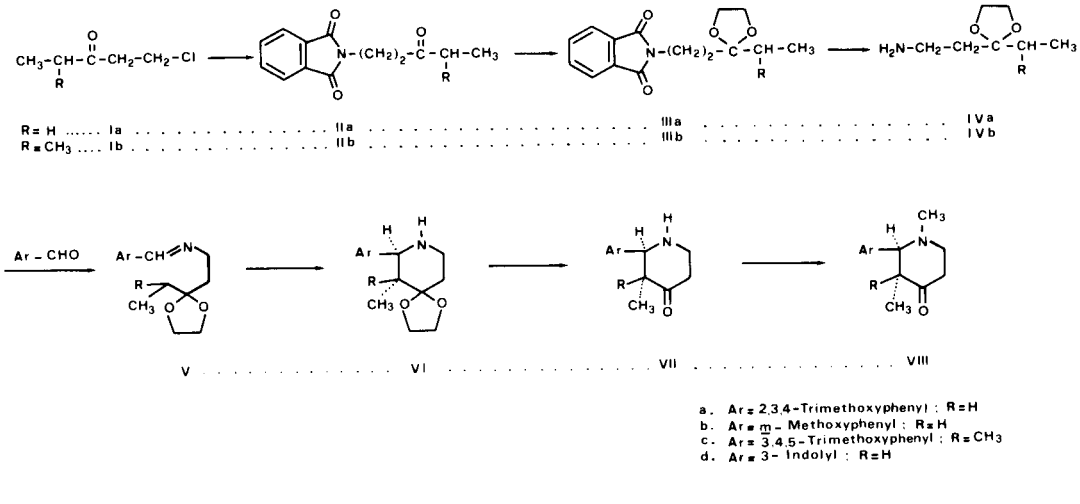
The research in the field of 4-piperidones (2) has generally been related to the synthesis of effective medicinal drugs and natural products. The 4-piperidone moiety is present in some simple structures bearing pharmacological effect upon the central nervous system (3) as well as in polylcyclic systems such as benzo[*a*]- and indolo[2,3-*a*]quinolizidin-2-ones, some of them with reserpine-like activity (4).

4-Piperidones are also valuable synthetic intermediates. Thus, from 4-piperidones the local anesthetics α- and β-eucaine (5), analgesics of the 4-phenylpiperidine (6), 4-propionanilidopiperidine (7), and 6,7-benzomorphan (8,9) groups, as well as some active spiroimidazolones (10) and spirohidantoines (11) have been synthesized. The oxidative cyclization of 1-benzyl-3-methoxycarbonyl-4-piperidones to 2,6-methano-2-benzazocines (12) and the synthesis of the indole alkaloids ellipticine (13) and uleine (14) are further examples of the synthetic usefulness of 4-piperidones.

In previous work we reported the synthesis of several 2-aryl-4-piperidones by Dieckmann cyclization of an appropriate β-aminodiester (15) and by Mannich reaction between an aromatic aldehyde and a β-aminoketone (16). We also described (17) the preparation of 2-aryl-3-acetylpyrrolidines by condensation between an aromatic aldehyde and a γ-amino ketone protected as ethylene ketal, followed by Mannich cyclization of the resulting imino ketal with dry hydrogen chloride. The acid-induced intramolecular cyclization between a cyclic iminium salt and the α-position of a ketal group (18,19) has been used in the synthesis of quinolizidine (20), indolizidine (20-23), and pyrrolizidine (23,24) alkaloids, as well as in that of octahydroindole derivatives related to mesembrine (25). However, except in our work (17), this methodology has not found application for the preparation of simple piperidine or pyrrolidine systems, that implies the use of a non-cyclic iminium salt.

In this context, we wish to report here the extent of the




Scheme I

Mannich type cyclization of iminoketals to the synthesis of 2-aryl-4-piperidones. Our present interest towards these systems lies on the fact that from 2-aryl-4-piperidones we have recently developed a new synthesis of *B-nor-* (26-28) and 7,8-benzomorphans (29-31).

The required iminoketals V were prepared in four steps (Scheme I) from 1-chloro-3-pentanone (Ia) (32) or 1-chloro-4-methyl-3-pentanone (Ib) (33), according to the procedure described for the preparation of 3-amino-2-butanone ethylene ketal (34).

The reaction between chloroketones I and potassium phthalimide led to phthalimidoketones II. Ketalation of II followed by hydrazinolysis afforded aminoketals IV, whose condensation with an aromatic aldehyde in anhydrous benzene (35) led to iminoketals V. The spectroscopic data of the above compounds are given in Table I. The most characteristic signals of imines V are the ir absorption about 1645 $cm^{-1}$ and a singlet at $\delta$ 8.1-8.4 due to the iminic proton in the nmr spectra.

Treatment of imine Vc with dry hydrogen chloride followed by hydrolysis with 20% hydrochloric acid afforded piperidone VIIc. Its hydrochloride shows an ir absorption at 1720 $cm^{-1}$ corresponding to the carbonyl group and nmr singlets (Table II) at $\delta$ 0.95 and 1.35 due to the equatorial and axial methyl groups, respectively, in the 3-position of the heterocyclic ring (36). When the reaction was carried out omitting the final acid hydrolysis, the main product was ethylene ketal VIc. Cyclization of Vb under analogous conditions afforded piperidone VIIb. However, imine Vd failed to give the expected cyclized product, probably because of the lability of the indole nucleus under the acidic reaction conditions.

Methylation of piperidones VIIb and VIIc with methyl iodide in acetone solution in the presence of anhydrous potassium carbonate led to *N*-methylpiperidones VIIIb and VIIIc, respectively. Table II shows the most characteristic ir and nmr data of the above piperidones, both as bases and as hydrochlorides. The *trans*-relationship between aryl and methyl groups in VIIb and VIIIb, as well as in all 3-methyl-4-piperidones and 3-methyl-4,4-(ethylenedioxy)piperidines described in this paper, was established from the chemical shift value of the doublet corresponding to the methyl group in the 3-position of the piperidine ring (Table II), characteristic for an equatorial methyl group (36,37), and from thermodynamic considerations. Thus, the electrophilic attack of the iminium salt upon the enol ether double bond formed by dioxolane ring opening can lead to two diastereomeric 4,4-ethylenedioxypiperidines. However, under the acidic reaction conditions, is possible

Table I

Spectroscopic Data

| Compound No. | IR ($cm^{-1}$) | NMR ($\delta$ values) (a,b) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Ar – H | Ar – CH = N | O – $CH_3$ | O – $CH_2$ – $CH_2$ – O | N – $CH_2$ | OC – $CH_2$ and OC – CH | C – $CH_3$ |
| IIa | 1710, 1775 (C = O) (c) | 7.5-8.0 m | — | — | — | 3.80 t | 2.45 q 2H<br>2.80 t 2H | 1.05 t |
| IIb | 1710, 1775 (C = O) (c) | 7.5-8.0 m | — | — | — | 3.82 t | 2.2-3.0 m 3H | 1.05 d |
| IIIa | 1710, 1770 (C = O) (c) | 7.4-7.9 m | — | — | 3.90 s | 3.73 t | 1.3-2.2 m 4H | 0.90 t |
| IIIb | 1710, 1775 (C = O) (c) | 7.4-7.8 m | — | — | 3.87 s | 3.65 t | 1.4-2.2 m 3H | 0.88 d |
| IVa | 3380 (N – H) (d) | — | — | — | 3.82 s | 2.65 t | 1.3-1.8 m 4H | 0.83 t |
| IVb | 3480 (N – H) (c) | — | — | — | 3.85 s | 2.65 t | 1.5-2.1 m 3H | 0.88 d |
| Va | 1640 (C = N) (d) | 6.55 d 1H<br>7.52 d 1H | 8.40 s | 3.75 s<br>3.80 s<br>3.85 s | 3.85 s | 3.55 t | 1.4-2.1 m 4H | 0.90 t |
| Vb | 1645 (C = N) (d) | 6.6-7.4 m | 8.12 s | 3.76 s | 3.83 s | 3.55 t | 1.4-2.1 m 4H | 0.90 t |
| Vc (e) | 1645 (C = N) (d) | 6.93 s | 8.15 s | 3.83 s<br>3.85 s<br>3.93 s | 3.85 s | 3.63 t | 1.7-2.2 m 3H | 0.99 d |
| Vd (e) | 3470 (N – H) (d)<br>1640 (C = N) | 6.8-7.7 m<br>8.0-8.3 m | 8.37 s | — | 3.90 s | 3.70 t | 1.5-2.2 m 4H | 0.95 t |

(a) Chemical shifts in carbon tetrachloride solution unless otherwise indicated (b) Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. (c) The ir spectrum in chloroform solution. (d) The ir spectrum in sodium chloride. (e) The nmr spectrum in deuteriochloroform solution.

Table II

Spectroscopic Data of 4-Piperidones and their Ethylene Ketals

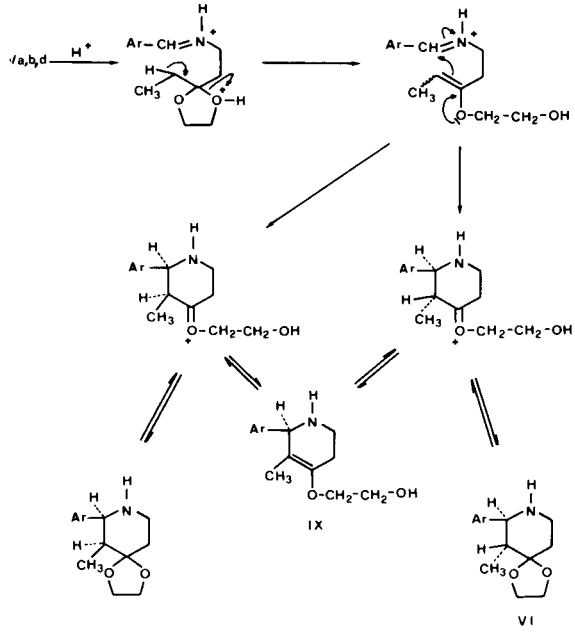
| Compound No. | IR ($cm^{-1}$) | NMR ($\delta$ values) (a,b) | | | | |
|---|---|---|---|---|---|---|
| | | Ar – H | $O-CH_3$ | $O-CH_2$ | $N-CH_3$ | $C-CH_3$ (c) |
| VIa | — | 6.45 d J = 9 Hz<br>6.85 d J = 9 Hz | 3.70 s 6H<br>3.75 s 3H | 3.85 s | — | 0.55 d |
| VIa•HCl | — | 6.65 d J = 9 Hz<br>7.47 d J = 9 Hz | 3.78 s 6H<br>3.92 s 3H | 3.92 s | — | 0.62 d |
| VIb | 3330 (N – H) (d) | 6.4-7.2 m | 3.62 s | 3.76 s | — | 0.50 d |
| VIb•HCl | — | 6.7-7.5 m | 3.80 s | 3.99 s | — | 0.65 d |
| VIc | — | 6.45 s | 3.65 s<br>3.75 s<br>3.85 s | 3.75 s | — | 1.00 s ax<br>0.64 s eq |
| VIc•HCl | — | 6.73 s | 3.78 s<br>3.83 s<br>3.98 s | 3.78 s | — | 1.26 s ax<br>0.73 s eq |
| VId | 3480 (N – H) (e) | 6.8-7.3 m 4H<br>7.5-7.8 m 1H<br>8.3 bs 1H | — | 3.95 s | — | 0.70 d |
| VId•HCl | 3340 (N – H) (f) | 7.0-7.8 m 5H<br>9.2 bs 1H | — | 4.02 s | — | 0.75 d |
| VIIa | 3330 (N – H) (d)<br>1700 (C = O) | 6.50 d J = 9 Hz<br>7.35 d J = 9 Hz | 3.85 s | — | — | 0.78 d |
| VIIa•HCl | 1725 (C = O) (e) | 6.65 d J = 9 Hz<br>7.50 d J = 9 Hz | 3.80 s 6H<br>3.95 s 3H | — | — | 0.83 d |
| VIIb (g) | 3320 (N – H) (d)<br>1710 (C = O) | 6.5-7.3 m | 3.70 s | — | — | 0.70 d |
| VIIb•HCl (h) | 1725 (C = O) (f) | 6.6-7.6 m | 3.72 s | — | — | 0.82 d |
| VIIc•HCl | 1720 (C = O) (e) | 6.78 s | 3.78 s 6H<br>3.83 s 3H | — | — | 1.35 s ax<br>0.95 s eq |
| VIIIa (g) | 1713 (C = O) (e) | 6.65 d J = 9 Hz<br>7.07 d J = 9 Hz | 3.80 s | — | 2.00 s | 0.75 d |
| VIIIa•HCl | 1720 (C = O) (f) | 6.92 d J = 9 Hz<br>7.95 d J = 9 Hz | 3.85 s<br>3.88 s<br>4.00 s | — | 2.58 d<br>J = 4 Hz | 0.85 d |
| VIIIb (g) | 1710 (C = O) (e) | 6.5-7.3 m | 3.70 s | — | 1.95 s | 0.65 d |
| VIIIb•HCl | 1725 (C = O) (f) | 6.6-7.5 m | 3.77 s | — | 2.61 s | 0.72 d |
| VIIIc (i) | 1705 (C = O) (e) | 6.54 s | 3.85 s | — | 2.09 s | 1.14 s ax<br>0.95 s eq |
| VIIIc•HCl (i) | 1730 (C = O) (f) | 7.60 b 1H<br>6.40 b 1H | 3.85 s 6H<br>3.80 s 3H | — | 2.65 d<br>J = 4 Hz | 1.60 s ax<br>1.00 s eq |
| VIIId | 3480 (N – H) (e)<br>1705 (C = O) | 6.9-7.4 m 4H<br>7.7-7.9 m 1H<br>8.7 bs 1H | — | — | 2.05 s | 0.75 d |
| VIIId•HCl | 1730 (C = O) (f) | 7.0-8.0 m | — | — | 2.48 bs | 0.78 d |

Table II

| | | | | | | |
|---|---|---|---|---|---|---|
| XIIa | — | 6.55 d J = 9 Hz<br>7.00 d J = 9 Hz | 3.85 s | 3.89 s | 1.90 s | 0.50 d |
| XIIa•HCl | — | 6.75 d J = 9 Hz<br>7.73 d J = 9 Hz | 3.75 s<br>3.80 s<br>3.83 s | 3.95 s | 2.40 d<br>J = 4 Hz | 0.63 d |
| XIIb | — | 6.4-7.2 m | 3.75 s | 3.85 s | 1.90 s | 0.45 d |
| XIIb•Picrate | — | 6.6-7.0 m | 4.02 s | 3.72 bs | 2.68 s | 0.70 d |
| XIIc | — | 6.2-6.6 bs | 3.70 s<br>3.75 s<br>3.85 s | 3.75 s | 1.90 s | 1.00 s ax<br>0.55 s eq |
| XIIc•Picrate | — | 6.32 s 1H<br>6.85 s 1H | 3.70 s<br>3.80 s<br>3.99 s | 3.80 s | 2.68 s | 1.40 s ax<br>0.75 s eq |
| XIId | 3250 (N – H) (f) | 6.8-7.4 m 4H<br>7.5-7.8 m 1H<br>8.4 bs 1H | — | 3.90 s | 2.02 s | 0.60 d |
| XIId•HCl | 3180 (N – H) (f) | 7.1-7.5 m 4H<br>8.1-8.2 m 1H<br>9.2 bs 1H | — | 3.98 s | 2.43 d<br>J = 4 Hz | 0.63 d |

(a) Chemical shifts in deuteriochloroform solution unless otherwise indicated. (b) Abbreviations: s = singlet, d = doublet, m = multiplet, b = broad. (c) J ≅ 6 Hz for doublet signals. (d) The ir spectrum in sodium chloride. (e) The ir spectrum in chloroform solution. (f) The ir spectrum in potassium bromide. (g) The nmr spectrum in carbon tetrachloride solution (h) The nmr spectrum in deuteriochloroform-dimethylsulfoxide solution. (i) Reference 16a.

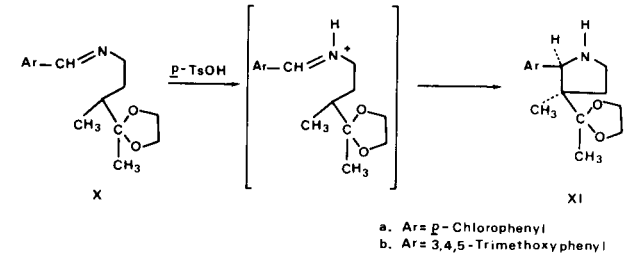
the isomer interconversion *via* the enol ether IX to give the thermodynamically more stable *trans*-substituted piperidines VI (38) (Scheme II).




Scheme II

In order to improve the moderate yields (≅50%) of the above imine cyclizations, we tested *p*-toluenesulfonic acid (39) as catalyst. Under these conditions, imines Va and Vb were transformed into ethylene ketals VIa and VIb in 87% and 58% yield, respectively. Similarly, the ethylene ketal VId, inaccessible through hydrogen chloride cyclization, was obtained from Vd in excellent yield (80%). The above aminoketals VI were converted into 4-piperidones either directly by hydrolysis with 20% hydrochloric acid or by methylation with methyl iodide and further hydrolysis (indolyl series).

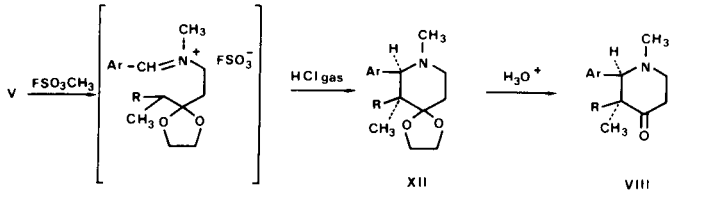
*p*-Toluenesulfonic acid proved also to be the catalyst of election for cyclizations leading to 2-arylpyrrolidine systems (Scheme III). Thus, treatment of the previously




Scheme III

described imine Xa with *p*-toluenesulfonic acid afforded the ethylene ketal XIa in 78% yield, higher than the one reported (51%) when using dry hydrogen chloride (17).

Finally, in order to achieve imine methylation and cyclization in a single step, we intended to generate the iminium salt required for the Mannich ring closure by using methyl fluorosulfonate (40). In fact, reaction of imines V with methyl fluorosulfonate in anhydrous methylene chloride at −30°, followed by treatment with dry hydrogen chloride and acid hydrolysis led, as expected, to 2-aryl-1-methyl-4-piperidones VIII (Scheme IV).

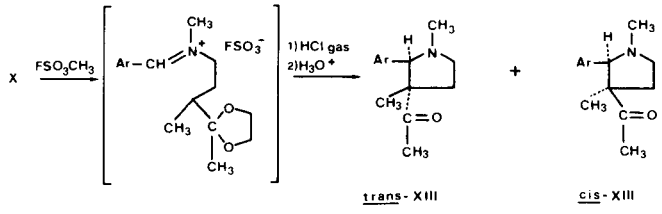


a. Ar= 2,3,4-Trimethoxyphenyl ; R= H
b. Ar= m-Methoxyphenyl ; R= H
c. Ar= 3,4,5-Trimethoxyphenyl ; R=$CH_3$

Scheme IV

The methyl fluorosulfonate method also gave satifactory results in cyclizations leading to pyrrolidine systems (41). By this procedure, from imines X nearly equimolarcular *cis-trans* mixtures of 2-aryl-3-acetyl-1,3-dimethylpyrrolidines XIIIa or XIIIb were obtained (Scheme V). The *cis* isomers were identical in all aspects to samples previously obtained from XIa or XIb (17). The relative configuration of the *trans*-isomers was inferred from their spectroscopic data (Table III). Thus, the most characteristic signals in the nmr spectra of *trans*-XIIIa and *trans*-XIIIb were singlets at δ 0.9 and 2.1 due to the methyl groups on the pyrrolidine 3-position and the carbonyl carbon atom, respectively. The former was strongly affected by the shielding effect of the aromatic ring, thus indicating a *cis*-methyl-phenyl relationship (compare with the chemical shift of the *cis* isomers, Table III) (42).

The different stereochemical result observed in cyclizations of $=\overset{+}{N}H-$ or $=\overset{+}{N}CH_3-$ iminium salts leading to the above pyrrolidine systems can be attributed to cinetic fac-



a. Ar= p-Chlorophenyl
b. Ar= 3,4,5-Trimethoxyphenyl

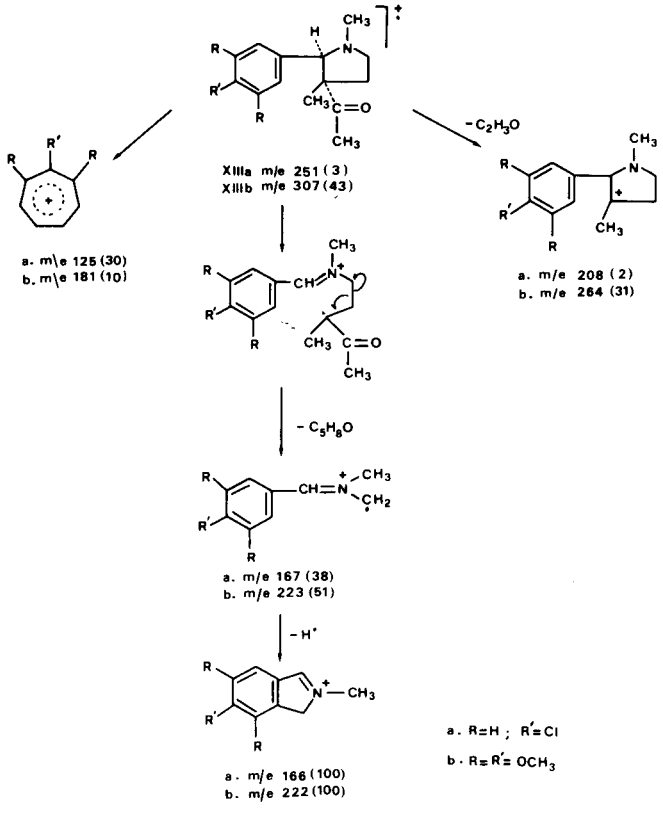
Scheme V

Table III

Spectroscopic Data of Pyrrolidine Systems

| Compound No. | IR ($cm^{-1}$) C=O | NMR (δ values) (a,b) Ar-H | $C_2$-H | N-$CH_3$ | $C_3$-$CH_3$ | CO-$CH_3$ |
|---|---|---|---|---|---|---|
| *cis*-XIIIa (c) | 1700 (d) | 7.20 s | 3.00 s | 2.12 s | 1.34 s | 1.59 s |
| *cis*-XIIIa•HCl | 1705 (e) | 7.68 d<br>7.31 d | 4.04-4.3 m | 3.00 s | 1.70 s | |
| *trans*-XIIIa | 1695 (f) | 7.17 s | 3.65 s | 2.12 s | 0.87 s | 2.08 s |
| *trans*-XIIIa•HCl | 1705 (e) | 7.62 d<br>7.25 d | 5.00 s | 2.80 s | 1.30 s | 2.20 s |
| *cis*-XIIIb (c) | 1695 (f) | 6.43 s | 2.90 s | 2.15 s | 1.39 s | 1.56 s |
| *cis*-XIIIb•HCl (c) | 1690 (e) | 6.86 s | 4.50 b | 2.90 bs | 1.6-1.8 b | |
| *trans*-XIIIb | 1700 (d) | 6.50 s | 3.60 s | 2.20 s | 0.93 s | 2.10 s |
| *trans*-XIIIb•HCl | 1705 (e) | 6.98 s | 4.83 d<br>J = 10 Hz | 2.70 d<br>J = 4 Hz | 1.40 s | 2.20 s |

(a) Chemical shifts in deuteriochloroform. (b) Abbreviations: s = singlet, d = doublet, m = multiplet, b = broad. (c) Reference 17. (d) The ir spectrum in sodium chloride. (e) The ir spectrum in potassium bromide. (f) The ir spectrum in chloroform solution.



a. m\e 125 (30)
b. m\e 181 (10)

XIIIa m/e 251 (3)
XIIIb m/e 307 (43)

a. m/e 208 (2)
b. m/e 264 (31)

a. m/e 167 (38)
b. m/e 223 (51)

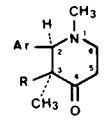
a. m/e 166 (100)
b. m/e 222 (100)

a. R=H ; R'=Cl
b. R= R'= $OCH_3$

Scheme VI

Table IV

$^{13}C$ NMR Chemical Shifts of 2-Aryl-1-methyl-4-piperidones (a)



VIII

| Compound No. | C-2 | C-3 | C-4 | C-5 | C-6 | C-$CH_3$ | N-$CH_3$ | O-$CH_3$ | Ar-1 | Ar-2 | Ar-3 | Ar-4 | Ar-5 | Ar-6 | Ar-7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VIIIa | 68.20 | 50.14 | 209.60 | 41.53 | 56.24 | 10.74 | 43.00 | 56.96<br>60.70<br>60.78 | 126.80 | 152.91<br>(152.50) | 141.90 | 152.50<br>(152.91) | 108.12 | 122.26 | — |
| VIIIb | 77.08 | 50.41 | 209.45 | 41.56 | 55.20 | 10.80 | 43.46 | 56.31 | 142.97 | 113.18<br>(112.92) | 159.89 | 112.92<br>(113.18) | 129.58 | 120.42 | — |
| VIIIc | 78.80 | 48.76 | 212.50 | 37.96 | 55.55 | 21.84<br>21.60 | 44.11 | 55.96<br>60.58 | 137.21 | 106.91 | 152.28 | 133.13 | 152.28 | 106.91 | — |
| VIIId (b) | 69.80 | 49.70 | 210.54 | 41.93 | 56.13 | 11.41 | 43.49 | — | — | 122.98 | 116.40<br>125.99 (c) | 119.50 | 122.30 | 120.05 | 111.36<br>136.72 (d) |

(a) Given in parts per million downfield relative to TMS in deuteriochloroform solution. (b) For the assignment of the indole nucleous, see reference 45. (c) Signal corresponding to the indole-3a carbon atom. (d) Signal corresponding to the indole-7a carbon atom.

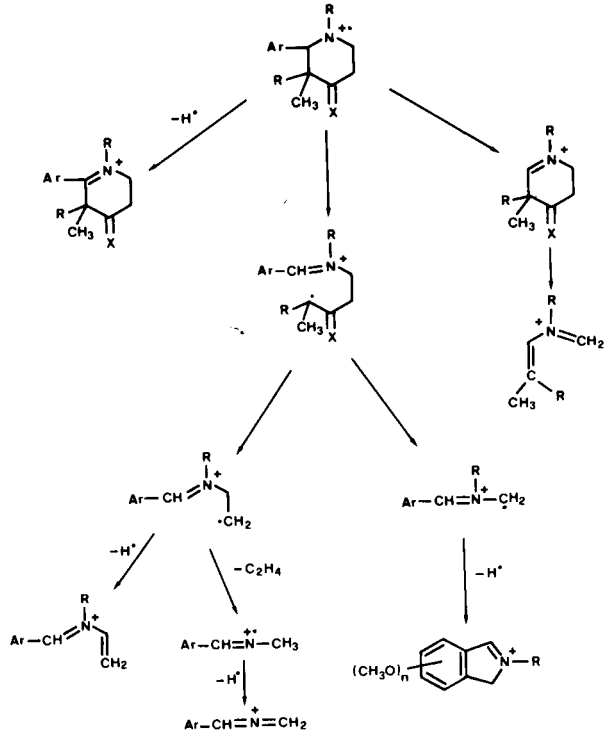
tors since, in this case, the isomer equilibration is not possible because of the lack of an hydrogen atom at the pyrrolidine 3-position.

The assignment of the signals in the $^{13}C$ nmr spectra of 2-aryl-1-methyl-4-piperidones (VIII) described in this work has been made (Table IV) on the basis of its multiplicity in the off-resonance decoupled spectra and from previously reported data for appropriately substituted 4-piperidones (16a, 43), applying the suitable substituent additivity values (44).

On the other hand, the mass spectral data of cyclized products obtained in this work are given in Table V.

Scheme VI depicts the more significant fragmentations of *trans*-pyrrolidines XIIIa and XIIIb, similar to those reported for related systems of the *cis*-series (16a,17). In both cases, the base peak is formed by ejection of methyl isopropenyl ketone followed by loss of a hydrogen atom to give an isoindolinium cation, as described for nicotine and substituted derivatives (46).

Finally, the preferred fragmentation pathways of 4-piperidones VI and VIII, as well as of the ethylene ketals VII and IX are shown in Scheme VII. All these compounds shown a common fragmentation pattern, similar to the one described for other 4-piperidone systems (47).



Scheme VII

Table V

Mass Spectral Data

| Compound No. | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VIa | m/e: | 323 ($M^+$) | 292 | 280 | 278 | 264 | 252 | 248 | 233 | 222 | 209 | 208 | 194 | 179 | 178 | 123 | 101 | 91 | 79 | 77 | 70 | 55 | | | |
| | I: | 6 | 8 | 43 | 39 | 7 | 7 | 10 | 27 | 43 | 22 | 31 | 100 | 26 | 24 | 12 | 40 | 14 | 17 | 16 | 10 | 17 | | | |
| VIb | m/e: | 263 ($M^+$) | 232 | 220 | 218 | 202 | 188 | 163 | 162 | 149 | 148 | 134 | 121 | 118 | 117 | 105 | 101 | 91 | 86 | 77 | 70 | 65 | 55 | 43 | |
| | I: | 14 | 4 | 68 | 100 | 7 | 9 | 27 | 33 | 35 | 85 | 60 | 16 | 17 | 19 | 25 | 35 | 23 | 29 | 23 | 10 | 14 | 19 | 19 | |
| VId | m/e: | 272 ($M^+$) | 241 | 229 | 227 | 197 | 172 | 171 | 157 | 156 | 149 | 144 | 143 | 130 | 129 | 128 | 101 | 77 | 70 | 57 | 55 | | | | |
| | I: | 22 | 8 | 33 | 54 | 16 | 24 | 49 | 54 | 27 | 32 | 59 | 100 | 56 | 19 | 14 | 33 | 19 | 15 | 24 | 25 | | | | |
| VIIa | m/e: | 279 ($M^+$) | 278 | 223 | 222 | 208 | 198 | 194 | 181 | 179 | 136 | 127 | 123 | 95 | 77 | 70 | 69 | 55 | | | | | | | |
| | I: | 75 | 9 | 54 | 100 | 46 | 25 | 63 | 37 | 58 | 37 | 17 | 21 | 38 | 42 | 25 | 33 | 46 | | | | | | | |
| VIIb | m/e: | 219 ($M^+$) | 218 | 204 | 190 | 176 | 163 | 162 | 148 | 134 | 117 | 105 | 91 | 77 | 70 | 65 | 55 | | | | | | | | |
| | I: | 96 | 11 | 6 | 8 | 17 | 36 | 92 | 91 | 100 | 30 | 55 | 34 | 32 | 10 | 13 | 9 | | | | | | | | |
| VIIIa | m/e: | 293 ($M^+$) | 292 | 278 | 262 | 236 | 222 | 208 | 195 | 194 | 179 | 178 | 163 | 162 | 151 | 148 | 135 | 134 | 133 | 126 | 107 | 91 | 84 | 77 | 55 |
| | I: | 100 | 47 | 25 | 21 | 42 | 27 | 46 | 30 | 21 | 89 | 30 | 19 | 17 | 26 | 25 | 17 | 14 | 29 | 19 | 27 | 25 | 46 | 34 | 25 |
| VIIIb | m/e: | 233 ($M^+$) | 232 | 176 | 162 | 161 | 148 | 126 | 121 | 118 | 105 | 91 | 84 | 77 | 55 | 42 | | | | | | | | | |
| | I: | 65 | 30 | 44 | 29 | 22 | 100 | 43 | 14 | 28 | 22 | 30 | 69 | 33 | 15 | 35 | | | | | | | | | |
| VIIIc | m/e: | 307 ($M^+$) | 306 | 292 | 276 | 264 | 236 | 222 | 221 | 208 | 195 | 194 | 181 | 180 | 134 | 127 | 98 | 91 | 89 | 77 | 55 | | | | |
| | I: | 100 | 30 | 15 | 4 | 11 | 45 | 57 | 25 | 50 | 25 | 15 | 20 | 17 | 13 | 10 | 23 | 15 | 24 | 22 | 17 | | | | |
| VIIId | m/e: | 242 ($M^+$) | 241 | 227 | 225 | 213 | 199 | 186 | 185 | 172 | 171 | 158 | 157 | 156 | 155 | 154 | 144 | 143 | 130 | 129 | 128 | 115 | 84 | 77 | 55 |
| | I: | 56 | 5 | 2 | 3 | 6 | 8 | 12 | 44 | 17 | 24 | 49 | 100 | 24 | 10 | 12 | 39 | 51 | 66 | 19 | 20 | 22 | 60 | 17 | 13 |
| XIIa | m/e: | 337 ($M^+$) | 336 | 322 | 306 | 294 | 293 | 292 | 276 | 262 | 236 | 222 | 208 | 195 | 194 | 179 | 170 | 101 | 96 | 84 | | | | | |
| | I: | 86 | 21 | 41 | 25 | 98 | 86 | 60 | 30 | 24 | 75 | 40 | 54 | 36 | 28 | 100 | 28 | 54 | 21 | 55 | | | | | |
| XIIb | m/e: | 277 ($M^+$) | 276 | 234 | 232 | 220 | 216 | 190 | 176 | 170 | 162 | 148 | 128 | 110 | 101 | 99 | 91 | 84 | 77 | 55 | 42 | | | | |
| | I: | 91 | 16 | 39 | 18 | 16 | 22 | 14 | 30 | 95 | 47 | 100 | 29 | 26 | 95 | 27 | 29 | 94 | 26 | 26 | 55 | | | | |
| XIId | m/e: | 286 ($M^+$) | 243 | 185 | 172 | 171 | 170 | 158 | 157 | 144 | 130 | 101 | 84 | 78 | 58 | 43 | | | | | | | | | |
| | I: | 33 | 26 | 53 | 46 | 20 | 13 | 40 | 86 | 53 | 79 | 53 | 20 | 59 | 60 | 100 | | | | | | | | | |
| *trans*-XIIIa | m/e: | 251 ($M^+$) | 249 | 234 | 208 | 206 | 168 | 167 | 166 | 132 | 131 | 125 | 111 | 89 | | | | | | | | | | | |
| | I: | 3 | 6 | 7 | 2 | 3 | 37 | 38 | 100 | 12 | 17 | 30 | 11 | 13 | | | | | | | | | | | |
| *trans*-XIIIb | m/e: | 307 ($M^+$) | 292 | 264 | 250 | 223 | 222 | 208 | 192 | 181 | 180 | 176 | 162 | 148 | 127 | 122 | 96 | 91 | 77 | 43 | | | | | |
| | I: | 43 | 20 | 31 | 11 | 51 | 100 | 57 | 26 | 10 | 20 | 17 | 11 | 14 | 26 | 16 | 24 | 13 | 16 | 26 | | | | | |

## EXPERIMENTAL

The infrared spectra (Tables I, II and III) were determined on a Perkin-Elmer model 577 spectrophotometer. Nuclear magnetic resonance spectra (Tables I, II and III) were recorded on a Perkin-Elmer model R-24B (60 MHz, tetramethylsilane at $\delta$ 0.00 as internal standard). Chemical shifts are reported as $\delta$ values in parts per million (ppm). The $^{13}C$ nmr (Table IV) spectra were determined on a Varian XL-200 spectrometer. The mass spectra (Table V) were obtained with Hewlett-Packard 5930A mass spectrometer. Melting points (Table VI) were determined on a Büchi apparatus and are uncorrected. Elemental analyses (Table VI) were performed by the Instituto de Química Bio-Orgánica, Barcelona.

1-Phthalimido-3-pentanone (IIa).

Potassium phthalimide (76.8 g, 0.41 mole) was added in small portions to a stirred solution of 50 g (0.41 mole) of 1-chloro-3-pentanone (Ia) (32) in 350 ml of *N,N*-dimethylformamide. The resulting suspension was refluxed for 20 hours. The reaction mixture was poured into 1 $\ell$ of water and extracted with 500 ml of chloroform. The organic extracts were washed with 2*N* aqueous sodium hydroxide and several times with water. After drying over anhydrous magnesium sulfate and evaporation of the solvent, 61 g (65%) of phthalimide IIa were obtained.

4-Methyl-1-phthalimido-3-pentanone (IIb).

Operating as above from 68.8 g (0.37 mole) of potassium phthalimide, 50 g (0.37 mole) of 1-chloro-4-methyl-3-pentanone (Ib) (33), and 350 ml of *N,N*-dimethylformamide, 90.9 g (62%) of phthalimido ketone Vb were obtained.

1-Phthalimido-3-pentanone Ethylene Acetal (IIIa).

A stirred solution of 59 g (0.25 mole) of phthalimidoketone IIa, 21.8 g (0.11 mole) of *p*-toluenesulfonic acid, 42.5 ml of ethyleneglycol, and 500 ml of anhydrous benzene was refluxed for 40 hours with removal of water

by a Dean-Stark trap. The reaction mixture was poured into an aqueous solution of potassium carbonate (ice cooled), and extracted with benzene. The organic extracts were washed several times with water, dried and evaporated to give 68.2 g (97%) of phthalimido ketal IIIa.

4-Methyl-1-phthalimido-3-pentanone Ethylene Acetal (IIIb).

Operating as above from 52.6 g (0.21 mole) of phthalimidoketone IIb, 17.6 g (92 mmoles) of *p*-toluenesulfonic acid, 34.8 ml of ethylene glycol, and 500 ml of anhydrous benzene, 53.4 g (86%) of phthalimido ketal IIIb were obtained.

1-Amino-3-pentanone Ethylene Acetal (IVa).

A solution of 15 g (54 mmoles) of phthalimidoketal IIIa, 9 ml of 80% hydrazine hydrate, and 150 ml of methanol was refluxed for 3 hours, and then the solvent was removed *in vacuo* at room temperature. The residue was cooled, and 100 ml of 20% aqueous sodium hydroxide were added. After stirring 15 minutes, the solution was extracted several times with chloroform. The combined organic extracts were washed with water, dried, and evaporated to yield 6.0 g (87%) of aminoketal IVa.

Table VI

| Compound | Mp, °C | Formula | Analyses | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Carbon % | | Hydrogen % | | Nitrogen % | | Chlorine % | |
| No. | (solvent) (a) | | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| IIa | 82-83 (A) | $C_{13}H_{13}NO_3$ | 67.53 | 67.47 | 5.66 | 5.69 | 6.05 | 6.25 | — | — |
| IIb | 90-91 (A) | $C_{14}H_{15}NO_3$ | 68.57 | 68.69 | 6.12 | 6.24 | 5.71 | 5.86 | — | — |
| IIIa | 114-115 (A) | $C_{15}H_{17}NO_4$ | 65.45 | 65.34 | 6.22 | 6.44 | 5.08 | 5.17 | — | — |
| IIIb | 70-72 (A) | $C_{16}H_{19}NO_4$ | 66.43 | 66.46 | 6.57 | 6.59 | 4.84 | 5.06 | — | — |
| Va | (b) | $C_{17}H_{25}NO_5 \cdot H_2O$ | 59.81 | 59.58 | 7.96 | 7.67 | 4.10 | 4.16 | — | — |
| Vb | (b) | $C_{15}H_{21}NO_3$ | 68.42 | 68.11 | 8.04 | 8.10 | 5.31 | 5.27 | — | — |
| Vc | (b) | $C_{18}H_{27}NO_5$ | 64.09 | 63.90 | 8.01 | 8.22 | 4.15 | 4.29 | — | — |
| Vd | (b) | $C_{16}H_{20}N_2O_2 \cdot \frac{1}{2}H_2O$ | 68.32 | 67.96 | 7.47 | 7.41 | 9.91 | 9.61 | — | — |
| VIa•HCl | 248-250 (A-E) | $C_{17}H_{26}ClNO_5$ | 56.69 | 57.01 | 7.22 | 7.32 | 3.89 | 4.23 | 9.85 | 10.05 |
| VIb•HCl | 203-204 (A-E) | $C_{15}H_{22}ClNO_3$ | 60.10 | 59.87 | 7.38 | 7.39 | 4.67 | 4.88 | 11.82 | 11.85 |
| VIc•HCl | 205-207 (A-F) | $C_{18}H_{28}ClNO_5$ | 57.84 | 57.81 | 7.49 | 7.75 | 3.74 | 4.00 | 9.48 | 9.63 |
| VId•HCl | 239-241 (A-F) | $C_{16}H_{21}ClN_2O_2$ | 62.27 | 62.59 | 6.80 | 6.85 | 9.07 | 8.95 | — | — |
| VIIa•HCl | 187-189 (A) | $C_{15}H_{21}ClNO_4$ | 57.05 | 57.19 | 7.02 | 7.06 | 4.43 | 4.47 | — | — |
| VIIb•HCl | 200-201 (A) | $C_{13}H_{18}ClNO_2$ | 58.96 | 59.35 | 7.23 | 6.96 | 5.29 | 5.47 | — | — |
| VIIc•HCl | 211-212 (A-F) | $C_{16}H_{24}ClNO_4 \cdot \frac{1}{2}H_2O$ | 56.72 | 56.63 | 7.19 | 7.33 | 4.02 | 4.32 | 10.21 | 10.34 |
| VIIIa•HCl | 192-194 (A-E) | $C_{16}H_{24}ClNO_4$ | 58.27 | 58.29 | 7.33 | 7.45 | 4.25 | 4.24 | 10.75 | 10.88 |
| VIIIb•HCl | 164-165 (A) | $C_{14}H_{20}ClNO_2$ | 62.33 | 62.46 | 7.47 | 7.50 | 5.19 | 5.45 | — | — |
| VIIId•HCl | 177-180 (A) | $C_{15}H_{19}ClN_2O$ | 64.63 | 64.67 | 6.82 | 6.74 | 10.05 | 10.00 | 12.74 | 13.10 |
| XIIa•HCl | 158-160 (A) | $C_{18}H_{28}ClNO_5$ | 57.83 | 57.89 | 7.55 | 7.56 | 3.74 | 4.05 | 9.48 | 9.87 |
| XIIb•Picrate | 178-180 (A) | $C_{22}H_{26}N_4O_{10}$ | 52.18 | 52.26 | 5.17 | 5.25 | 11.06 | 10.88 | — | — |
| XIIc•Picrate | 186-188 (A) | $C_{25}H_{32}N_4O_{12}$ | 51.73 | 52.04 | 5.55 | 5.53 | 9.65 | 9.43 | — | — |
| XIId•HCl | 245-247 (A-E) | $C_{17}H_{23}ClN_2O_2$ | 63.25 | 63.15 | 7.13 | 6.95 | 8.68 | 8.33 | — | — |
| *trans*-XIIIa•Picrate | 220-222 (A) | $C_{20}H_{20}ClN_4O_8$ | 49.95 | 49.81 | 4.19 | 4.21 | 11.65 | 11.37 | — | — |
| *trans*-XIIIb•HCl | 172-174 (A-E) | $C_{17}H_{26}ClNO_4$ | 59.38 | 59.33 | 7.62 | 7.63 | 4.07 | 4.19 | 10.31 | 10.60 |

(a) Solvents: A = acetone; E = ether; F = ethanol. (b) Purified by distillation at 200-250°/0.5 mm Hg (oven temperature) on a Büchi GKR-50 Kugelrohr.

1-Amino-4-methyl-3-pentanone Ethylene Acetal (IVb).

Operating as above from 16 g (55 mmoles) of phthalimido ketal IIIb, 9 ml of 80% hydrazine hydrate, and 200 ml of methanol, 6.5 g (74%) of amino ketal IVb were obtained.

3,3-Ethylenedioxy-*N*-(2,3,4-trimethoxybenzylidene)pentylamine (Va).

A solution of 6.8 g (35 mmoles) of amino ketal IVa and 5.9 g (40 mmoles) of 2,3,4-trimethoxybenzaldehyde in 150 ml of anhydrous benzene was stirred at 0° for 30 minutes, at room temperature for 1 hour, and under reflux for 4 hours. After 16 hours of additional reflux with removal of water by a Dean-Stark trap, the solvent was evaporated to give 11 g (85%) of imine Va.

3,3-Ethylenedioxy-*N*-(*m*-methoxybenzylidene)pentylamine (Vb).

Operating in the same manner from 22 g (0.15 moles) of aminoketal IVa and 17 g (0.13 moles) of *m*-methoxybenzaldehyde in 350 ml of anhydrous benzene, 39 g (98%) of imine Vb were obtained.

3,3-Ethylenedioxy-4-methyl-*N*-(3,4,5-trimethoxybenzylidene)pentylamine (Vc).

Operating as above from 4.5 g (28 mmoles) of aminoketal IVb and 4.9 g (25 mmoles) of 3,4,5-trimethoxybenzaldehyde in 150 ml of anhydrous benzene, 8.5 g (89%) of imine Vc were obtained.

3,3-Ethylenedioxy-*N*-(3-indolylmethylidene)pentylamine (Vd).

Operating in the same manner from 12.8 g (89 mmoles) of amino ketal IVa and 11.4 g (79 mmoles) of indole-3-carbaldehyde in 250 ml of anhydrous benzene, 16.2 (75%) of imine Vd were obtained.

*trans*-2-(*m*-Methoxyphenyl)-3-methyl-4-piperidone (VIIb).

A stirred solution of imine Vb (8.8 g, 33 mmoles) in 60 ml of anhydrous methylene chloride was saturated with hydrogen chloride gas for 90 minutes and then refluxed under nitrogen for 21 hours. After cooling, the solvent was removed to give an oil which was dissolved in 30 ml of methanol and 50 ml of 20% hydrochloric acid. The solution was stirred at 60° for 1 hour, concentrated, extracted with benzene, basified with solid potassium carbonate, and extracted with chloroform. The chloroform phase was dried and evaporated to give 3.9 g (55%) of piperidone VIIb.

3,3-Dimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (VIIc) and its Ethylene Acetal (VIc).

Operating as above from 5.4 g (16 mmoles) of imine Vc in 50 ml of anhydrous methylene chloride saturated with hydrogen chloride gas, and then hydrolysis with aqueous 20% hydrochloric acid and methanol, 2.4 g (50%) of piperidone VIIc were obtained.

When the reaction was carried out omitting the final hydrolysis, a 1:4 mixture of piperidone VIIc and its ethylene ketal VIc was obtained. Pure VIc was isolated by column chromatography through silica gel (chloroform as eluent).

*trans*-3-Methyl-2-(2,3,4-trimethoxyphenyl)-4-piperidone Ethylene Acetal (VIa).

A stirred mixture of imine Va (2.7 g, 8.3 mmoles) and anhydrous *p*-toluenesulfonic acid (3.6 g, 19 mmoles) in 100 ml of anhydrous benzene was refluxed under nitrogen atmosphere for 1 hour. The cooled mixture was poured into a 20% aqueous potassium carbonate solution and extracted with benzene. The extracts were washed with 20% aqueous potassium carbonate solution, dried, and evaporated to yield 2.4 g (87%) of ethylene ketal VIa.

*trans*-2-(*m*-Methoxyphenyl)-3-methyl-4-piperidone Ethylene Acetal (VIb).

Operating in the same manner from 1.7 g (9.5 mmoles) of imine Vb and 2.3 g (12 mmoles) of anhydrous *p*-toluenesulfonic acid in 100 ml of anhydrous benzene, 1 g (58%) of ethylene ketal VIb was obtained.

*trans*-2-(3-Indolyl)-3-methyl-4-piperidone Ethylene Acetal (VId).

Operating in the same manner from 16 g (59 mmoles) of imine Vd and 14.7 g (77 mmoles) of anhydrous *p*-toluenesulfonic acid in 250 ml of anhydrous benzene, 13 g (80%) of solid ethylene ketal VId were obtained. An analytical sample was purified by column chromatography through silica gel (99:1 chloroform-methanol as eluent).

*cis*-2-(*p*-Chlorophenyl)-3-(1,1-ethylenedioxyethyl)-3-methylpyrrolidine (XIa).

Operating in the same manner from 1 g (3.5 mmoles) of imine Xa (17) and 2.75 g (14.4 mmoles) of anhydrous *p*-toluenesulfonic acid in 100 ml of anhydrous benzene, 0.82 g (78%) of the previously described (17) ethylene ketal XIa were obtained.

*trans*-1,3-Dimethyl-2-(2,3,4-trimethoxyphenyl)-4-piperidone (VIIIa) and its Ethylene Acetal (XIIa).

A solution of 2.7 ml (34 mmoles) of methyl fluorosulfonate in 10 ml of anhydrous methylene chloride was slowly added at -30° under nitrogen to a stirred solution of 11 g (34 mmoles) of imine Va in 50 ml of anhydrous methylene chloride. The mixture was stirred at −30° for 2 hours and at room temperature for 16 hours. The solution was saturated with hydrogen chloride gas, and then stirred at room temperature for 30 minutes and under reflux for 3 hours. The solvent was evaporated to give an oil which was dissolved at 0° with 100 ml of 20% hydrochloric acid. The aqueous solution was extracted with benzene, basified with solid potassium carbonate, and extracted several times with ether. The ethereal extracts were dried and evaporated to give 6 g of a 4:1 mixture of ethylene ketal XIIa and piperidone VIIIa. From this mixture, pure XIIa was obtained after several recrystallizations of its hydrochloride from acetone.

Five grams of the above 4:1 mixture were dissolved in 20% hydrochloric acid (75 ml) and methanol (35 ml). The solution was heated at 60° for 3 hours, poured into a 20% aqueous potassium carbonate solution (ice cooled), and extracted with ether. The extracts were dried and evaporated to give 2.3 g of pure piperidone VIIIa.

*trans*-2-(*m*-Methoxyphenyl)-1,3-dimethyl-4-piperidone Ethylene Acetal (XIIb).

Operating as above from 3.7 g (14 mmoles) of imine Vb, 1.2 ml (15 mmoles) of methyl fluorosulfonate, and 60 ml of anhydrous methylene chloride, 1.6 g (50%) of ethylene ketal XIIb were obtained.

1,3,3-Trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (VIIIc) and its ethylene Acetal (XIIc).

A solution of imine Vc (10 g, 29.6 mmoles) and methyl fluorosulfonate (2.8 ml, 34 mmoles) in 110 ml of anhydrous methylene chloride was treated as above. The resulting oil was dissolved in 200 ml of 20% hydrochloric acid, and the solution was stirred at room temperature for 10 hours. After usual workup, 6.1 g (67%) of piperidone VIIIc (15,16a) were obtained. Pure ethylene ketal XIIc was isolated, after usual workup, by column chromatography (silica gel, 98:2 chloroform-methanol as eluent) from an aliquot part of the reaction mixture prior to hydrolysis.

*cis*- and *trans*-3-Acetyl-2-(*p*-chlorophenyl)-1,3-dimethylpyrrolidine (XIIIa).

Operating as above from 40 g (0.14 moles) of imine Xa (17), 12.3 ml (0.15 mole) of methyl fluorosulfonate, and 180 ml of anhydrous methylene chloride, 35.7 g (60%) of a 1:1 mixture of *cis* and *trans* pyrrolidines XIIIa were obtained after usual acid hydrolysis and workup. The above mixture was microdistilled at 160-170°/0.2 mm Hg (oven temperature) to give an oil which was converted its hydrochloride. Recrystallization from anhydrous acetone-ether yielded pure *cis*-XIIIa hydrochloride (17). From the mother liquors, *trans*-XIIIa hydrochloride was obtained.

*cis*- and *trans*-3-Acetyl-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine (XIIIb).

Operating as above from 11 g (34 mmoles) of imine Xb (17), 3 ml (37 mmoles) of methyl fluorosulfonate, and 70 ml of anhydrous methylene

chloride, 4.7 g (45%) of a 1:1 mixture of *cis* and *trans* pyrrolidines XIIIb were obtained after usual acid hydrolysis and workup. The previously reported (17) *cis*-XIIIb isomer was isolated by column chromatography through silica gel (7:3 benzene-chloroform as eluent). Pure *trans*-XIIIb isomer was obtained on elution with 2:8 benzene-chloroform followed by recrystallization (acetone) of its hydrochloride.

*trans*-2-(*m*-Methoxyphenyl)-1,3-dimethyl-4-piperidone (VIIIb).

A. A mixture of 3.9 g (18 mmoles) of piperidone VIIb, 50 ml of anhydrous acetone, 2.5 g (18 mmoles) of methyl iodide, and 5.5 g of anhydrous potassium carbonate was stirred at 0° for one hour. After filtration and evaporation, 3.7 g (90%) of piperidone VIIIb were obtained.

B. A solution of 1 g (3.6 mmoles) of ethylene ketal XIIb, 50 ml of 20% hydrochloric acid, and 30 ml of methanol was stirred at 60° for 2 hours. After cooling, the solution was concentrated, basified with solid potassium carbonate, and extracted with chloroform. The organic extracts were dried and evaporated to give 0.59 g (63%) of piperidone VIIIb.

1,3,3-Trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (VIIIc).

Operating as in the above method A from 2.4 g (8 mmoles) of piperidone VIIc, 50 ml of anhydrous acetone, 2.4 g of anhydrous potassium carbonate, and 1.1 g (8 mmoles) of methyl iodide, 2.3 g (92%) of piperidone VIIIc (15, 16a) were obtained.

*trans*-2-(3-Indolyl)-1,3-dimethylpiperidone Ethylene Acetal (XIId).

A mixture of VId (16 g, 58 mmoles), anhydrous acetone (275 ml), methyl iodide (8.3 g, 58 mmoles), and anhydrous potassium carbonate (8 g) was stirred at 0° for 30 minutes. After usual workup, 14.5 g (87%) of ethylene ketal XIId were obtained. An analytical sample was obtained by column chromatography (silica gel, 99:1 chloroform-methanol as eluent).

*trans*-3-Methyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (VIIa).

A solution of ethylene ketal VIa (0.5 g, 1.5 mmoles), 20% hydrochloric acid (30 ml), and methanol (10 ml) was stirred at 60° for 4 hours. After cooling, the solution was worked up in the usual way to give 0.23 g (55%) of piperidone VIIa.

*trans*-2-(3-Indolyl)-1,3-dimethyl-4-piperidone (VIIId).

A solution of ethylene ketal XIId (7 g, 24 mmoles), 20% hydrochloric acid (200 ml), and methanol (200 ml) was stirred at 60° for 1 hour. After usual workup, 4.5 g (77%) of piperidone VIIId were obtained. An analytical sample was obtained by column chromatography through silica gel (elution with 96:4 methylene chloride-methanol) followed by crystallization of the hydrochloride.

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