A Reinvestigation of the Stevens Rearrangement of 1-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium Salts

Joan Bosch, Mario Rubiralta, Antonio Domingo and José Sistaré

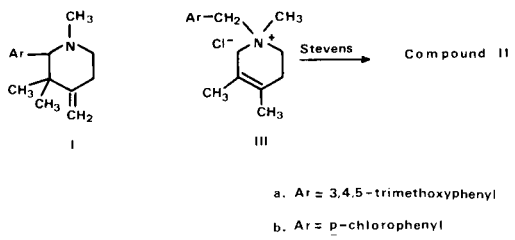
Department of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona, Spain

Received June 25, 1980

Authentic samples of 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (Ia) and 2-(*p*-chlorophenyl)-1,3,3-trimethyl-4-methylenepiperidine (Ib) are prepared by Mannich condensation between 4-methyl-1-methylamino-3-pentanone hydrochloride (VI) and an aromatic aldehyde, followed by a Wittig reaction on the resulting 4-piperidone. Comparing the physical and spectroscopic properties of Ia and Ib with those of the methylene derivatives IIa and IIb obtained as by-products in the Stevens rearrangement of 1-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium salts IIIa and IIIb, respectively, it is shown that the assignment previously made for IIa and IIb is incorrect. Spectroscopic analysis (ir, ^{1}H nmr, ^{13}C nmr, ms) of these compounds and of its hydrogenation products VIII allows the structural and stereochemical assignment of IIa as *cis*-3-isopropenyl-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine and of IIb as *cis*-2-(*p*-chlorophenyl)-3-isopropenyl-1,3-dimethylpyrrolidine. The formation of these rearrangement products is mechanistically interpreted as a Stevens [3,2] type process.

J. Heterocyclic Chem., **18**, 47 (1981).

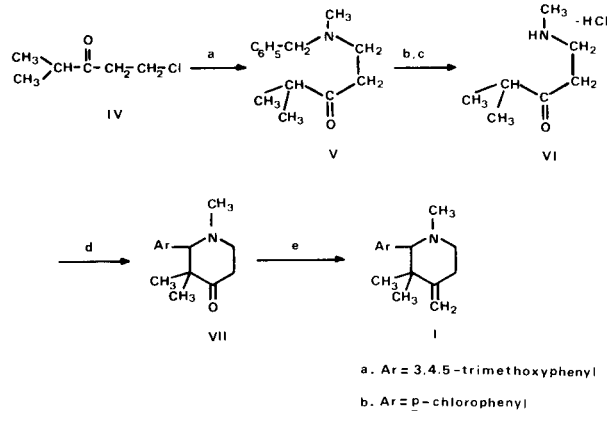
In a previous work (1) we prepared the 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (Ia) by an unequivocal way and we proved that its physical and spectroscopic data differred from those of the methylene derivative IIa which had been obtained as a by-product in the Stevens rearrangement of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (IIIa) and to which that structure had been previously attributed (2) (Scheme I).



Scheme I

Since the structural assignment of IIa had been based on Jacobson's previous one (3) for a compound IIb coming from the Stevens rearrangement of 1-(*p*-chlorobenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium chloride (IIIb), to which he had attributed a 2-(*p*-chlorophenyl)-1,3,3-trimethyl-4-methylenepiperidine structure, we intended both to prove this assignment and to establish definitively the structure of the rearrangement products IIa and IIb (4). For our purpose, we first planned the unequivocal synthesis of 2-(*p*-chlorophenyl)-1,3,3-trimethyl-4-methylenepiperidine (Ib) and next the detailed spectroscopic analysis of the methylene derivatives IIa and IIb, and their hydrogenation products.

The synthesis of 4-methylenepiperidine Ib has been carried out by an intramolecular Mannich condensation between *p*-chlorobenzaldehyde and an enolizable β-amino ketone followed by a Wittig reaction over the resulting 4-piperidone (Scheme II).



Reagents: a. $CH_3-NH-CH_2-C_6H_5$; b. HCl–ether; c. H_2 Pd-C 10%; d. Ar–CHO, p-TsOH, benzene-toluene; e. $(C_6H_5)_3P=CH_2$, THF.

Scheme II

Thus, reaction between 1-chloro-4-methyl-3-pentanone (IV) (5) and *N*-methylbenzylamine, according to the procedure described for the preparation of 1-benzylmethylamino-3-hexanone (6), afforded 1-benzylmethylamino-4-methyl-3-pentanone (V) with an excellent yield. Its transformation into the secondary amine VI required for the Mannich condensation was carried out by hydrogenolysis of the corresponding hydrochloride using palladium on charcoal as catalyst. Condensation between *p*-chlorobenzaldehyde and the amino ketone hydrochloride VI in presence of an equimolecular amount of *p*-toluenesulfonic acid in benzene-toluene, with simultaneous removal by azeotropic distillation of water formed, afforded the

0022-152X/81/010047-08$02.25

Table I

Compound No.	Ir (cm^{-1}) $C=CH_2$	M.p. °C (solvent) (a)	Chemical Shift in Deuteriochloroform (δ values) (b) $C-CH_3$	$N-CH_3$	$=CH_2$	Ar-H	C_2-H
Ia	1645 (c)	-------	0.90 s eq 1.09 s ax	2.00 s	4.67 s	6.51 s	2.56 s
Ia·HCl	1650 (d)	249-251 (A)	1.05 s eq 1.52 s ax	2.61 d J = 5 Hz	5.02 s	6.48 d 7.62 d	3.65 d J = 10 Hz
Ib	1650 (c)	-------	0.86 s eq 1.02 s ax	1.92 s	4.69 s	7.25 s	2.65 s
Ib·HCl	1647 (d)	257-259 (A-E)	0.98 s eq 1.44 s ax	2.56 d J = 5 Hz	5.00 s	7.36 m 3H 8.20 m 1H	3.85 d J = 10 Hz
IIa	1630 (d)	-------	1.24 s (6H)	2.19 s	4.71 s	6.51 s	2.87 s
IIa·HCl	1635 (d)	208-210 (A)	1.18 b 1.42 s	2.81 d J = 5 Hz	5.14 q 5.21 s	6.94 s	4.00 d J = 10 Hz
IIb	1636 (c)	-------	1.22 s (6H)	2.12 s	4.71 s	7.23 b	2.90 s
IIb·HCl	1640 (d)	209-211 (A-E)	1.16 b 1.48 s	2.85 d J = 5 Hz	5.13 q 5.21 s	7.40 d 7.70 d	4.33 d J = 10 Hz

(a) Solvents: A = acetone; E = ether. (b) Abbreviations: s = singlet, d = doublet, m = multiplet, b = broad singlet, q = quartet. (c) Sodium chloride. (d) Potassium bromide.

piperidone VIIb. Its ir spectrum shows an absorption at 1710 cm^{-1} due to the carbonyl group. In its nmr spectrum singlets are observed at δ 2.95, 2.02, 1.05, and 0.85 for the axial proton in the 2-position, the *N*-methyl group and the axial and equatorial methyl groups, respectively, in the 3-position of the heterocyclic ring. These data of the unequivocally prepared piperidone VIIb are different from the ones described by Jacobson (3) (δ 3.00, methine proton; δ 2.18, *N*-methyl group; and δ 1.60 and 1.38, *C*-methyl groups) for the ketone obtained by ozonolysis of the methylene derivative IIb, to which he attributed a 2-(*p*-chlorophenyl)-1,3,3-trimethyl-4-piperidone structure.

The Wittig reaction between piperidone VIIb and triphenylmethylenephosphorane affords 2-(*p*-chlorophenyl)-1,3,3-trimethyl-4-methylenepiperidine (Ib) in good yield (7). Its hydrochloride shows a melting point, 257-259°, different from the previously reported one (209-211°) for the compound IIb obtained in the Stevens rearrangement (3). Its spectroscopic data are also different from those of the rearrangement product (Table I).

Similarly, from 3,4,5-trimethoxybenzaldehyde and aminoketone hydrochloride VI we have prepared 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (VIIa) (8), identical in all its aspects to the one we had previously obtained (1) by Dieckmann cyclization and that was transformed (1) into the methylenepiperidine Ia.

The data of Table I show conclusively that the previously made assignments for the rearrangement products IIa (2) and IIb (3) are incorrect, and that these compounds do not have a 2-aryl-1,3,3-trimethyl-4-methylenepiperidine structure.

Thence we intended to elucidate the structure of compounds IIa and IIb, whose preparation we reproduced through Stevens rearrangement of tetrahydropyridinium salts IIIa (2) and IIIb (3), respectively, with identical results to the ones previously described (9).

Structural Elucidation of the Rearrangement Products IIa and IIb.

a).

The mass spectra of these compounds (Table III) show parent peaks at m/e 305 and 249, respectively, which agrees with those of the synthetically prepared 2-aryl-1,3,3-trimethyl-4-methylenepiperidines Ia and Ib. This, together with the results from the elemental analysis (Table V) of compounds I and II show them to be isomeric structures.

b).

In the ir spectra, IIa and IIb show an absorption at 1630 and 1636 cm^{-1}, respectively, for a carbon-carbon double bond which, together with the absorptions at 3083 and 888 cm^{-1}, indicates the presence of a terminal methylene group. This grouping is also observed in the nmr spectrum as a signal at δ 4.71 due to the two olefinic protons. In the hydrochloride this signal is displaced at lower fields and, owing to the magnetic nonequivalence of the two protons, it splits in a singlet and a quartet (J = 1.2 Hz, allylic coupling with the higher field methyl group, proved by spin-decoupling experiments).

c).

The aromatic region in the nmr spectrum of compound IIa presents a singlet for two protons at δ 6.51, indicating therefore a tetrasubstituted aromatic ring. On this account we must refuse the possibility of this compound coming from a Sommelet-Hauser reaction (10), which would yield a pentasubstituted aromatic ring. Similarly, compound IIb has four aromatic protons (disubstituted benzene).

d).

The singlet at δ 2.19 (IIa) and δ 2.12 (IIb) point out the existence of an *N*-methyl group which corresponds to a tertiary amine because of the magnitude (11) of the paramagnetic shift (~0.6 ppm) observed in the nmr spectra of the respective hydrochlorides.

e).

Both compounds display a singlet (δ 2.87 for IIa and δ 2.90 for IIb) for a methine proton which, owing to its chemical shift and multiplicity, is assigned to the one of the α-position regarding a nitrogen atom, an aryl group and a tetrasubstituted carbon atom. This assignment agrees with the fact that in the hydrochloride these signals are paramagnetically shifted at δ 4.00 and δ 4.33, respectively, and appear as doublets (J = 10 Hz) because of its coupling with the N^+-H. Thus, on irradiating at δ 11.8 (N^+-H signal of IIb.HCl) the δ 4.33 doublet collapsed to a singlet, confirming the presence of an α-amino group.

f).

In the nmr spectra of both IIa and IIb, a singlet for two *C*-methyl groups (δ 1.24 and δ 1.22, respectively) is observed. In the hydrochloride these signals are split into two singlets, one of them slightly shielded (Δδ = 0.06 ppm) and the other moderately deshielded (Δδ = 0.18 ppm for IIa; 0.26 ppm for IIb) in relation to the base (Table I). These observations discard the existence of a 3,3-dimethylpiperidine moiety since in these systems there is a remarkable chemical shift difference between the axial and equatorial methyl groups on 3-position, caused by the deshielding effect of the nitrogen lone pair (12). Furthermore, in these systems a noteworthy downfield shift in the hydrochloride with regard to the base is observed (12), this effect being higher for the C_3-CH_3 axial group (Δδ ~ 0.4 ppm) than for the equatorial one (Δδ ~ 0.15 ppm) (13).

g).

Finally, a complex group of signals in the δ 1.4-3.4 region is observed. Its integration shows them to correspond to four protons and its chemical shift and multiplicity is characteristic of protons belonging to a N-CH_2-CH_2 grouping in a cyclic system.

Nevertheless, the key for the structural assignment was given by the double bond catalytic hydrogenation of IIa and IIb. In either case only one compound was obtained (VIIIa and VIIIc, respectively). Spectroscopic data point out the disappearance of the double bond, while its nmr spectrum (Table II) shows a singlet at δ 1.03 due to only one *C*-methyl group and two doublets (J = 6 Hz) due to two *C*-methyl groups. Moreover, we can observe two singlets due to *N*-methyl and *N*-methine groups, respectively, the latter adjacent to an aryl group and a quaternary carbon atom. In the case of IIb the reduction of the double bond is accompanied by the hydrogenolysis of the C-Cl bond as we can observe by analysis (Table V), mass spectra (Table III), and integration of the aromatic region signals in the nmr spectrum (14).

The multiplicity of the *C*-methyl signals can only be interpreted considering that during the catalytic hydrogenation an isopropyl group whose methyl groups are magnetically nonequivalent is formed (15). This implies that the double bond of the methylene derivatives II belongs to an isopropenyl group. In the compound VIIIa

Table II

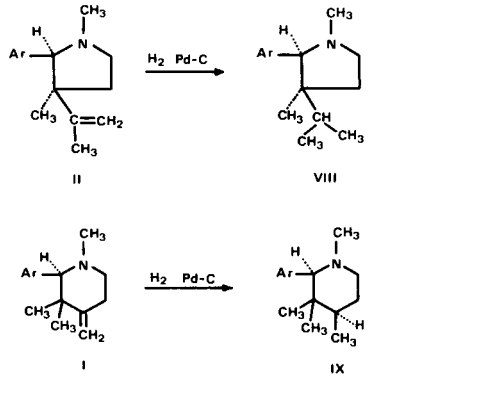
Chemical Shifts in Deuteriochloroform (δ values) (a)

Compound No.	CH-CH_3	C-CH_3	N-CH_3	C_2-H	Ar-H	O-CH_3
VIIIa	0.37d J = 6 Hz 0.83d J = 6 Hz	1.03 s	2.17 s	2.88 s	6.53 s	3.80 s
VIIIa·HCl	0.20d J = 6 Hz 0.88d J = 6 Hz	1.18 s	2.77 d J = 5 Hz	3.75 (b)	6.40 s 1H 7.00 b 1H	3.90 s
VIIIc	0.30d J = 6 Hz 0.80d J = 6 Hz	1.03 s	2.17 s	3.00 s	7.23 s	-----
VIIIc·HCl	0.27 (c) 0.85d J = 6 Hz	1.30 s	2.65 s	4.10 s	7.40 b	-----
IXa	0.94b	0.68 s eq 0.90 s ax	2.02 s	2.65 s	6.52 b (d)	3.80 s
IXa·HCl	1.00d J = 6 Hz	0.85 s eq 1.23 s ax	2.52 d J = 5 Hz	3.73 b	6.33 s 1H 7.40 s 1H	3.85 s 6H 3.98 s 3H
IXc	0.90d J = 6 Hz	0.63 s eq 0.77 s ax	1.89 s	2.52 s	7.13 s	-----
IXc·HCl	1.00d J = 6 Hz	0.80 s eq 1.16 s ax	2.52 d J = 5 Hz	3.92 d J = 10 Hz	7.35 m 3H 8.00 m 1H	-----

(a) Abbreviations: s = singlet, d = doublet, b = broad signal, m = multiplet. (b) Partially masked signal. (c) Deformed doublet. (d) Base width 36 Hz.

the presence of the isopropyl group has been confirmed by spin-decoupling experiments since on irradiating at δ 1.5 the doublets at δ 0.83 and δ 0.37 simultaneously become singlets. The appearance of a methyl group at abnormally high fields (δ 0.37 in VIIIa, δ 0.30 in VIIIc) for an isopropyl group points out that in the preferred conformation this methyl group is shielded by the aromatic nucleus (16).

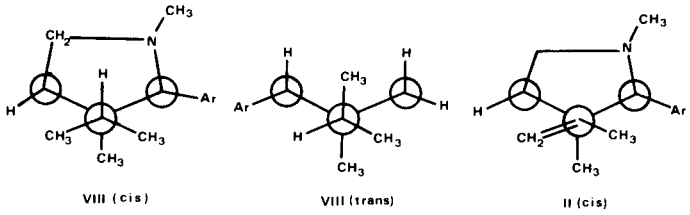
The precedent spectroscopic data are only compatible with 2-aryl-3-isopropyl-1,3-dimethylpyrrolidine systems (Scheme III) and therefore the structure of the rearrangement products IIa and IIb is established as 3-isopropenyl-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine and 2-(*p*-chlorophenyl)-3-isopropenyl-1,3-dimethylpyrrolidine, respectively.



Scheme III

On the other hand, as expected for the 4-methylenepiperidine systems Ia and Ib, catalytic hydrogenation of these compounds (Scheme III) afforded tetramethylpiperidines (IXa and IXc, respectively) whose nmr spectra (Table II) show two singlets for the methyl groups in the 3-position and only one doublet for the C-4 equatorial methyl group. The stereochemical assignment of this methyl was deduced from its multiplicity as a doublet deformed by virtual coupling (17), a fact that in cyclic systems such as IX is generally observed when the methyl substituent is equatorial (18).

For the stereochemical assignment of the pyrrolidines VIIIa and VIIIc we must consider Newman projections through the 3-pyrrolidine and the central isopropyl carbon atoms in the three staggered conformations corresponding to the *cis* and *trans* isomers. The most stable conformation for the *cis* isomer (Scheme IV) is the one having an hydrogen atom in the 1,3-interaction region with the ring where both isopropyl methyl groups show clearly different environments, one being strongly affected by the shielding effect of the aromatic ring. This explains the non-equivalence of the methyl groups and the appearance of one of them at exceptionally high fields. On the other hand, in the most stable conformation of the *trans* isomer (lacking methyl-phenyl type 1,3-interactions) none of the isopropyl methyl groups falls within the diamagnetic screening zone of the benzene nucleus. In this case the observed signal at δ 0.3-0.4 is not explainable at all despite the expected magnetic nonequivalence of the two isopropyl methyl groups. Thence, a phenyl-isopropyl *cis* relation is assigned to the hydrogenation products VIII.

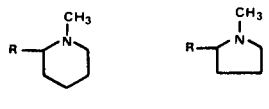


Scheme IV

This stereochemical assignment also explains the appearance of only one singlet at δ 1.2-1.3 for the two *C*-methyl groups in the nmr spectra of rearrangement products IIa and IIb. The allylic methyl group appears at abnormally high fields (19) due to the shielding effect of the aryl group, in a *cis* position with regard to the isopropenyl radical (Scheme IV). This signal collapses casually with the singlet corresponding to the methyl at C_3. The assignment of the methyl groups in the corresponding hydrochlorides (Table I) has been achieved by spin decoupling experiments since the one appearing at higher fields is coupled (allylic coupling, J = 1.2 Hz) to one of the olefinic protons.

Finally, in accordance with the presence of a pyrrolidine nucleus and not of a piperidine one, the signal of the *N*-methyl group in the nmr spectrum of compounds IIa (δ 2.19) and IIb (δ 2.12) appears at lower fields than in 2-aryl-*N*-methylpiperidines Ia (δ 2.00) and Ib (δ 1.92). This agrees with: i) the larger chemical shift of a *N*-methyl group in *N*-methylpyrrolidines than in *N*-methylpiperidines (11); and ii) with the fact that an *N*-methyl group in pyrrolidine systems are less shielded by an adjacent aryl group than in piperidine ones (Scheme V) (20).

Chemical Shifts in Deuteriochloroform (δ values)



R=H	2.21	2.33	Ref. 11
R=3-Pyridyl	1.97	2.15	Ref. 11

Scheme V

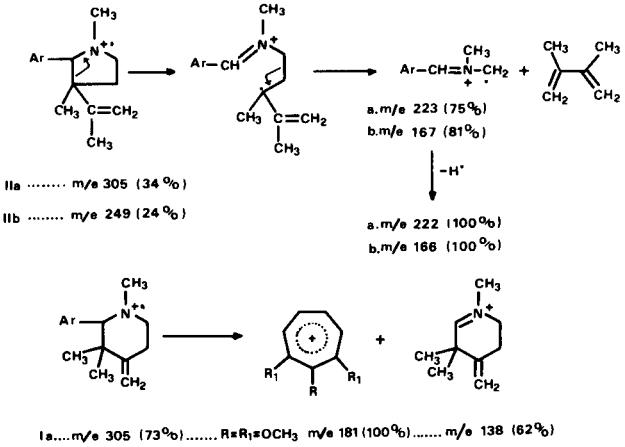
Table III

Mass Spectral Data

Ia	m/e:	305 (M^+)	290	262	247	231	194	181	179	138	124		
	I%:	73	27	23	11	40	86	100	20	62	20		
Ib	m/e:	251	249 (M^+)	234	206	171	168	166	154	152	140	138	127	125
	I%:	9	25	23	13	11	12	24	12	22	12	100	12	37
IIa	m/e:	305 (M^+)	224	223	222	208	192	181						
	I%:	34	9	75	100	42	13	10						
IIb	m/e:	251	249 (M^+)	169	168	167	166	132	125					
	I%:	8	24	27	34	81	100	17	22					
VIIIa	m/e:	307 (M^+)	223	222	208	192								
	I%:	12	84	100	42	11								
VIIIc	m/e:	217 (M^+)	133	132	117	91								
	I%:	13	46	100	13	12								

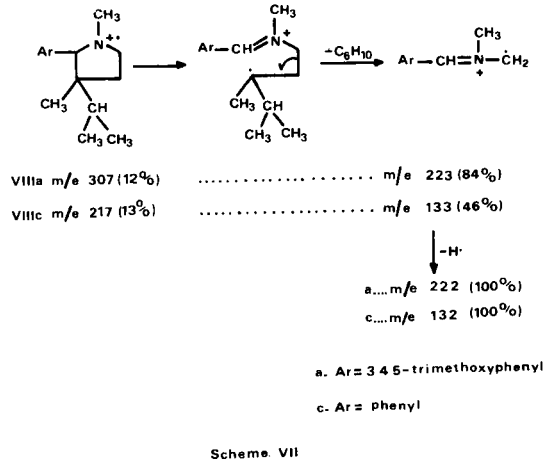
The mass spectra (Table III) and the ^{13}C nmr (Table IV) data of the rearrangement products II and of the corresponding hydrogenation compounds VIII confirm the proposed structures, *cis*-2-aryl-3-isopropenyl-1,3-dimethylpyrrolidine and *cis*-2-aryl-3-isopropyl-1,3-dimethylpyrrolidine, respectively.

Scheme VI depicts the more significant fragmentations of compounds IIa and IIb (3) that exhibit a common fragmentation pattern. In contrast, the 4-methylenepiperidines I upon electron impact undergo different fragmentation processes affording characteristic fragments for the corresponding tropylium ion and for $C_9H_{16}N$ at m/e 138 coming from the cleavage of the C_2-Ar bond. The fact that in the rearrangement products II the abundance of the tropylium ion was only 10-20% relative to that of the base peak shows clearly an easy loss of 2,3-dimethylbutadiene in accordance with a 3-isopropenyl-3-methylpyrrolidine structure.



Scheme VI

The most characteristic fragmentations of the hydrogenation products VIIIa and VIIIc (Scheme VII) can be similarly explained.



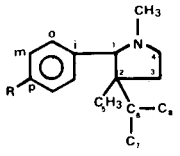
Scheme VII

The assignment of the signals in the ^{13}C nmr spectra (Table IV) have been made on the basis of its multiplicity in the off-resonance decoupled spectra and by comparison with the chemical shift values of *N*-methylpyrrolidine (21) and nicotine (22) (as an example of 2-arylpyrrolidine) applying the appropriate additivity values (23). The chemical shift values for the carbon atoms of the isopropenyl radical are in accordance with the ones observed for limonene and carvone (24). On the other hand, in compound VIIIc the two isopropyl methyl groups are, as in the ^1H nmr spectrum, nonequivalent (25) with a chemical shift difference of 0.7 ppm.

The structures of 2-aryl-3-isopropenyl-1,3-dimethylpyrrolidine we propose for the methylenederivatives II obtained by the Stevens rearrangement of *N*-benzyltetrahydropyridinium salts IIIa and IIIb can be interpreted by the mechanisms postulated for this type of reactions (10,26). The treatment of these salts with a strong base affords the ylide X which, according to the process indicated in Scheme VIII, evolves opening the

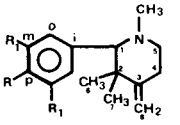
Table IV

Carbon-13 Chemical Shifts (a)



IIb R=Cl
VIIIc R=H

Compound	1	2	3	4	5	6	7	8
IIb	81.58	51.67	37.21	54.66	21.75	149.07	27.20	112.37
VIIIc	82.80	48.90	37.10	54.50	23.00	32.60	18.20	18.90
	ipso	*o*	*m*	*p*	$N\text{-}CH_3$			
IIb	138.68	127.69	129.81	132.52	41.04			
VIIIc	141.30	127.70	129.30	126.80	41.30			

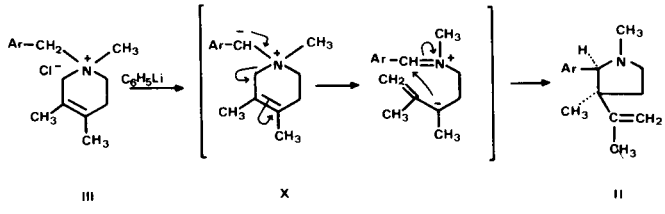


Ia. R_1=R=OCH_3
Ib. R_1=H ; R=Cl

	1	2	3	4	5	6	7	8
Ia	80.10	40.20	154.90	32.90	58.40	22.90	25.60	105.30
Ib	79.10	40.20	154.50	32.80	58.40	22.60	25.40	105.60
	ipso	*o*	*m*	*p*	$O\text{-}CH_3$	$O\text{-}CH_3$	$N\text{-}CH_3$	
Ia	137.40	107.60	152.50	136.60	56.20	60.90	45.20	
Ib	138.60	127.70	131.40	132.80	----	----	45.20	

(a) The chemical shifts are given in ppm downfield from TMS.

tetrahydropyridine ring and forming an allylic carbanion (27). Its cyclization by allylic attack on the resulting iminium salt leads to the 2-arylpyrrolidine system. Therefore, in accordance with the nomenclature adopted for these reactions (26) this process is a Stevens [3,2] rearrangement.



III X II

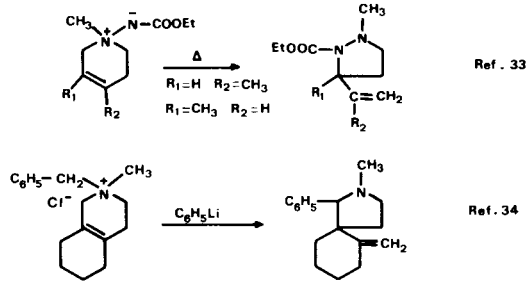
a. Ar= 3 4 5-trimethoxyphenyl

b. Ar= p-chlorophenyl

Scheme VIII

It must be pointed out that the pyrrolidines II come from a benzylide, a fact rather unusual in the Stevens rearrangement of 1-benzyl-1,2,5,6-tetrahydropyridinium salts where the major products are 2-benzyltetrahydropyridines deriving from an allylic ylide formed in the first step of the process (29). Nevertheless, the preferential formation of a benzyl ylide in the Stevens rearrangement of other allylbenzylammonium (30) and allylbenzylsulfonium (31) salts has been described.

Stevens [3,2] type processes, as the ones observed with the ammonium salts III, have been described regarding several ammonium and sulfonium salts (30-32), where the basic treatment causes the allylic migration of an allyl group from the positively charged heteroatom to an adjacent carbon atom on which the ylide was initially formed. Nevertheless, the processes more related to the ones we have described in this paper are those depicted in Scheme IX, which imply a ring contraction formally identical to the one that affords the compounds IIa and IIb (33) (34).



Ref. 33

Ref. 34

Scheme IX

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-24 B Spectrometer (60 MHz, tetramethylsilane at δ 0.0 ppm as internal standard) with deuteriochloroform as a solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). The ^{13}C nmr spectra were recorded on a Varian CFT-20 spectrometer. Infrared spectra were determined on a Perkin-Elmer model 577 Spectrophotometer. The mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Elemental analyses were performed by Instituto de Química Orgánica Aplicada de Cataluña, Barcelona.

1-Benzylmethylamino-4-methyl-3-pentanone (V).

A solution of *N*-methylbenzylamine (159 g., 1.32 mole) in 200 ml. of dry ether was gradually added to a stirred ice-cooled solution of 90 g. (0.66 mole) of 1-chloro-4-methyl-3-pentanone (IV) (5) in 500 ml. of dry ether. The cooling was removed and the mixture was stirred at 30° for 9 hours. The precipitate formed was filtered off and washed with ether. The combined ethereal solutions were washed twice with 2*N* sodium hydroxide

Table V

Analyses

Compound	M.p. °C (a)	Formula	Carbon %		Hydrogen %		Nitrogen %		Chlorine %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Ib·HCl	257-259	$C_{15}H_{21}Cl_2N$	62.93	62.85	7.39	7.43	4.89	4.81	24.77	24.75
V·HCl	152-153	$C_{14}H_{22}ClNO$	65.74	65.79	8.67	8.65	5.47	5.50	13.86	13.80
VI·HCl	108-109 (b)	$C_7H_{16}ClNO$	50.75	50.68	9.73	9.75	8.45	8.44	21.40	21.60
VIIa·HCl	247-248	$C_{17}H_{26}ClNO_4$	59.38	59.15	7.62	7.75	4.07	4.15	10.31	10.52
VIIb·HCl	227-229	$C_{14}H_{19}ClNO$	58.34	58.40	6.64	6.83	4.86	4.62	24.60	24.62
VIIIa·HCl	191-192	$C_{18}H_{30}ClNO_3$	62.87	62.73	8.79	8.91	4.07	4.09	10.31	10.36
VIIIc·HCl	176-177	$C_{15}H_{24}ClN$	70.98	70.85	9.53	9.66	5.52	5.64	13.96	13.93
IXa·HCl	220-222	$C_{18}H_{30}ClNO_3$	62.87	62.79	8.79	8.91	4.07	4.21	10.31	10.47
IXc·HCl	270-271	$C_{15}H_{24}ClN$	70.98	70.73	9.53	9.24	5.52	5.23	13.96	13.83

(a) Recrystallized from acetone. (b) Hygroscopic.

and dried over potassium carbonate. After evaporation of the solvent 135 g. (93%) of V were obtained; ir (chloroform): 1705 cm^{-1}; nmr: 1.05 (d, 6H, J = 7 Hz, C-CH_3), 2.15 (s, 3H, N-CH_3), 2.65 (s, 4H, CH_2), 3.45 (s, 2H, CH_2-Ar), 7.25 (s, 5H, Ar-H). Hydrochloride: ir (potassium bromide): 1705 cm^{-1} (C=O); nmr: 1.13 (d, 6H, J = 6 Hz, C-CH_3), 2.70 (s, 3H, N-CH_3), 3.30 (b, 4H, CH_2), 4.30 (s, 2H, CH_2-Ar), 7.55 (m, 5H, Ar-H).

Amino ketone V was also obtained in 97% yield by heating at 100° for 16 hours in the presence of anhydrous potassium carbonate (15.3 g., 0.1 mole) a vigorously stirred mixture of chloro ketone IV (15 g., 0.1 mole) and *N*-methylbenzylamine (13.4 g., 0.1 mole).

4-Methyl-1-methylamino-3-pentanone Hydrochloride (VI).

A suspension of V hydrochloride (10 g., 0.04 mole) in 50 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (0.5 g.). When the absorption ceased, the catalyst was filtered off and the clear solution evaporated to give 5.4 g. (84%) of the hydrochloride VI. An analytical sample recrystallized from acetone melted at 108-109° (hygroscopic); ir (potassium bromide): 1705 cm^{-1} (C=O); nmr: 1.15 (d, 6H, J = 6 Hz, C-CH_3); 2.70 (s, 3H, N-CH_3), 3.22 (b, 4H, CH_2). The hydrochloride VI was treated with an aqueous solution of potassium carbonate and extracted with ether to give the free base; ir (chloroform): 1705 cm^{-1}; nmr: 1.07 (d, 6H, J = 6 Hz, C-CH_3), 2.35 (s, 3H, N-CH_3), 2.70 (m, 4H, CH_2).

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

To a solution of 9.8 g. (0.05 mole) of 3,4,5-trimethoxybenzaldehyde in 200 ml. of anhydrous benzene, 9.5 g. (0.05 mole) of *p*-toluenesulfonic acid monohydrate were added. Then a suspension of 9.2 g. (0.05 mole) of the hydrochloride VI in 100 ml. of anhydrous toluene was slowly added and the mixture was stirred at reflux overnight, with removal of water by a Dean-Stark trap. After removing the solvent an oil was obtained which was dissolved in 20% ethanolic potassium hydroxide and stirred at 40° for thirty minutes. The inorganic precipitate was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 2*N* hydrochloric acid and extracted with benzene. The aqueous layer was basified by addition of solid potassium carbonate (ice cooling), the free base being extracted with ether. Drying and evaporation of organic layer followed by concentration *in vacuo* gave 9.5 g. (62%) of VIIa; ir (chloroform): 1705 cm^{-1} (C=O); nmr: 0.95 (s, 3H, C-CH_3 eq), 1.14 (s, 3H, C-CH_3 ax), 2.09 (s, 3H, N-CH_3), 2.90 (s, 1H, C_2-H), 3.85 (s, 9H, O-CH_3), 6.54 (s, 2H, Ar-H). Hydrochloride: ir (potassium bromide): 1730 cm^{-1} (C=O); nmr: 1.00 (s, 3H, C-CH_3 eq), 1.60 (s, 3H, C-CH_3 ax), 2.65 (d, 3H, J = 4 Hz, N-CH_3), 3.80 (s, 3H, O-CH_3), 3.85 (s, 6H, O-CH_3), 4.00 (b, 1H, C_2-H), 6.40 (b, 1H, Ar-H), 7.60 (b, 1H, Ar-H).

2-(*p*-Chlorophenyl)-1,3,3-trimethyl-4-piperidone (VIIb).

Operating in the same manner from 6.7 g. (0.05 mole) of *p*-chlorobenzaldehyde in 200 ml. of anhydrous benzene, 9.1 g. (0.05 mole) of *p*-toluenesulfonic acid monohydrate and 8 g. (0.05 mole) of the hydrochloride VI suspended in 100 ml. of anhydrous toluene an oily residue was obtained and purified by column chromatography through a silica gel column. On elution with benzene 5 g. (41%) of VIIb were separated; ir (chloroform): 1710 cm^{-1} (C=O); nmr (carbon tetrachloride): 0.85 (s, 3H, C-CH_3 eq), 1.05 (s, 3H, C-CH_3 ax), 2.02 (s, 3H, N-CH_3), 2.95 (s, 1H, C_2-H), 7.20 (s, 4H, Ar-H). Hydrochloride: ir (potassium bromide): 1725 cm^{-1} (C=O); nmr: 1.00 (s, 3H, C-CH_3 eq), 1.50 (s, 3H, C-CH_3 ax), 2.72 (d, 3H, J = 4 Hz, N-CH_3), 4.56 (d, 1H, J = 10 Hz, C_2-H), 7.40 (m, 3H, Ar-H), 8.15 (m, 1H, Ar-H).

2-(*p*-Chlorophenyl)-1,3,3-trimethyl-4-methylenepiperidine (Ib).

Methyltriphenylphosphonium bromide (13.5 g., 38 mmoles) was slowly added, under nitrogen atomosphere, to a solution of 23 ml. (40 mmoles) of 1.6*M* ethereal *n*-butyllithium and 50 ml. of anhydrous ether, the mixture being stirred for 3 hours at room temperature. A solution of 6.8 g. (26 mmoles) of piperidone VIIb in 100 ml. of freshly distilled tetrahydrofuran was added and the mixture was refluxed for 24 hours. The precipitate was removed by filtration and washed with ether. The ethereal extracts were put together, washed with water until neutral reaction and dried over calcium chloride. After evaporation of the solvent an oil was obtained which was purified by column chromatography through silica gel. On elution with hexane-benzene 3/7, 6 g. (92%) of Ib were obtained.

cis-3-Isopropyl-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine (VIIIa).

A solution of 230 mg. (0.75 mmole) of IIa in 100 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (70 mg.). When the absorption ceased, the catalyst was filtered off and the clear solution evaporated to give 200 mg. of an oil which was identified as VIIIa.

cis-1,3,3,4-Tetramethyl-2-(3,4,5-trimethoxyphenyl)piperidine (IXa).

Operating in the same manner, from 0.4 g. (1.2 mmole) of 4-methylenepiperidine Ia, 300 mg. of IXa were obtained.

cis-3-Isopropyl-1,3-dimethyl-2-phenylpyrrolidine (VIIIc).

A solution of 1 g. (4 mmoles) of IIb in 100 ml. of absolute ethanol and 10 ml. of triethylamine was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (200 mg.). When the absorption ceased, the catalyst was filtered off and the clear solution evaporated to give 0.65 g. of VIIIc.

cis-1,3,3,4-Tetramethyl-2-phenylpiperidine (IXc).

Operating in the same manner from 0.3 g. (1.2 mmole) of 4-methylenepiperidine Ib, 260 mg. of IXc were obtained.

Acknowledgment.

We acknowledge to Dr. R. Faure of the Université d'Aix-Marseille III for running the carbon-13 nmr spectra.

REFERENCES AND NOTES

(1) J. Bosch, A. Domingo, F. López and M. Rubiralta, *J. Heterocyclic Chem.*, **17**, 241 (1980).

(2) J. Bosch, J. Canals and R. Granados, *ibid.*, **12**, 1117 (1975).

(3) A. E. Jacobson, *J. Org. Chem.*, **31**, 1569 (1966).

(4) The formation of a compound of similar structure has been reported (3) in the Stevens rearrangement of 1-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium chloride.

(5) M. Sharma, U. R. Ghatak and P. C. Dutta, *Tetrahedron*, **19**, 985 (1963).

(6) G. Büchi, S. T. Gould and F. Naf, *J. Am. Chem. Soc.*, **93**, 2492 (1971).

(7) The high yields obtained in the Wittig reaction on piperidones VIIa (1) and VIIb contrast with the ones reported for cyclohexanones; A. Maercker, *Org. React.*, **20**, 270 (1967).

(8) When the Mannich condensation took place in basic medium (*p*H 9-12) at different conditions of time and temperature (6,8a) autocondensation products of the β-amino ketone VI were obtained. In the runs with ethanol at reflux (8b) or ethanol-glacial acetic acid (8c) the starting products were recovered; (a) J. T. Wrobel and W. M. Golebiewski, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, 593 (1975); (b) C. R. Ganellin and R. G. W. Spickett, *J. Med. Chem.*, **8**, 619 (1965); (c) K. HohenloheOehringen, *Monatsch. Chem.*, **94**, 1222 (1963).

(9) Separation of IIb from the reaction mixture was better carried out by column chromatography than by fractionated distillation and successive recrystallizations of the hydrochloride as reported in the original work (3).

(10) S. H. Pine, *Org. React.*, **18**, 403 (1970).

(11) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).

(12) T. M. Moyenehan, K. Schofield, R. A. Y. Jones and R. A. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(13) This effect is observed in the 2-aryl-1,3,3-trimethyl-4-methylenepiperidines Ia and Ib. Thus, the value Δδ (salt-base) in Ia is 0.45 ppm for the axial methyl group and 0.14 ppm for the equatorial one (0.42 ppm and 0.13 ppm, respectively, in Ib).

(14) It is known how easily aryl halides undergo catalytic hydrogenolysis in basic medium; R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, p. 46 and 125. In the first catalytic hydrogenation assays on IIb carried out in neutral medium (ethanol) both reduction of the double bond and partial hydrogenolysis of the C-Cl bond were observed. In order to facilitate the study of hydrogenation products triethylamine was added to the ethanolic medium. In these conditions only compound VIIIc was obtained.

(15a) M. L. Martin and G. J. Martin, *Bull. Soc. Chim. France*, 2117 (1966); (b) M. van Gorkon and G. E. Hall, *Quart. Rev.*, **22**, 14 (1968). (c) W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975).

(16) Many cases have been reported where the chemical shift of the two methyl groups of an isopropyl radical is different due to a conformational preference and to a selective anisotropic effect by a neighboring phenyl group; (a) A. Reisse, D. Cagniant and P. Cagniant, *Bull. Soc. Chim. France*, 2110 (1969); (b) M. Kajart and L. Radics, *Chem. Commun.*, 784 (1967); (c) H. Kessler and B. Zeeh, *Tetrahedron*, **24**, 6825 (1968).

(17) Virtual coupling is observed in CH_A-CH_B-CH_3 type systems when J_{AB} is of the same order of magnitude as the chemical shift difference between H_A and H_B. Its presence is shown through the X_3 protons signal which is more complex and has an apparent coupling constant lower than usually; (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, New York, N.Y., 1972, p. 147; (b) A. F. Casy, "PMR Spectroscopy in Medicinal Chemistry", Academic Press, New York, N.Y., 1971, p. 204. (c) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(18) Under these circumstances the C-4 methine proton adopts an axial disposition that originates a coupling constant of high magnitude with the axial hydrogen of the adjacent position; (a) M. M. A. Hassan and A. F. Casy, *Org. Magn. Reson.*, **2**, 197 (1970); (b) A. F. Casy, *Tetrahedron*, **22**, 2711 (1966).

(19) The isopropenyl methyl signal in the nmr spectrum of limonene appears at δ 1.70. C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Vol. 1 45D (1974).

(20) In 2-aryl-*N*-methylpiperidine and 2-aryl-*N*-methylpyrrolidine systems, the aryl group is in a plane approximately at right angles to that of the heterocyclic ring, shielding therefore the N-CH_3 group. This effect is slightly smaller when dealing with a pentagonal pyrrolidine ring owing to the greater angle formed by the Ar-CH-N and the CH-N-CH_3 bonds. This contributes to increase the difference of chemical shift between the N-CH_3 groups of piperidine and pyrrolidine systems.

(21) D. G. Hawthorne, S. R. Johns and R. I. Willing, *Aus. J. Chem.*, **29**, 315 (1976).

(22) W. O. Crain, W. C. Wildman and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 990 (1971).

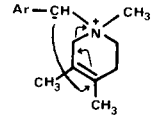
(23) E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", Verlag Chemie, Weinheim, 1978, p. 139 and 213.

(24) G. Englert, *Helv. Chim. Acta*, **58**, 2367 (1975).

(25a) J. I. Kroschwitz, M. Winkur, H. J. Reich and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 5929 (1969); (b) J. Dabrowski and A. Ejchat, *Org. Magn. Reson.*, **4**, 131 (1972); (c) A. Vigevani, *Org. Magn. Reson.*, **6**, 513 (1974).

(26) A. R. Lepley and A. G. Giumanini, "Mechanisms of Molecular Migrations", Vol. 3, B. S. Thyagarajan, Interscience, New York, N.Y., 1971, p. 297.

(27) In this paper we formulate the Stevens rearrangement as an ionic process of dissociation-recombination from a nitrogen ylide, mechanism which explains many of the results observed in these rearrangements. Nevertheless, the radical pair and the concerted mechanism also describe important aspects of these reactions (26,28). If the rearrangement is considered as a [2,3] sigmatropic process the evolution of the ylide X must be formulated as:



Scheme X

(28a) M. J. S. Dewar and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. I*, 1839 (1974); (b) W. D. Ollis, M. Rey and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 543 (1975); (c) S. H. Pine and J. Cheney, *J. Org. Chem.*, **40**, 871 (1975).

(29) This reaction constitutes the key step of a synthetic route to 6,7-benzomorphans. For a review see: D. C. Palmer and M. J. Strauss, *Chem. Rev.*, **77**, 1 (1977).

(30) C. L. Bumgardner, *J. Chem. Soc.*, **85**, 73 (1963).

(31) R. W. C. Cose, A. M. Davis, W. D. Ollis, C. Smith and I. O. Sutherland, *Chem. Commun.*, 293 (1969).

(32a) P. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 1289 (1967); (b) R. B. Bates and D. Feld, *Tetrahedron Letters*, 417 (1968); (c) B. M. Trost and R. LaRochelle, *ibid.*, 3327 (1968); (d) G. M. Blackburn, W. D. Ollis, J. D. Plackett, C. Smith and I. O. Sutherland, *Chem. Commun.*, 186 (1968); (e) J. E. Baldwin, R. E. Hackler and D. P. Kelly, *ibid.*, 538 (1968); (f) J. E. Baldwin and D. P. Kelly, *ibid.*, 899 (1968); (g) W. Kirmse and M. Kapps, *Chem. Ber.*, **101**, 1004 (1968); (h) V. Ceré, C. Paolucci, S. Pollicino, E. Sandri and A. Fava, *J. Org. Chem.*, **43**, 4826 (1978); (i) E. Vedejs, M. J. Arco, D. W. Powell, J. M. Renga and S. P. Singer, *ibid.*, **43**, 4831 (1978).

(33) T. Tsuchiya, H. Sashida and H. Sawanishi, *Chem. Pharm. Bull.*, **26**, 2880 (1978).

(34) R. Maeda and E. Ohsugi, *ibid.*, **16**, 897 (1968).