Synthesis of 1'-Methylspiro[3*H*-indole-3,n'-piperidines] from 1-Methyl-n-piperidinecarbaldehydes

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1'-Methylspiro[3*H*-indole-3,n'-piperidines] **2** can be obtained from the 1-methyl-n-piperidinecarbaldehydes **1** by the Fischer reaction of their phenylhydrazones. The Fischer reaction provides different kinds of products -3*H*-indole, indole and oxindole- which depend on the N atom position in the piperidine ring.

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Our laboratory is involved in an investigation of indole and indoline derivatives, such as 1'-(3-dimethylaminopropyl)spiro[cycloalkane-1,3'-indolines] as antidepressant drugs. In this way, we have reported the preparation of spiro[cycloalkane-1,3'-3*H*-indoles] by means of the Fischer reaction of the phenylhydrazones of the appropriate cycloalkane carbaldehydes. Moreover, we have demonstrated that under acid conditions the phenylhydrazones of the cycloalkane carbaldehydes yield the cycloalkane[*b*]indoles as a rearrangement product instead of the expected spiro-[cycloalkane-1,3'-3*H*-indole] [1].

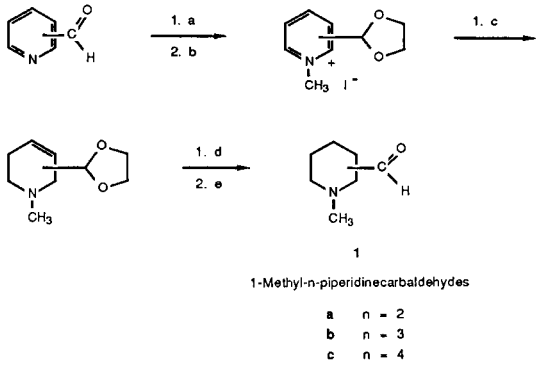
This paper describes the preparation of 1-methylspiro-[3*H*-indole-3,n'-piperidine] **2** by Fischer reaction of the phenylhydrazones of the 1-methyl-n-piperidinecarbaldehydes **1** (for n = 2, 3 or 4).

Pyridinecarbaldehydes were the starting products for the synthesis of **1**, which requires several steps. In the first step, pyridinecarbaldehydes were transformed to the n-(1,3-dioxolan-2-yl)pyridines to protect the aldehyde group. Then, the treatment of the pyridine ring with methyl iodide allowed to obtain the n-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide.

In a second step, these 1-methylpyridinium salts were reduced, first by means of the sodium borohydride in water and after by complete catalytic hydrogenation, using platinum oxide.

Finally, the 1-methyl-n-piperidinecarbaldehydes were obtained by hydrolysis of the dioxolane protecting group, Scheme 1.

Scheme 1



1

1-Methyl-n-piperidinecarbaldehydes

a n = 2
b n = 3
c n = 4

Reagents: [a] $HO(CH_2)_2OH$, H^+; [b] ICH_3; [c] $NaBH_4$; [d] H_2, PtO_2; [e] H_2O, H^+

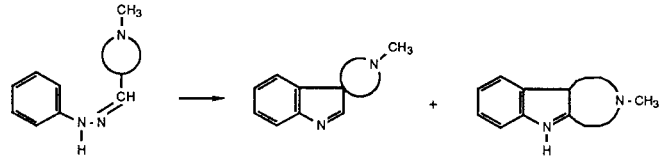
In the above mentioned reduction with sodium borohydride of the 1-methylpyridinium salts, can be obtained several reduction products. Thus, 2-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide yields three products, which can be explained, according to the mechanism proposed to the reduction of other pyridinium salts with the same reducing agent [2] [3]. In effect, an initial attack of the hydride ion: a) on the 2-position of the 1-methylpyridinium ring yields the 6-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine, b) on the 6-position of the pyridinium ring yields the 2-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine and c) on the 4-position of the pyridinium ring yields, after two consecutive reactions, the 2-(1,3-dioxolan-2-yl)-1-methylpiperidine.

The reduction of the 3- or 4-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide with sodium borohydride, yields a tetrahydropyridine derivative. This product results by attack of the hydride ion on the 2-position of the 1-methylpyridinium ring.

As it is usual in these reactions tetrahydropyridine-borane complexes were isolated as side-products. The yield in the amine-borane complexes increases with the reaction time. These complexes can be quantitatively transformed into the respective tetrahydropyridine by reflux in ethanol.

On the other hand, the preparation of the n-(1,3-dioxolan-2-yl)-1-methylpiperidines was carried out by platinum catalytic hydrogenation of the respective tetrahydropyridines, as referred above. It is remarkable that the hydrogenation of the 3- or 4-(1,3-dioxolan-2-yl)tetrahydropyridines derivatives gave the corresponding 3- or 4-(1,3-dioxolan-2-yl)piperidine and also the 3- or 4-(4-hydroxy-2-oxabutyl)-1-methylpiperidine. The last rises by hydrogenolysis of the allyl type dioxolane [4] as the main product or a byproduct of the reaction respectively. The catalytic hydrogenation of the 2-(1,3-dioxolan-2-yl)tetra-

Table 1



2 3

1'-Methylspiro[3H-indole-3,n'piperidines]

a n = 2
b n = 3
c n = 4

Phenylhydrazone of	Catalyst	Solvent	T(°C)	t(h)	**2a** (%)	**3** (%)	[a] (%)
1a	H_2SO_4 (20%)	H_2O	95	10	23	– –	[b]
1a	AcOH (85%)	AcOH (85%)	95	24	16	– –	[b]
1a	– –	EG	180	24	– –	– –	[b]

Phenylhydrazone of	Catalyst	Solvent	T(°C)	t(h)	**2b** (%)	**3** (%)	[a] (%)
1b	H_2SO_4 (20%)	H_2O	95	2	– –	80	– –
1b	AcOH (85%)	AcOH (85%)	95	12	– –	– –	[b]
1b	– –	EG	180	24	– –	– –	[b]

Phenylhydrazone of	Catalyst	Solvent	T(°C)	t(h)	**2c** (%)	**3** (%)	[a] (%)
1c	H_2SO_4 (20%)	H_2O	95	2	85	– –	– –
1c	AcOH (85%)	AcOH (85%)	95	15	38	– –	26 [c]
1c	– –	EG	180	15	57	– –	– –

[a] Another reaction products. [b] Complex mixture of products. [c] 1-Methylspiro[oxindole-3,4'-piperidine]. EG = Ethyleneglycol.

hydropyridine derivatives, gives only the 2-(1,3-dioxolane-2-yl)-1-methylpiperidine and hydrogenolysis products were not detected.

Finally, the hydrolysis step of the n-(1,3-dioxolan-2-yl)-1-methylpiperidines, to obtain the 1-methyl-n-piperidinecarbaldehydes was carried out with aqueous sulfuric acid (20%). The reaction conditions were found for every compound (see Experimental section).

The spiro-3*H*-indoles **2** were obtained by means of the Fischer reaction of the phenylhydrazones of the aldehydes **1** using as catalyst, sulfuric acid, acetic acid or thermal conditions. In Table 1, are summarized the results of these analyses.

In a previous paper we described the acid-catalyzed rearrangement of spiro[cycloalkane-1,3'-3*H*-indoles] to the respective cycloalkane[*b*]indoles [1], with sulfuric acid as the catalyst. Similarly, an analysis of this rearrangement was carried out. Table 1 shows that only the 1-methylspiro-[3*H*-indole-3,3'-piperidine] rearranges to their indole derivative **3**. The 1-methylspiro[3*H*-indole-3,n'-piperidines] with n = 2 or n = 4 were treated under strongly acid conditions and the indole rearrangement products were not detected. In this way, the nitrogen atom of the piperidine ring, in the 3*H*-indoles **2**, seems to provide greater chemical inertia than the spirocycloalkane parents to the rearrangement reaction.

The Fischer reaction of the phenylhydrazone of **1a** afforded the 3*H*-indole **2a** in poor yield, under the acid catalyst attempted, which can be due to the formation of an enamine intermediate [5] with the aggroupation N-C = C-N.

The Fischer reaction of the phenylhydrazone of **1b** in acetic acid or ethyleneglycol afforded a complex mixture of products. When sulfuric acid was used as the catalyst, a rearrangement indole derivative was the only product isolated. Two isomers are possible in this rearrangement reaction (Scheme 2), following the mechanism previously described [1], but only one product was isolated. The benzene-induced solvent shift in the ^{1}H-nmr spectra [6] [7] allowed to identify this compound as the 4-methyl-1,2,3,4,5,6-hexahydroazepine[3,4-*b*]indole. All the attempts to avoid the rearrangement reaction to the indole derivative were unsuccessful.

Scheme 2

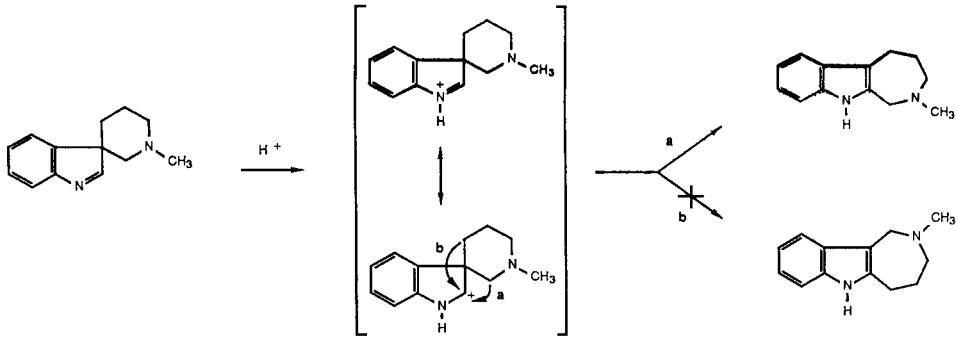
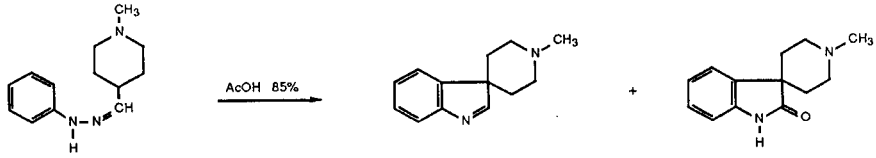


Table 2



2c

(°C)	Time hours	2c (%)	Oxindole (%)
95	15	38	26
95	24	32	34
95	34	23	47
95	72	7	62

The Fischer reaction of the phenylhydrazone of **1c** in sulfuric acid or ethyleneglycol afforded the 3*H*-indole **2c** in good yield. However, it is noticeable that the treatment of the phenylhydrazone of **1c** with acetic acid as the catalyst, gave a mixture of the 3*H*-indole **2c** and another product, which was identified as the 1-methylspiro[oxindole-3,4'-piperidine]. From Table 2, can be deduced that the ratio of the yields between the 3*H*-indole to the oxindole depends on the time of the reaction.

EXPERIMENTAL

Melting points were determined by using a Reichert stage microscope and are uncorrected. Infrared spectra were recorded using an SP 1100 Phillips Pye Unicam Spectrophotometer. Nuclear Magnetic Resonance spectra were recorded at 200 Mz using a Bruker WM-200-SY spectrometer. Chemical shifts are given relative to internal tetramethylsilane. Elemental analyses were performed with a Model 240 Perkin-Elmer analyzer.

1-Methylpiperidinecarbaldehydes (**1**).

a. Preparation of the n-(1,3-Dioxolan-2-yl)pyridines.

A solution of 0.09 mole of the n-pyridinecarbaldehydes, 0.18 mole of the ethylene glycol and 0.10 mole of the *p*-toluenesulfonic acid was boiled during 4 hours, to remove water azeotropically. The mixture was cooled, made basic with aqueous sodium hydroxide and extracted with dichloromethane. The solvent was evaporated and the residual oil distilled under vacuum to give a colorless liquid with the following yields and spectral data:

2-(1,3-Dioxolan-2-yl)pyridine.

This compound had bp 146°/5 mm, 84% yield; nmr (deuteriochloroform): δ 8.61 (m, 1H, H-6), 7.70 (m, 1H, H-4), 7.53 (m, 1H, H-3), 7.27 (m, 1H, H-5), 5.84 (s, 1H, O-CH-O), 4.12 (m, 4H, O-CH_2)$_2$-O); ir (film): 1095, 1050 and 990 (st C-O-C-O-C).

3-(1,3-Dioxolan-2-yl)pyridine.

This compound had bp 150°/1 mm, 87% yield, nmr (deuteriochloroform): δ 8.64 (m, 1H, H-2), 8.55 (m, 1H, H-6), 7.70 (m, 1H, H-4), 7.30 (m, 1H, H-5), 5.79 (s, 1H, O-CH-O), 4.05 (m, 4H, O-(CH_2)$_2$-O); ir (film): 1090, 1030 and 980 (st C-O-C-O-C).

4-(1,3-Dioxolan-2-yl)pyridine.

This compound had bp 120°/5 mm, 90% yield; nmr (deuteriochloroform): δ 8.60 (m, 2H, H-2, H-6), 7.34 (m, 2H, H-3, H-5), 5.76 (s, 1H, O-CH-O), 4.00 (m, 4H, O-(CH_2)$_2$-O); ir (film): 1090, 1030 and 990 (st C-O-C-O-C).

b. Preparation of the n-(1,3-Dioxolan-2-yl)-1-methylpyridinium Iodide.

To 0.08 mole of the n-(1,3-dioxolan-2-yl)pyridine was added dropwise a solution of 0.16 mole of methyl iodide in 50 ml of the diethyl ether, at 10-15°. The mixture was stirred for 10 hours and allowed to stand at 5° overnight. The solid was filtered off and washed with diethyl ether. The n-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide was purified by solution in methanol and precipitated with a mixture of the ethyl acetate-hexane to give a solid with the following yields and spectral data:

2-(1,3-Dioxolan-2-yl)-1-methylpyridinium Iodide.

This compound was obtained as an orange solid, mp 122-124°, 85% yield; nmr (deuteriochloroform): δ 9.06 (m, 1H, H-6), 8.63 (m, 1H, H-4),

8.19 (m, 1H, H-3), 8.13 (m, 1H, H-5), 6.47 (s, 1H, O-CH-O), 4.37 (s, 3H, CH_3), 4.09 (m, 4H, O-$(CH_2)_2$-O).

Anal. Calcd. for $C_9H_{12}INO_2$: C, 36.88; H, 4.12; N, 4.78. Found: C, 36.54; H, 4.01; N, 4.92.

3-(1,3-Dioxolan-2-yl)-1-methylpyridinium Iodide.

This compound was obtained as a yellow solid, mp 183-185°, 90% yield; nmr (deuteriochloroform): δ 9.10 (m, 1H, H-2), 9.02 (m, 1H, H-6), 8.60 (m, 1H, H-4), 8.17 (m, 1H, H-5), 6.07 (s, 1H, O-CH-O), 4.38 (s, 3H, CH_3), 4.05 (m, 4H, O-$(CH_2)_2$-O).

Anal. Calcd. for $C_9H_{12}INO_2$: C, 36.88; H, 4.12; N, 4.78. Found: C, 36.61; H, 4.17; N, 4.81.

4-(1,3-Dioxolan-2-yl)-1-methylpyridinium Iodide.

This compound was obtained as a yellow solid, mp 156-158°, 95% yield; nmr (deuteriochloroform): δ 9.00 (m, 2H, H-2, H-6), 8.12 (m, 2H, H-3, H-5), 6.08 (s, 1H, O-CH=), 4.36 (s, 3H, CH_3), 4.02 (m, 4H, O-$(CH_2)_2$-O).

Anal. Calcd. for $C_9H_{12}INO_2$: C, 36,88; H, 4.12; N, 4.78. Found: C, 36.49; H, 4.01; N, 4.69.

c. Reduction of the n-(1,3-Dioxolan-2-yl)-1-methylpyridinium Iodide.

To 0.12 mole of sodium borohydride was added dropwise a solution of 0.06 mole of the n-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide in 50 ml of water at 10-15°. The mixture was stirred at room temperature during 30 minutes. The aqueous solution was extracted with dichloromethane. The organic solution was dried over magnesium sulfate and evaporated to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:1), to provide several reduction products.

The reduction of the 2-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide gave the following products:

2-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine-borane.

This compound was obtained as a yellow oil, 30% yield; nmr (deuteriochloroform): δ 5.70 (m, 3H, O-CH-O, HC=CH), 3.90 (m, 4H, O-$(CH_2)_2$-O), 3.2 (m, 3H, H-2, H-6), 2.65 (s, 3H, CH_3), 2.28 (m, 2H, H_2-3); ir (film): 2290, 2400 (st BH).

Anal. Calcd. for $C_9H_{18}BNO_2$: C, 59.05; H, 9.91; N, 7.65. Found: C, 58.79; H, 9.78; N, 7.57.

2-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine.

This compound was obtained as a yellow oil, 25% yield; nmr (deuteriochloroform): δ 5.71 (m, 2H, HC=CH), 5.01 (d, 1H, O-CH-O, J = 5.1 Hz), 3.90 (m, 4H, O-$(CH_2)_2$-O), 2.9 (m, 1H, H-2), 2.63 (m, 2H, H_2-6), 2.49 (s, 3H, CH_3), 2.15 (m, 2H, H_2-3); ir (film): 1670 (st C=C).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.78; H, 8.93; N, 8.27. Found: C, 63.46; H, 8.82; N, 8.12.

6-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine.

This compound was obtained as a yellow oil, 15% yield; nmr (deuteriochloroform): δ 5.95 (m, 2H, HC=CH), 4.90 (d, 1H, O-CH-O, J = 4.2 Hz), 3.90 (m, 4H, O-$(CH_2)_2$-), 2.9 (m, 1H, H-6), 2.83 (m, 2H, H_2-2), 2.50 (s, 3H, CH_3), 2.15 (m, 2H, H_2-3); ir (film): 1670 (st C=C).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.78; H, 8.93; N, 8.27. Found: C, 63.46; H, 8.89; N, 8.36.

2-(1,3-Dioxolan-2-yl)-1-methylpiperidine.

This compound was obtained as a yellow oil in 20% yield.

The reduction of the 3-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide gave the following products:

5-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine-borane.

This compound was obtained as a yellow oil, 28% yield; nmr (deuteriochloroform): δ 5.98 (m, 1H, HC=C), 5.13 (s, 1H, O-CH-O), 3.90 (m, 4H, O-$(CH_2)_2$-O), 3.54 (m, 1H, H-6), 2.93 (t, 2H, H_2-2, J [5] 5.6 Hz), 2.48 (s, 3H, CH_3), 2.23 (m, 2H, H_2-3); ir (film): 2270, 2400 (st BH).

Anal. Calcd. for $C_9H_{18}BNO_2$: C, 59.05; H, 9.91; N, 7.65. Found: C, 59.37; H, 9.78; N, 7.61.

5-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine.

This compound was obtained as a colorless oil, 54% yield; nmr (deuteriochloroform): δ 5.96 (m, 1H, HC=C), 5.18 (s, 1H, O-CH-O), 3.95 (m, 4H, O-$(CH_2)_2$-O), 2.97 (m, 2H, H_2-6), 2.52 (m, 2H, H_2-2), 2.38 (s, 3H, CH_3), 2.23 (m, 2H, H_2-3); ir (film): 1660 (st C=C).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.87; H, 8.93; N, 8.27. Found: C, 63.72; H, 8.79; N, 8.14.

The reduction of the 4-(1,3-dioxolan-2-yl)-1-methylpyridinium iodide gave the following products:

4-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine-borane.

This compound was obtained as a colorless solid, mp 85-87°, 30% yield, nmr (deuteriochloroform): δ 5.83 (m, 1H, HC=C) 5.21 (s, 1H, O-CH-O); 3.97 (m, 4H, O-$(CH_2)_2$-O), 3.65 (m, 1H, H-6), 3.23 (m, 1H, H-6), 3.03 (m, 1H, H_2-2), 2.57 (s, 3H, CH_3), 2.30 (m, 2H, H_2-3); ir (film): 2280, 2400 (st BH).

Anal. Calcd. for $C_9H_{18}BNO_2$: C, 59.05; H, 9.91; N, 7.65. Found: C, 58.98; H, 9.97; N, 7.63.

4-(1,3-Dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine.

This compound was obtained as a yellow oil, 60% yield; nmr (deuteriochloroform): δ 5.87 (m, 1H, HC=C), 5.19 (s, 1H, O-CH-O), 3.94 (m, 4H, O-$(CH_2)_2$-O), 2.97 (m, 2H, H_2-6), 2.55 (m, 2H, H_2-2), 2.36 (s, 3H, CH_3), 2.22 (m, 2H, H_2-3); ir (film): 1670 (st C=C).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.87; H, 8.93; N, 8.27. Found: C, 63.67; H, 8.86; N, 8.12.

d. Preparation of the 1-Methyl-n-piperidinecarbaldehydes.

A solution of 2-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine, 6-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine and 2-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine-borane in methanol, was hydrogenated at room temperature in a pressure of 40 psi in the presence of platinum oxide. When the absorption ceased, approximately 4 hours, the catalyst was filtered off, and the solution was evaporated to give an oil, which was purified by column chromatography eluting with chloroform-methanol (5:1) to give the 2-(1,3-dioxolan-2-yl)-1-methylpiperidine as colorless oil in 87% yield.

2-(1,3-Dioxolan-2-yl)-1-methylpiperidine.

This compound had nmr (deuteriochloroform): δ 4.98 (d, 1H, O-CH-O, J = 3.5 Hz), 3.92 (m, 4H, O-$(CH_2)_2$-O), 2.38 (s, 3H, CH_3), 2.90 (m, 1H, H_{eq}-6), 2.19 (m, 1H, H-2), 2.0-1.4 (broad, 7H, H_{ax}-6, H_2-3, H_2-4, H_2-5).

The hydrolysis of the dioxolane group of the 2-(1,3-dioxolan-2-yl)-1-methylpiperidine was carried out with an aqueous solution of sulfuric acid (10%) under nitrogen atmosphere, at 80° during 40 hours. The solution was cooled to ice bath temperature, made basic with aqueous sodium hydroxide (10%) and extracted with dichloromethane. The organic solution was dried over magnesium sulfate and evaporated to give the 1-methyl-2-piperidinecarbaldehyde **1a** (65% of yield) as a colorless liquid.

2,4-Dinitrophenylhydrazone of the aldehyde **1a** is an orange solid of mp 220-222°.

Compound **1a** had nmr (deuteriochloroform): δ 9.50 (d, 1H, HCO, J = 3.7 Hz), 2.90 (m, 1H, H_{eq}-6), 2.45 (m, 1H, H-2), 2.27 (s, 3H, CH_3), 2.0-1.5 (broad, 7H, H_{ax}-6, H_2-3, H_2-3, H_2-5); ir (film): 1735 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.80; H, 5.57; N, 22.79. Found: C, 50.29; H, 5.67; N, 22.59.

A solution of 6 mmoles of the 5-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine in 50 ml of methanol was hydrogenated at room temperature in a pressure of 40 psi, in the presence of platinum oxide (60 mg). When the absorption ceased, approximately 1 hour, the catalyst was filtered off and the solvent evaporated to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:1) to give the 3-(1,3-dioxolan-2-yl)-1-methylpiperidine (30% of yield), as a colorless liquid and the 3-(4-hydroxy-2-oxabutyl)-1-methylpiperidine (57% of yield), as a yellow liquid.

The hydrogenation of the 5-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine-borane under the same conditions described above, was unsuccessful and the amine-borane complex was all recovered.

3-(Dioxolan-2-yl)-1-methylpiperidine.

This compound had nmr (deuteriochloroform): δ 4.67 (d, 1H, O-CH-O, J = 4.8 Hz), 3.90 (m, 4H, O-$(CH_2)_2$-O), 2.89 (m, 2H, H_{eq}-2, H_{eq}-6), 2.29 (s, 3H, CH_3), 2.1-1.5 (broad, 7H, H_{ax}-2, H-3, H_2-4, H_2-5, H_{ax}-6).

3-(4-Hydroxy-2-oxabutyl)-1-methylpiperidine.

This compound had nmr (deuteriochloroform): δ 3.9 (broad, 1H, OH), 3.70 (m, 2H, CH_2-hydroxyl), 3.50 (m, 2H, O-CH_2-C-O), 3.35 (d, 2H, piperidine-CH_2-O, J = 6.4 Hz), 2.89 (m, 2H, H_{eq}-2, H_{eq}-6), 2.36 (s, 3H, CH_3), 2.01 (m, 2H, H_{ax}-2, H_{ax}-6), 1.68 (m, 5H, H_2-4, H_2-5, H-3); ir (film): 3520 (st OH), 1150, 1080 (st C-O-C).

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.02; H, 11.21; N, 8.17.

The hydrolysis of the dioxolane group of the 3-(1,3-dioxolan-2-yl)-1-methylpiperidine was carried out with sulfuric acid (10%), under nitrogen atmosphere at room temperature, during 7 hours. Thus, the 1-methyl-3-piperidinecarbaldehyde was obtained as a colorless liquid in 60% of yield.

The 2,4-dinitrophenylhydrazone of the aldehyde **1b** is an orange solid of mp 188-190°.

Compound **1b** had nmr (deuteriochloroform): δ 9.65 (s broad, 1H, HCO), 2.80 (m, 2H, H_{eq}-2, H_{eq}-6), 2.44 (m, 1H, H-3), 2.29 (s, 3H, CH_3), 1.90 (m, 2H, H_{ax}-2, H_{ax}-6), 1.7 (m broad, 4H, H_2-4, H_2-5); ir (film): 1730 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.80; H, 5.57; N, 22.78. Found: C, 50.66; H, 5.49; N, 22.62.

A solution of 0.095 mole of the 4-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine and 0.025 mole of the 4-(1,3-dioxolan-2-yl)-1-methyl-1,2,3,6-tetrahydropyridine-borane in 100 ml of methanol was hydrogenated at 60° in a pressure of 40 psi in the presence of platinum oxide (200 mg). When the absorption ceased, approximately 35 hours, the catalyst was filtered off and the solvent evaporated to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:1), to give the 4-(1,3-dioxolan-2-yl)-1-methylpiperidine (86% of yield), as a colorless liquid, and the 4-(4-hydroxy-2-oxabutyl)-1-methylpiperidine (5% of yield), as a yellow oil.

4-(1,3-Dioxolan-2-yl)-1-methylpiperidine.

This compound had nmr (deuteriochloroform): δ 4.61 (d, 1H, O-CH-O, J = 4.7 Hz), 3.90 (m, 4H), 2.90 (m, 2H, H_{eq}-2, H_{eq}-6), 2.26 (s, 3H, CH_3), 1.92 (m, 2H, H_{ax}-2, H_{ax}-2), 1.78 (m, 2H, H_{eq}-3, H_{eq}-5), 1.50 (m, 3H, H_{ax}-3, H-4, H_{ax}-5).

4-(4-Hydroxy-2-oxabutyl)-1-methylpiperidine.

This compound had nmr (deuteriochloroform): δ 3.72 (m, 2H, CH_2-hydroxyle), 3.53 (m, 2H, O-CH_2-C-O), 3.34 (d, 2H, piperidine-CH_2-O, J = 6.3 Hz), 3.1 (broad, 1H, OH), 2.89 (m, 2H, H_{eq}-2, H_{eq}-6), 1.95 (m, 2H, H_{ax}-2, H_{ax}-6), 1.74 (m, 2H, H_{eq}-3, H_{eq}-5), 1.70 (m, 1H, H-4), 1.35 (m, 2H, H_{ax}-3, H_{ax}-5); ir (film): 3520 (st OH), 1150, 1070 (st C-O-C).

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.02; H, 11.21; N, 8.23.

The hydrolysis of the dioxolane group of the 4-(1,3-dioxolan-2-yl)-1-methylpiperidine was carried out with sulfuric acid (10%) under nitrogen atmosphere at room temperature during 2 hours. Thus, the 1-methyl-4-piperidinecarbaldehyde was obtained as a colorless liquid in 70% of yield.

The 2,4-dinitrophenylhydrazone of the aldehyde **1c** is a yellow solid of mp 238-240°.

Compound **1c** had nmr (deuteriochloroform): δ 9.65 (d, 1H, HCO, J = 1.3 Hz), 2.69 (m, 2H, H_{eq}-2, H_{eq}-6), 2.28 (s, 3H, CH_3), 2.14 (m, 1H, H-4), 2.00 (m, 2H, H_{ax}-2, H_{ax}-6), 1.84 (m, 2H, H_{eq}-3, H_{eq}-5), 1.64 (m, 2H, H_{ax}-3, H_{ax}-5); ir (film): 1730 (st C=O).

Anal. (2,4-dinitrophenylhydrazone) Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.80; H, 5.57; N, 22.78. Found: C, 50.71; H, 5.61; N, 22.69.

1-Methylspiro[3*H*-indole-3,n'-piperidines] (**2**).

Results of the Fischer reaction of the phenylhydrazones of the 1-methyl-n-piperidinecarbaldehydes **1** are summarized in Table 1. In this experimental section, only the best or representative results are considered.

1-Methylspiro[3*H*-indole-3,2'-piperidine] (**2a**).

The phenylhydrazone of the aldehyde **1a** was obtained by azeotropic benzene-water distillation. The phenylhydrazone of **1a** (4 mmoles) and 50 ml of sulfuric acid (20%) were stirred under nitrogen atmosphere, at 95° during 10 hours. The mixture was cooled to room temperature, made alkaline with aqueous sodium hydroxide and extracted with dichloromethane. Solvent was removed to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:2), to provide **2a** in 23% of yield, as a yellow oil; nmr (deuteriochloroform): δ 8.67 (s, 1H, H-N=C), 7.3 (m, 4H, aromatic), 2.90 (m, 1H, H_{eq}-6), 2.60 (s, 3H, CH_3), 2.31 (m, 1H, H_{ax}-6), 1.7 (m, 6H, H_2-3, H_2-4, H_2-5); ir (film): 1600 (st C=N), 770 (aromatic); ms: (70 eV) 200 (M^+, 21%), 201 (45%), 186 (8%), 172 (100%), 143 (7%), 130 (33%), 115 (8%), 103 (9%).

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.98. Found: C, 77.78; H, 8.18; N, 13.81.

1-Methylspiro[3*H*-indole-3,3'-piperidine] (**2b**).

The phenylhydrazone of the aldehyde **1b** was obtained by azeotropic benzene-water distillation. The phenylhydrazone of the aldehyde **1b** (1.1 mmoles) and 50 ml of sulfuric acid (20%) were stirred, under nitrogen atmosphere, at 95° during 2 hours. The mixture was cooled, made alkaline with sodium hydroxide (10%) and extracted with dichloromethane. Solvent was evaporated to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:2), to provide the 4-methyl-1,2,3,4,5,6-hexahydroazepine[3,4-*b*]indole (80% yield), as a yellow solid, mp 157-159°; nmr (deuteriochloroform): δ 8.05 (broad, 1H, N-H), 7.3 (m, 4H, aromatic), 3.94 (s, 2H, H_2-5), 3.12 (m, 2H, H_2-1), 2.88 (m, 2H, H_2-3), 2.40 (s, 3H, CH_3), 1.90 (m, 2H, H_2-2); nmr (hexadeuteriobenzene): 8.06 (broad, 1H, N-H), 7.3 (m, 4H, Ar-H), 3.63 (s, 2H, H_2-5), 2.92 (m, 2H, H_2-1), 2.74 (m, 2H, H_2-3), 2.33 (s, 3H, CH_3-N), 1.71 (m, 2H, H_2-2); ir (potassium bromide): 3420 (st N-H), 760 (aromatic); ms: (70 eV) 200 (M^+, 25%), 157 (63%), 156 (40%), 143 (25%), 130 (30%), 115 (18%), 102 (10%).

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.98. Found: C, 77.86; H, 8.11; N, 13.92.

1-Methylspiro[3*H*-indole-3,4'-piperidine] (**2c**).

a) The phenylhydrazone of the aldehyde **1c** was obtained by azeotropic benzene-water distillation. The phenylhydrazone of the aldehyde **1c** (5.5 mmoles) and 150 ml of sulfuric acid (20%) were stirred, under nitrogen atmosphere, at 95° during 2 hours. The solution was cooled, made alkaline with sodium hydroxide (10%) and extracted with dichloromethane. The solvent was dried and evaporated to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:2), to provide **2c** (85% yield) as colorless crystals mp 103-105°: nmr (deuteriochloroform): δ 8.39 (s, 1H, H-N=C), 7.3 (m, 4H, aromatic), 2.93 (m, 2H, H_{eq}-2, H_{eq}-6), 2.54 (m, 2H, H_{ax}-2, H_{ax}-6), 2.46 (s, 3H, CH_3), 2.04 (m, 2H, H_{ax}-3, H_{ax}-5), 1.66 (m, 2H, H_{eq}-3, H_{ax}-5); ir (potassium bromide): 1605 (st C=N), 770 (aromatic); ms: (70 eV) 200 (M^+, 100%), 201 (15%), 156 (32%), 143 (10%), 130 (8%), 115 (15%), 152 (9%).

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.98. Found: C, 77.84; H, 8.13; N, 13.87.

b) The phenylhydrazone of **1c** (1.6 mmoles) and 50 ml of acetic acid (85%) was stirred, under nitrogen atmosphere, at 95° during 15 hours. The mixture was cooled, made basic with sodium hydroxide (10%) and extracted with dichloromethane. The solvent was evaporated to give an oil, which was chromatographed on a silica gel column, eluting with chloroform-methanol (5:2), to provide **2c** (38% yield) and the 1-methylspiro[oxindole-3,4'-piperidine] (26% yield), as colorless crystals mp

178-180°.

1-Methylspiro[oxindole-3,4'-piperidine].

This compound had nmr (deuteriochloroform): δ 7.9 (broad, 1H, N-H), 7.2 (m, 4H, aromatic), 3.16 (m, 2H, H_{ax}-2, H_{ax}-6), 2.87 (m, 2H, H_{eq}-2, H_{eq}-6), 2.56 (s, 3H, CH_3), 2.19 (m, 2H, H_{ax}-3, H_{ax}-5), 1.96 (m, 2H, H_{eq}-3, H_{eq}-5); ir (potassium bromide): 3400 (st N-H), 1720 (st CO), 740 (aromatic), ms: (70 eV) 216 (M^+, 49), 201 (3%), 146 (13%), 130 (9%), 117 (9%), 71 (100%).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.45; N, 12.95. Found: C, 72.39; H, 7.31; N, 12.90.

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