Reinvestigation of the Stevens Rearrangement of 1-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium Salts. II. Synthesis of 2-Aryl-3-isopropenyl-1,3-dimethylpyrrolidines

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cis-2-Aryl-3-isopropenyl-1,3-dimethylpyrrolidines IIa and IIb have been synthesized by an unambiguous way, thus confirming the structure of the methylene derivatives obtained as by-products in the Stevens rearrangement of 1-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium salts Ia and Ib. The synthesis is based on the acid-induced intramolecular cyclization between an iminium salt and the α-position of a ketal group. Thus, condensation between amino ketal XXI, prepared *via* Gabriel synthesis from 5-chloro-3-methyl-2-pentanone, and the appropriate aldehyde afforded imines XXI. Their treatment with dry hydrogen chloride followed by acid hydrolysis and methylation gave 3-acetylpyrrolidines IV, which were transformed into the isopropenyl derivatives II by reaction with methyl-lithium and further dehydration.

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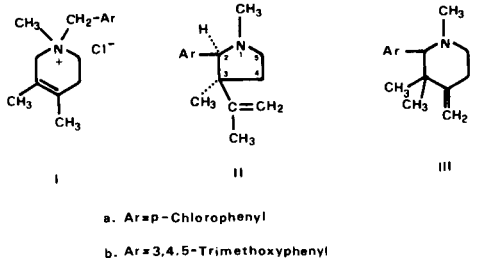
In a previous paper (1) we established that the methylene derivatives obtained as by-products in the Stevens rearrangement of 1-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium salts Ia (2) and Ib (3) have a *cis*-2-aryl-3-isopropenyl-1,3-dimethylpyrrolidine (II) structure and not a 2-aryl-1,3,3-trimethyl-4-methylenepiperidine (III) one as previously claimed (2,3). We attained this conclusion: i) by comparing the physical and spectroscopic data of rearrangement products IIa and IIb with those of authentic samples of 4-methylenepiperidines IIIa (1) and IIIb (1,4) prepared through unambiguous ways, and ii) by a detailed spectroscopic analysis (ir, ^{1}H nmr, ^{13}C nmr, ms) of compounds IIa, IIb and their hydrogenation products (1). Now, we wish to report the unequivocal synthesis of the rearrangement products IIa and IIb to confirm definitively the proposed structures.



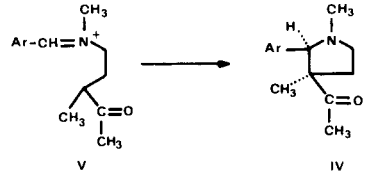
a. Ar=p-Chlorophenyl

b. Ar=3,4,5-Trimethoxyphenyl

Scheme I

There are some general methods for preparing 2-arylpyrrolidine systems. Thus, the thermal rearrangement of aryl cyclopropyl imines (5), widely used in alkaloid synthesis (6), involves the formation of C^5-N bond in the key step of the process. On the other hand, the intramolecular condensation of aryl 3-aminoalkyl ketones (7) followed by reduction of the resulting imine or iminium salt involves the formation of C^2-N bond in the key step of cyclization. Finally, Dieckmann cyclization of appropriate amino diesters affords 2-aryl-3-ethoxycarbonyl-4-pyrrolidones (8) by formation of pyrrolidine C^3-C^4 bond. These synthetic ways were considered unsuitable for our purposes because of the difficulty in attaining the required substitution both in the initial product and in the pyrrolidine system once the cyclization has been effected (9), and in controlling the *cis/trans* relation between the pyrrolidine C^2- and C^3-substituents.

Since 3-acetylpyrrolidines IV can be considered direct precursors of the rearrangement products II, we planned the synthesis of these systems by formation of C^2-C^3 bond through a Mannich type intramolecular condensation between an activated carbon atom and an iminium salt as V (Scheme II).



Scheme II

This cyclization has an additional interest because it will allow to verify if the observed stereoselectivity in the formation of compounds II by Stevens rearrangement is reproduced. As in the synthesis that we planned, the postulated mechanism for the rearrangement (1) implies the cyclization of a nucleophilic carbon atom upon an iminium salt.

For this purpose we have tried three different approaches that differ in the procedure employed for generating the required iminium salt. Two of them involve the oxidation of an appropriate *N*-benzyl-γ-aminoketone, either by direct treatment with mercuric acetate or through the *N*-oxide. In these cases, in order to evaluate if the procedure was suitable for the preparation of 2-arylpyrrolidines IIa and IIb, it was tried over a model com-

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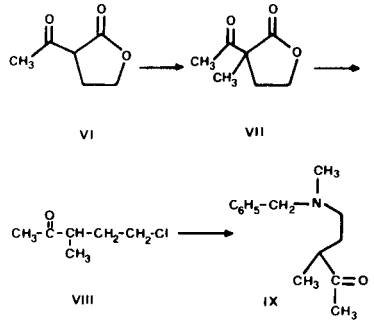
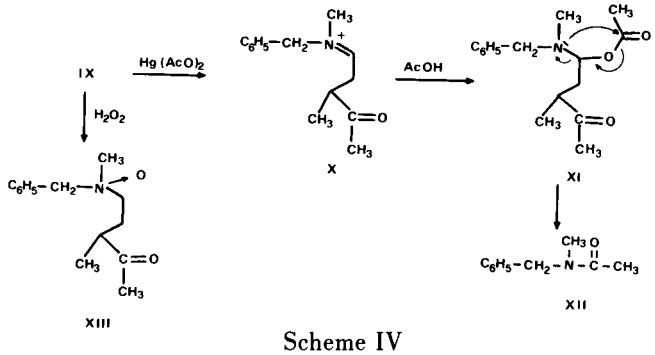
pound IX, synthetically more available, in which the aryl group was phenyl. The third approach to iminium salts of the V type consisted in the condensation between an aromatic aldehyde and a γ-aminoketone whose carbonyl group was protected in order to avoid intramolecular condensation reactions.



Scheme III

Aminoketone IX has been prepared from keto lactone VI following the reaction sequence depicted in Scheme III. The alkylation of VI with methyl iodide in the presence of anhydrous potassium carbonate in acetone (10) afforded the non-enolizable butyrolactone VII in 80% yield, higher than those described when the alkylation was carried out with other bases (11). Chloroketone VIII was obtained (11b-d) by distillation of VII with 10% hydrochloric acid, and it was transformed into the amine IX by reaction with *N*-methylbenzylamine in presence of anhydrous potassium carbonate.

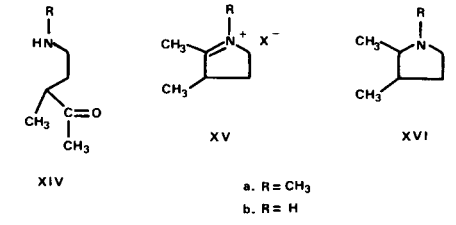
The oxidation of tertiary amines to iminium salts with mercuric acetate in acetic media (12) has been widely developed in alkaloid synthesis, since this salts can cyclize by an electrophilic attack upon an aromatic ring (13) or, as in the synthesis that we intend, upon the α-position of a carbonyl group (14). In our case, reaction of IX with an excess of mercuric acetate in refluxing diluted acetic acid took place with a quick oxidation as evidenced the formation of the expected amount of mercurous acetate. Nevertheless, after the precipitation of salts and mercury complexes with hydrogen sulfide, as usual in these reactions, amine IX was recovered (15). This result can be explained by considering that the initially formed iminium salt is reduced by hydrogen sulfide, thus preventing its cyclization (16). When the oxidation was carried out in glacial acetic acid (13e,g) in order to promote the cyclization before the hydrogen sulfide treatment, only *N*-benzyl-*N*-methylacetamide XII was isolated, indicating therefore the formation of the non conjugated iminium salt X (Scheme IV). The attack of acetate anion on X gives the acetoxy amine XI, which evolves towards the acetamide XII through a similar process to amine demethylation by Polonovski reaction (17).



Scheme IV

The modified (18) Polonovski reaction (17,19) has also been frequently applied to generate iminium salts (20) used as Mannich reagents (21). The *N*-oxide XIII, required to form an iminium salt of type V, has been prepared by oxidation of amine IX with hydrogen peroxide in ethanol. Nevertheless, when treated with trifluoroacetic anhydride under modified Polonovski reaction conditions (18) a complex mixture was obtained, in which no formation of type IV cyclization products could be detected, dissuading a further study.

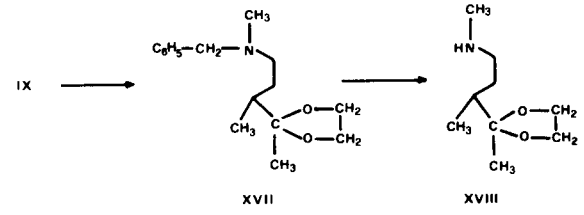
The above results prompted us to assay the preparation of the requisite type V iminium salt by condensation between an aromatic aldehyde and an appropriately functionalized amine. However, the amino ketone XIVa required for this process could not be used since γ-aminoketones undergo intramolecular cyclizations affording pyrrolines. Thus, hydrogenolysis in acid medium of *N*-benzylamine IX afforded, after absorption of one equivalent of hydrogen, the pyrrolinium salt XVa, which was further reduced to 1,2,3-trimethylpyrrolidine XVIa (22). Similarly, the primary amine XIVb cyclizes spontaneously, even in strong acid medium, to pyrroline hydrochloride XVb, as we have proved in the acid hydrolysis of phthalimido ketone XIX, whose preparation we describe further on.



Scheme V

We thought that these difficulties could be solved using the amine XVIII in which the carbonyl group is protected as its ethylene ketal. The presence of the ketal function was expected to constitute no inconvenience for the later Mannich cyclization, since it is known that ketal α-positions can act as nucleophilic centers in acylation (23) and halogenation (24) reactions. Similarly, processes bas-

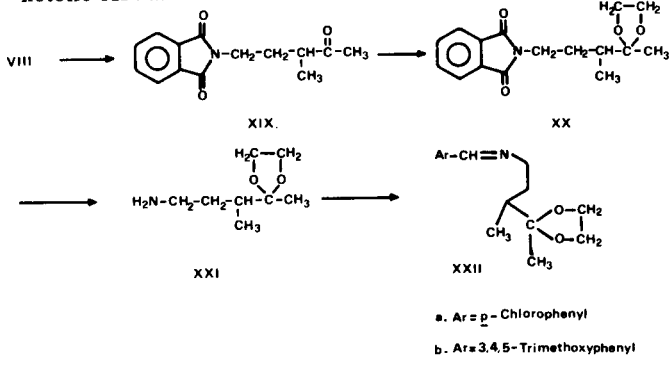
ed on acid-induced cyclizations of the α-carbon of ketal functions upon iminium salts have been frequently used in alkaloid synthesis (25). These reactions proceed through an enol ether as intermediate, since in acidic medium dioxolanes are in equilibrium with the corresponding open forms. Electrophilic attack of the iminium salt upon the resultant enol ether double bond promotes the cyclization (26).



Scheme VI

The preparation of amino ketal XVIII was carried out in excellent yields by ketalation of amino ketone IX with ethylene glycol in the usual conditions and further hydrogenolysis of the resultant benzylamine XVII (Scheme VI). This last reaction had to be effected over the base XVII in neutral medium instead of the hydrochloride, as usual in these reactions (27), because amino ketal XVIII is extremely sensitive to acids. Moisture traces in acid media transform it into the pyrrolinium salt XVa by ketal hydrolysis followed by intramolecular condensation (28).

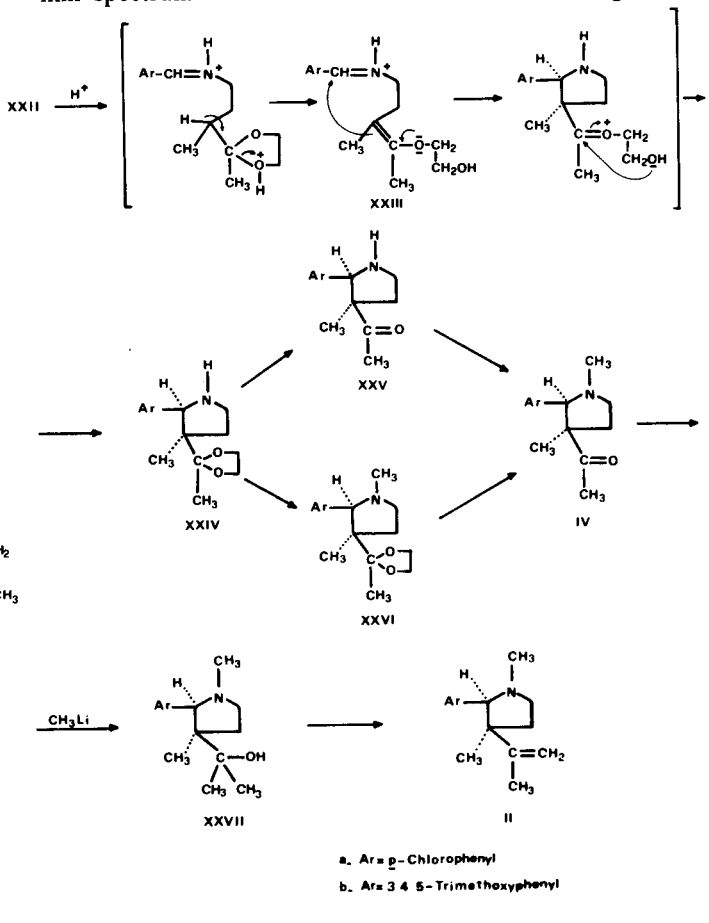
Mannich condensation between *p*-chlorobenzaldehyde and amino ketal XVIII was attempted under a variety of experimental conditions although 2-arylpyrrolidine IVa was never detected. When the reaction was carried out in glacial acetic acid and ethanol (29) the initial products were recovered, while in presence of anhydrous *p*-toluenesulfonic acid in anhydrous benzene at reflux (30) the pyrrolinium salt XVa was isolated together with the starting aldehyde and its ethylene ketal. This result is explained by transacetalation between *p*-chlorobenzaldehyde and amino ketal XVIII in the anhydrous acidic reaction medium followed by cyclization of the resultant γ-amino ketone XIVa.



Scheme VII

To circumvent the above difficulties we planned the formation of iminium salt Va-ethylene ketal by an alternative way involving the methylation of imine XXIIa, which was prepared by condensation between *p*-chlorobenzaldehyde and the primary amine XXI in anhydrous benzene (31). In turn, amine XXI was prepared from chloro ketone VIII, according to a sequence similar to the one used in the preparation of 3-amino-2-butanone ethylene ketal (32), by reaction with potassium phthalimide followed by ketalation and subsequent hydrazinolysis of the resultant phthalimido ketal XX (Scheme VII). Nevertheless, imine XXIIa was recovered unchanged when treated with methyl bromide or iodide under several conditions of time and temperature, and under pressure in a sealed tube.

Because of the difficulties encountered in the above approaches to iminium salts of type V or V-ethylene ketal our efforts were next directed toward the cyclization of imine XXIIa. It was satisfactorily attained by treating XXIIa with dry hydrogen chloride under strictly anhydrous conditions for 24 hours in refluxing ether-methylene chloride. The insoluble hydrochloride that precipitates from the reaction mixture afforded, after basification, 2-arylpyrrolidine XXIVa in 51% yield. In its nmr spectrum we can observe the absence of the signals



Scheme VIII

Table I

Spectroscopic Data

Compound No.	Ir (cm^{-1})	Nmr (δ values) (a,b) Ar-H	Ar-CH_2	OCH_2	N-CH_2	N-CH_3	O-C-CH_3	CH-CH_3
IX (c)	1710 (C=O) (d)	7.20 s	3.40 s	---	2.30 t	2.07 s	2.15 s	1.00 d J = 6 Hz
IX·HCl	1705 (C=O) (e)	7.40 m	4.20 s	---	3.00 t	2.68 s	2.15 s	1.18 d J = 6 Hz
XII	1630 (C=O) (e)	7.18 s	4.45 bs	---	---	2.80 s	2.00 s	---
XIII	1700 (C=O) (e)	7.45 m	4.43 s	---	2.9-3.2 m	3.00 s	2.15 s	1.20 d J = 6 Hz
XVII (c)	1070, 1155 (C-O) (d)	7.15 s	3.25 d 3.52 d J = 13 Hz	3.75 s	2.0-2.5 m	2.10 s	1.15 s	0.85 d J = 6 Hz
XVII·HCl	1070, 1155 (C-O) (f)	7.50 m	4.18 bs	3.90 s	2.9-3.4 m	2.70 bs	1.25 s	1.00 d J = 6 Hz
XVIII	——	---	---	3.85 s	2.4-2.8 m	2.42 s	1.22 s	0.93 d J = 6 Hz
XIX (c)	1700, 1770 (C=O) (f)	7.65 m	---	---	3.55 t	---	2.10 s	1.10 d J = 6 Hz
XX (c)	1695, 1768 (C=O (f)	7.65 m	---	3.82 s	3.64 t	---	1.18 s	1.05 d J = 6 Hz
XXI (c)	3360 (N-H) (d)	---	---	3.85 s	2.75 bt	---	1.20 s	0.95 d J = 6 Hz
XXIIa (c)	1640 (C=N) (d)	7.28 d, 2H J = 10 Hz 7.58 d, 2H J = 10 Hz	8.10 s (g)	3.80 s	3.55 bt	---	1.18 s	0.98 d J = 6 Hz
XXIIa·HCl	1680 (C=N) (f)	7.50 d, 2H J = 10 Hz 8.45 d, 2H J = 10 Hz	8.85 bs (g)	3.90 s	~4.00 (h)	---	1.23 s	1.02 d J = 6 Hz
XXIIb	1640 (C=N) (d)	6.90 s	8.10 s (g)	3.85 s	3.60 t	---	1.23 s	1.00 d J = 6 Hz

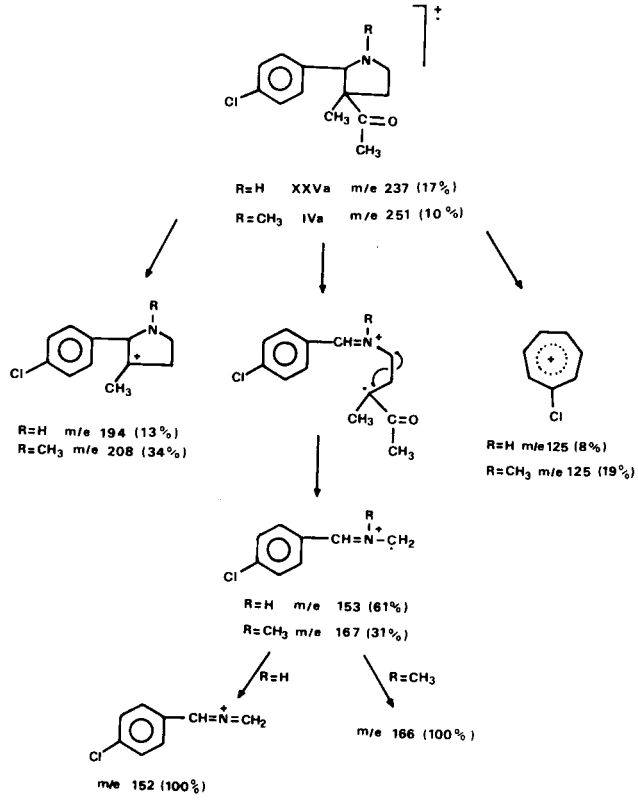
(a) Chemical shifts in deuteriochloroform solution unless otherwise indicated. (b) Abbreviations: s = singlet; d = doublet; t = triplet; m = multiplet; b = broad. (c) Nmr spectrum in carbon tetrachloride solution. (d) Ir spectrum in sodium chloride. (e) Ir spectrum in chloroform solution. (f) Ir spectrum in potassium bromide. (g) Ar-CH=N signal. (h) Masked.

corresponding to the N=CH (δ 8.10, singlet) and CH-CH_3 (δ 0.98, doublet) protons of imine XXIIa and the presence of a singlet at δ 1.35 for the methyl group in the 3 position of the pyrrolidine ring, pointing out that the cyclization has taken place. Other characteristic signals are a singlet at δ 0.87 due to the methyl group on the ketal carbon atom and a multiplet at δ 3.00-4.00 due to dioxolane ring protons.

The cyclization proceeds through the enol ether XXIIIa formed by opening the dioxolane ring, which undergoes an electrophilic attack by the iminium salt generated by protonation of the imine in the anhydrous acidic medium of the reaction (Scheme VIII).

When cyclization was effected on a sample of imine XXIIa impurified with *p*-chlorobenzaldehyde, 3-acetylpyrrolidine XXVa was directly obtained because of the aldehyde transacetalation with the starting imine or the initially formed pyrrolidine XXIVa. The presence of benzaldehyde ethylene acetal in the non aminated fraction coming from the reaction supports this interpretation.

The hydrolysis of ethylene ketal XXIVa with 20% hydrochloric acid at room temperature afforded 3-acetylpyrrolidine XXVa. Its ir spectrum shows absorptions at 3340 cm^{-1} and 1690 cm^{-1} corresponding to N-H and C=O groups, respectively. The nmr spectrum shows, as most



Scheme IX

Table II

Spectroscopic Data

Compound No.	Ir (cm^{-1})	Nmr (δ values) (a,b) Ar-H	C^2-H	N-CH_3	C^3-CH_3	O-C-CH_3
IVa	1700 (C=O) (c)	7.20 s	3.00 s	2.12 s	1.34 s	1.59 s
IVb	1695 (C=O) (d)	6.43 s	2.90 s	2.15 s	1.39 s	1.56 s
IVb·HCl	1690 (C=O) (e)	6.86 s	4.50 b	2.90 bs	---1.6-1.8 b---	
XXIVa·Picrate	---	7.40 s	4.37 dd	---	1.40 s	0.83 s
XXVa	3340 (N-H) (c)	7.20 s	3.85 s	---	1.40 s	1.60 s
	1690 (C=O)					
XXVa·HCl	1695 (C=O) (e)	7.28 s	4.40 s	---	1.45 s	1.70 s
XXVb	1685 (C=O) (c)	6.35 s	~3.90 (g)	---	1.40 s	1.58 s
XXVb·HCl	1695 (C=O) (e)	6.60 s	4.35 b	---	1.50 s	1.70 s
XXVIa (f)	---	7.15 s	2.85 s	2.04 s	1.22 s	0.80 s
XXVIa·Picrate	---	7.48 s	---	2.88 s	1.40 s	0.72 s
XXVIIa (f)	3100-3600 (O-H) (d)	7.25 bs	2.95 s	2.15 s	1.15 s	1.00 s
						0.55 s
XXVIIa·HCl	3140-3600 (O-H) (d)	7.40 m	4.35 d	2.90 d	1.30 s	1.30 s
			J = 10 Hz	J = 5 Hz		0.60 s
XXVIIb (f)	3100-3600 (O-H) (c)	6.40 b, 1H	3.00 s	2.20 s	1.18 s	1.08 s
		6.75 b, 1H				0.65 s
XXVIIb·HCl	3200-3450 (O-H) (e)	6.35 bs, 1H	~4.00 (g)	2.85 bs	1.26 s	1.26 s
		7.70 bs, 1H				0.68 s

(a) Chemical shifts in deuteriochloroform solution unless otherwise indicated. (b) Abbreviations: s = singlet; d = doublet; m = multiplet; b = broad. (c) Ir spectrum in sodium chloride. (d) Ir spectrum in chloroform solution. (e) Ir spectrum in potassium bromide. (f) Nmr spectrum in carbon tetrachloride solution. (g) Masked with the signal of methoxyl groups.

characteristic signals, singlets: i) at δ 1.40 due to the methyl group on pyrrolidine 3-position, ii) at δ 1.60 due to the acetyl methyl group, iii) at δ 3.85 due to the C-2 methine proton, and iv) at δ 7.20 for the aromatic protons. In the hydrochloride these signals are shifted at lower fields: methyl groups appear at δ 1.45 and 1.70, whereas the C^2-methine proton resonates at δ 4.40. The mass spectrum of XXVa (Scheme IX) confirms a 2-aryl-3-acetylpyrrolidine structure. Thus, upon electron impact pyrrolidine XXVa (parent peak at m/e 237) undergoes different fragmentation processes affording characteristic fragments at m/e 125 for the tropylium ion and at m/e 194 by loss of acetyl. However, the most significant fragmentation is the one leading to the base peak at m/e 152 according to a fragmentation pattern observed in related 2-arylpyrrolidine systems (1).

The stereochemical assignment of the C^2- and C^3-pyrrolidine substituents in compounds XXIVa and XXVa was established from the chemical shift values of the methyl groups on the ketal and the carbonyl carbon atoms (δ 0.87 and 1.60, respectively). The shielding of these signals regarding all the non-cyclic ketones and ethylene ketals described in this work (Table I) indicates a *cis*-relation between the acetyl group and the aromatic ring (33). Therefore, the intramolecular Mannich condensation leading to the 2-arylpyrrolidine system XXIVa reproduces the stereoselectivity observed in the formation of methylene derivative IIa by Stevens rearrangement (2), thus suggesting that the factors controlling the formation of pyrrolidine C^2-C^3 bond are probably similar in both cases.

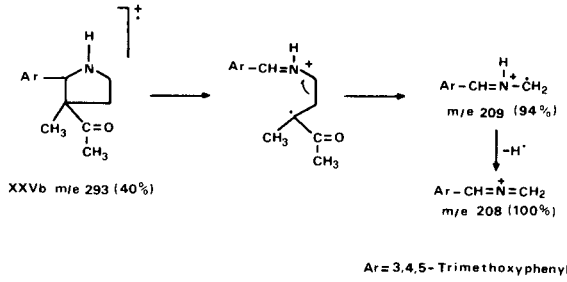
The methylation of XXVa with methyl iodide in anhydrous acetone in presence of anhydrous potassium carbonate afforded *cis*-3-acetyl-2-(*p*-chlorophenyl)-1,3-dimethylpyrrolidine (IVa). Its spectroscopic data were identical to those reported by Jacobson (2) for the ketone obtained by ozonolysis of the methylene derivative IIa isolated as a by-product in the Stevens rearrangement of tetrahydropyridinium salt Ia. This confirms the structure of *cis*-2-(*p*-chlorophenyl)-3-isopropenyl-1,3-dimethylpyrrolidine that we proposed (1) for the rearrangement product IIa. Alternatively, 3-acetylpyrrolidine IVa was obtained by methylation of XXIVa and subsequent hydrolysis of the ketal function in the resultant pyrrolidine XXVIa. The ir spectrum of IVa shows an absorption at 1700 cm^{-1} for the carbonyl group. In the nmr spectrum singlets are observed at δ 1.34, 1.59, 2.12, and 3.00 due to C^3-, carbonyl-, and *N*-methyl groups and to the C_2-H methine proton, respectively. The δ 1.59 value for the CO-methyl group again indicates a *cis* aryl/acetyl relative configuration (33). Scheme IX depicts the most characteristic fragmentations of *N*-methylpyrrolidine IVa, which are similar to those of XXVa, above described.

Acetylpyrrolidine IVa is an immediate precursor of 3-isopropenylpyrrolidine IIa, final objective of the synthesis. This transformation was carried out in 85% overall yield by reaction with methyl-lithium followed by dehydration (thionyl chloride, pyridine) of the resultant tertiary alcohol XXVIIa (34). The ir spectrum of alcohol XXVIIa shows a broad absorption at 3100-3600 cm^{-1} and in its nmr

spectrum singlets are observed at δ 2.95, 2.15 and 1.15 for the C-2 methine proton and for the methyl groups on nitrogen and on the 3-position of the pyrrolidine ring, respectively. The methyl groups of the 2-hydroxy-2-propyl substituent are magnetically non-equivalent and appear as singlets at δ 1.00 and 0.55.

Because of the success in preparing 3-isopropenylpyrrolidine IIa through a synthetic route based on the intramolecular ring closure between an imine salt and the α-position of a ketal group we intended to extend the scope of this approach to the preparation of the similar pyrrolidine IIb in which the aryl group is 3,4,5-trimethoxyphenyl (Scheme VIII). Thus, condensation between 3,4,5-trimethoxybenzaldehyde and the primary amine XXI afforded imine XXIIb. Its treatment with dry hydrogen chloride in anhydrous ether-methylene chloride solution at reflux followed by acid hydrolysis gave directly *cis*-3-acetylpyrrolidine XXVb. The nmr spectrum of XXVb shows, as characteristic signals, singlets at δ 1.40, 1.58 and 6.35 for the methyl group in the 3-position, the acetyl methyl group and the aromatic protons, respectively. The chemical shift of the carbonyl methyl group allows again to establish (33) a *cis* relation between aryl and acetyl substituents. The mass spectrum of XXVb (Scheme X) shows a base peak at m/e 208 coming from a characteristic fragmentation of these pyrrolidine systems (1).

Finally, methylation of XXVb with methyl iodide followed by reaction with methyl-lithium yielded a tertiary alcohol XXVIIb whose dehydration afforded the desired *cis*-3-isopropenylpyrrolidine IIb (34).



Scheme X

Isopropenyl derivatives IIa and IIb prepared by the above unambiguous ways were identical in their physical (Rf in thin-layer chromatography, melting points of its hydrochloride) and spectroscopic data (ir, nmr both of the bases and of the hydrochlorides) to the methylene derivatives obtained as by-products in the Stevens rearrangement of Ia (2) and Ib (3). This conclusively confirms their structural assignment as *cis*-2-aryl-3-isopropenyl-1,3-dimethylpyrrolidines (1).

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). 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 (Table III) were performed by Instituto de Química Bio-Orgánica, Barcelona.

Table III

Analyses

Compound No.	M.p. °C (solvent) (a)	Formula	Carbon %		Hydrogen %		Nitrogen %		Chlorine %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IVa·HCl	183-185 (A)	$C_{14}H_{19}Cl_2NO$	58.34	58.60	6.64	6.73	4.86	5.13	24.60	24.42
IVb·HCl	187-189 (A)	$C_{17}H_{26}ClNO_4$	59.38	59.37	7.62	7.52	4.07	4.09	10.31	10.64
IX·HCl	134-136 (A)	$C_{14}H_{22}ClNO$	65.74	65.38	8.67	8.46	5.47	5.40	---	---
XVb·Picrate	118-120 (F)	$C_{12}H_{14}N_4O_7$	44.18	44.40	4.32	4.39	17.17	17.36	---	---
XVIa·Picrate	212-214 (F)	$C_{13}H_{18}N_4O_7$	45.62	45.32	5.30	4.96	16.37	16.21	---	---
XVII·HCl	145-147 (A-E)	$C_{16}H_{26}ClNO_2$	64.09	64.42	8.74	8.70	4.67	4.73	11.82	12.10
XIX	59-60 (A-P)	$C_{14}H_{15}NO_3$	68.56	68.59	6.16	6.10	5.71	5.63	---	---
XX	70-72 (A-P)	$C_{16}H_{19}NO_4$	66.43	66.71	6.62	6.68	4.84	4.94	---	---
XXI	70°/0.5 mm (b)	$C_8H_{17}NO_2$	60.35	60.08	10.76	10.82	8.80	8.36	---	---
XXIIa	----	$C_{15}H_{20}ClNO_2$	63.94	64.03	7.15	7.36	4.97	4.93	12.58	12.28
XXIIb	220°/0.2 mm (b)	$C_{18}H_{27}NO_5 \cdot \frac{1}{2}H_2O$	62.41	62.33	8.15	8.50	4.04	4.25	---	---
XXIVa·Picrate	171-172 (F)	$C_{21}H_{23}ClN_4O_9$	49.37	49.61	4.54	4.52	10.97	11.06	6.94	7.30
XXVa·HCl	218-220 (A-E)	$C_{13}H_{17}Cl_2NO$	56.95	56.73	6.25	5.95	5.11	4.93	25.86	26.08
XXVb·HCl	172-174 (A-E)	$C_{16}H_{24}ClNO_4$	58.27	58.56	7.34	7.32	4.25	4.29	---	---
XXVIa·Picrate	151-153 (F)	$C_{22}H_{25}ClN_4O_9$	50.35	50.49	4.80	4.83	10.67	10.59	6.75	7.00
XXVIIa	180°/0.2 mm (b)	$C_{15}H_{22}ClNO$	67.28	67.01	8.28	8.22	5.23	5.30	13.24	13.47
XXVIIb·HCl	209-211 (A-E)	$C_{18}H_{28}ClNO_4$	60.41	60.28	7.89	7.63	3.91	3.78	9.91	9.80

(a) Solvents: A = acetone; E = ether; F = ethanol; P = petroleum ether. (b) Purified by distillation on a Büchi GKR-50 Kugelrohr.

5-Benzylmethylamino-3-methyl-2-pentanone (IX).

In a flask provided of mechanical stirring 20 g. (0.14 mole) of 5-chloro-3-methyl-2-pentanone (VIII) (11b-d), 18 g. (0.14 mole) of *N*-methylbenzylamine, and 19 g. of anhydrous potassium carbonate were placed. The reaction mixture was stirred for five hours at 110° and then 100 ml. of 2*N* hydrochloric acid and 100 ml. of ether were added. The acidic aqueous solution was basified with potassium carbonate and extracted with ether. The organic extracts were dried and evaporated, giving 19 g. (62%) of amino ketone IX.

Mercuric Acetate Oxidation of 5-Benzylmethylamino-3-methyl-2-pentanone (IX).

a).

To a solution of 2 g. (9 mmoles) of amino ketone IX in 100 ml. of 40% aqueous acetic acid, 20 g. (62.6 mmoles) of mercuric acetate were added. The resulting mixture was heated at 100° under an atmosphere of nitrogen for 8 hours, after what a precipitate of mercurous acetate was observed. Hydrogen sulfide gas was bubbled for two hours through the mixture heated at 100°. The precipitate was filtered off and the filtrate was basified with potassium carbonate and extracted with ether. Concentration of the dried ethereal extract yielded 1 g. of starting ketone IX.

b).

The acidic filtrate obtained operating as above was basified, then methanol and sodium borohydride were added and the mixture was refluxed for two hours. Ethanol was removed *in vacuo* and the aqueous solution was extracted with ether to give 130 mg. of 5-benzylmethylamino-3-methyl-2-pentanol; ir (chloroform): 3300-3500 cm^{-1} (O-H); nmr (carbon tetrachloride): 0.85 (d, J = 6 Hz, 3H, CH-CH_3), 1.08 (d, J = 6 Hz, 3H, COH-CH_3), 2.10 (s, 3H, N-CH_3), 3.40 (s, 2H, Ar-CH_2), 3.70 (m, 1H, C*H*-OH), 7.20 (s, 5H, Ar-H).

c).

To a solution of 1 g. (4.5 mmoles) of amino ketone IX in 48 ml. of glacial acetic acid, 6 g. (18.8 mmoles) of mercuric acetate were added. The mixture was refluxed under nitrogen atmosphere for 6 hours. The resulting suspension was heated at 100° and was treated with hydrogen sulfide gas for twenty minutes. The prepcipitate was filtered off and the filtrate was refluxed for 5 hours. The residue was basified with 10% aqueous potassium carbonate and extracted with ether. The combined ethereal extracts were dried and evaporated under reduced pressure and a mixture of starting ketone IX and *N*-benzyl-*N*-methylacetamide (XII) (major product) was obtained. Their separation was achieved by column chromatography through silica gel. Acetamide XII was identified by comparison (tlc, nmr, ir) with an authentic sample obtained from *N*-methylbenzylamine and acetic anhydride.

5-Benzylmethylamino-3-methyl-2-pentanone *N*-Oxide (XIII).

To a solution of 0.5 g. (2.3 mmoles) of amino ketone IX in 50 ml. of absolute ethanol, 30 ml. (11 moles) of 30% hydrogen peroxide were added and the solution was stirred for 24 hours at room temperature. After evaporation of the solvent under reduced pressure, 0.5 g. (91%) of *N*-oxide XIII were obtained.

Catalytic Hydrogenation of 5-Benzylmethylamino-3-methyl-2-pentanone (IX).

A solution of 14 g. (0.05 mole) of amino ketone IX hydrochloride in 100 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in presence of 10% palladium on charcoal (1 g.). When the volume corresponding to one equivalent of hydrogen was absorbed the catalyst was filtered off and the filtrate evaporated to give 6.5 g. (89%) of an oil identified as 1,2,3-trimethyl-1-pyrrolinium chloride (XVa); ir (chloroform): 1680 cm^{-1} (C=N^+); nmr: 1.35 (d, 3H, J = 6 Hz, CH-CH_3), 2.40 (s, 3H, =C-CH_3), 3.60 (s, 3H, N^+-CH_3), 4.30 (m, 2H, N^+-CH_2). The picrate recrystallized from ethanol had a m.p. 187-190°; ir (potassium bromide): 1680 cm^{-1} (C=N^+).

1,2,3-Trimethylpyrrolidine (XVIa).

A solution of 250 mg. (1.7 mmoles) of pyrrolinium chloride XVa in 30 ml. of absolute ethanol was hydrogenated over 50 mg. of 10% palladium on charcoal at room temperature. When the absorption ceased, the catalyst was filtered off and the filtrate evaporated to give 140 mg. of XVIa hydrochloride; nmr: 1.15 (d, 3H, J = 6 Hz, CH-CH_3), 1.45 (d, 3H, J = 6 Hz, CH-CH_3), 2.95 (d, 3H, J = 5 Hz, N^+-CH_3). The picrate obtained from the free base and recrystallized from ethanol gave a m.p. 212-214° [lit. (35a) m.p. 211-212°, water; (35b) 214°, ethanol].

5-Benzylmethylamino-3-methyl-2-pentanone Ethylene Acetal (XVII).

A solution of 20 g. (91 mmoles) of amino ketone IX, 20 ml. of ethylene glycol, 400 ml. of anhydrous benzene, and 17 g. (90 mmoles) of *p*-toluenesulfonic acid was refluxed with stirring for 24 hours with removal of water by a Dean-Stark trap. The reaction mixture was poured into an aqueous solution of potassium carbonate (ice cooling) and extracted with benzene. The benzene extracts were washed several times with water, dried over anhydrous magnesium sulfate and evaporated, affording 20.5 g. (85%) of XVII; ms (m/e, %) 263 (M^+, 1), 220 (7), 135 (8), 134 (72), 92 (10), 91 (100), 87 (38), 65 (8).

3-Methyl-5-methylamino-2-pentanone Ethylene Acetal (XVIII).

A solution of 5. g. (19 mmoles) of amine XVII in 50 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure over 0.5 g. of 10% palladium on charcoal. When the absorption ceased the catalyst was filtered off and the filtrate evaporated to give 3.1 g. (94%) of amino ketal XVIII.

5-Phthalimido-3-methyl-2-pentanone (XIX).

Potassium phthalimide (63.6 g., 0.35 mole) was added in small portions to a stirred solution of 40 g. (0.29 mole) of 5-chloro-3-methyl-2-pentanone (VIII) (11b-d) in 315 ml. of *N,N*-dimethylformamide, and the resulting suspension was refluxed for 8 hours. The reaction mixture was poured into 1 l. 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, 46 g. (65%) of phthalimide XIX were obtained; ms: (m/e, %) 245 (M^+, 5), 227 (4), 202 (7), 174 (96), 161 (84), 160 (100), 148 (11), 133 (22), 130 (24), 105 (15), 104 (26), 77 (30), 76 (30), 72 (28).

Acid Hydrolysis of 5-Phthalimido-3-methyl-2-pentanone (XIX).

A solution of 6 g. (0.02 mole) of phthalimido ketone XIX and 100 ml. of 20% hydrochloric acid was refluxed with stirring for three hours. The precipitate was filtered and the aqueous solution was evaporated under reduced pressure affording 3 g. of an hygroscopic solid identified as 2,3-dimethyl-1-pyrroline hydrochloride (XVb); ir (chloroform): 1680 cm^{-1} (C=$\overset{+}{N}$); nmr: 1.40 (d, 3H, J = 6 Hz, CH-CH_3), 2.65 (s, 3H, =C-CH_3), 3.50 (m, 1H, =C-CH), 4.10 (b, 2H, $\overset{+}{N}$-CH_2), 7.60 (s, 1H, $\overset{+}{N}$-H). A sample of XVb hydrochloride was basified with 10% aqueous potassium carbonate and extracted with ether to give 2,3-dimethyl-1-pyrroline; ir (chloroform): 1650 cm^{-1} (C=N); nmr: 1.12 (d, 3H, J = 6 Hz, CH-CH_3), 1.95 (s, 3H, =C-CH_3), 3.65 (m, 2H, =N-CH_2). The picrate recrystallized from absolute ethanol gave a m.p. 118-120°.

5-Phthalimido-3-methyl-2-pentanone Ethylene Acetal (XX).

A solution of 11 g. (45 mmoles) of phthalimido ketone XIX, 4 g. (0.02 mole) of *p*-toluenesulfonic acid, 9 ml. of ethylene glycol, and 200 ml. of anhydrous benzene was refluxed with stirring for 12 hours with removal of water by Dean-Stark trap. The reaction mixture was poured into an aqueous solution of potassium carbonate (ice cooled) and extracted with benzene. The benzene extracts were washed several times with water, dried and evaporated, affording 11.2 g. (86%) of the phthalimido ketal XX.

5-Amino-3-methyl-2-pentanone Ethylene Acetal (XXI).

A solution of 8 g. (27 mmoles) of phthalimido ketal XX, 4 ml. of 80% hydrazine hydrate, and 70 ml. of ethanol was refluxed for 2 hours. The

reaction mixture was cooled and 40 ml. of 20% aqueous sodium hydroxide were added. After stirring 15 minutes the solution was extracted several times with ether. The combined organic extracts were washed with water, dried and evaporated, yielding 3.5 g. (81%) of amino ketal XXI. Attempts to obtain the hydrochloride of XXI were unsuccessful, pyrroline hydrochloride XVb being isolate even under strict anhydrous conditions.

4,4-Ethylenedioxy-3-methyl-*N*-(*p*-chlorobenzylidene)pentylamine (XXIIa).

A solution of 15 g. (94 mmoles) of amino ketal XXI and 10 g. (71 mmoles) of *p*-chlorobenzaldehyde in 600 ml. of anhydrous benzene was stirred for 1 hour at 0°, 4 hours at room temperature and 4 hours at reflux. After 4 hours more of refluxing with removal of water formed by a Dean-Stark trap, the solvent was evaporated to afford 18 g. (90%) of imine XXIIa. The hydrochloride obtained from the free base could not recrystallize because of its decomposition.

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

Operating in the same manner from 10 g. (62 mmoles) of amino ketal XXI and 9.2 g. (47 mmoles) of 3,4,5-trimethoxybenzaldehyde in 200 ml. of anhydrous benzene, 14.5 g. (92%) of imine XXIIb were obtained; hydrochloride, ir (chloroform): 1670 cm^{-1} (C=N$^+$).

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

A solution of 16 g. (56 mmoles) of imine XXIIa in 50 ml. of anhydrous methylene chloride and 100 ml. of anhydrous ether was saturated with hydrogen chloride gas for 3 hours and then refluxed under nitrogen for 24 hours. After cooling, the mixture was decanted. The dark residue remaining in the flask was treated with a 10% aqueous potassium carbonate solution and extracted with ether. The extract was dried over magnesium sulfate and evaporated to give 6.9 g. (51%) of pyrrolidine XXIVa.

cis-3-Acetyl-2-(*p*-chlorophenyl)-3-methylpyrrolidine (XXVa).

A solution of 0.9 g. (3.2 mmoles) of ethylene ketal XXIVa and 50 ml. of 20% hydrochloric acid was stirred for two hours at room temperature. The reaction mixture was basified with potassium carbonate and extracted several times with ether. The combined ethereal extracts were dried and evaporated to give 670 mg. (88%) of acetylpyrrolidine XXVa; ms: (m/e, %) 237 (M$^+$, 17), 194 (13), 155 (17), 154 (41), 153 (60), 152 (100), 125 (8), 118 (25), 117 (15).

cis-3-Acetyl-3-methyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine (XXVb).

A solution of 10 g. (29 mmoles) of imine XXIIb in 70 ml. of anhydrous methylene chloride and 200 ml. of anhydrous ether was saturated with hydrogen chloride gas for 3 hours, and then refluxed under nitrogen for 24 hours. After cooling, the solvent was removed affording an oil which was dissolved in 20% hydrochloric acid and stirred for 1 hour at room temperature. The aqueous solution was extracted with benzene, basified with potassium carbonate, and extracted once with ether. The ethereal layer was dried and evaporated, affording 1.6 g. of 2,3-dimethyl-1-pyrroline. The aqueous solution was extracted with chloroform. The organic extracts were dried and evaporated, affording 3.9 g. (45%) of 3-acetylpyrrolidine XXVb; ms: (m/e, %) 293 (M$^+$, 40), 209 (94), 208 (100), 194 (40), 178 (53).

cis-2-(*p*-Chlorophenyl)-3-(1,1-ethylenedioxyethyl)-1,3-dimethylpyrrolidine (XXVIa).

To a solution of 9 g. (37 mmoles) of ethylene ketal XXIVa in 100 ml. of anhydrous acetone, 17.7 g. (0.12 mole) of methyl iodide and 3 g. of potassium carbonate were added. The reaction mixture was stirred at 0° for one hour, filtered and the solvent removed to afford 5.4 g. (54%) of ethylene ketal XXVIa. An analytical sample was obtained by column chromatography (silica gel, elution with benzene/chloroform 95/5) followed by crystallization of the picrate.

cis-3-Acetyl-2-(*p*-chlorophenyl)-1,3-dimethylpyrrolidine (IVa).

a).

To a solution of 3.9 g. (16 mmoles) of acetylpyrrolidine XXVa in 50 ml. of anhydrous acetone, 1 g. of anhydrous potassium carbonate and 9.1 g. (64 mmole) of methyl iodide were added. The reaction mixture was stirred at 0° for 30 minutes, filtered and the solvent removed to give 2.6 g. (63%) of pyrrolidine IVa; ms: (m/e, %) 251 (M$^+$, 10), 208 (34), 168 (37), 167, (31), 166 (100), 131 (18), 125 (19).

b).

A solution of 0.9 g. (3 mmoles) of ethylene ketal XXVIa and 50 ml. of 20% hydrochloric acid was stirred for 2 hours at room temperature. The reaction mixture was basified and extracted with ether. The ethereal extracts were dried and evaporated to give 650 mg. (85%) of pyrrolidine IVa.

cis-3-Acetyl-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine (IVb).

Operating as above from 1 g. (3.4 mmole) of XXVb in 80 ml. of anhydrous acetone, 300 mg. of anhydrous potassium carbonate, and 4.5 g. (31 mmole) of methyl iodide, 850 mg. (82%) of pyrrolidine IVb were obtained.

cis-(*p*-Chlorophenyl)-3-(2-hydroxy-2-propyl)-1,3-dimethylpyrrolidine (XXVIIa).

To a solution of 300 mg. (1.2 mmoles) of acetylpyrrolidine IVa in 30 ml. of anhydrous ether, a solution of 6 ml. (12 mmoles) of 2*M* ethereal methyl-lithium and 10 ml. of anhydrous ether were added under nitrogen atmosphere. The resulting mixture was refluxed for two hours, cooled and poured into 100 ml. of water. The aqueous solution was extracted with ether, and the combined ethereal extracts were dried and evaporated to give 300 mg. (95%) of carbinol XXVIIa.

cis-3-(2-Hydroxy-2-propyl)-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine (XXVIIb).

Operating in the same manner from 1 g. (3.2 mmoles) of 3-acetylpyrrolidine IVb in 80 ml. of freshly distilled anhydrous tetrahydrofuran and 16 ml. (32 mmole) of 2*M* ethereal methyl lithium, after 6 hours reflux 880 mg. (85%) of carbinol XXVIIb were obtained.

2-(*p*-Chlorophenyl)-3-isopropenyl-1,3-dimethylpyrrolidine (IIa).

a).

Methyltriphenylphosphonium bromide (420 mg., 1.1 mmole) was slowly added under nitrogen atmosphere over a solution of 0.55 ml. (1.1 mmole) of 2*M* ethereal *n*-butyllithium and 10 ml. of anhydrous ether. The resulting mixture was stirred for 3 hours at room temperature. A solution of 200 mg. (0.8 mmole) of 3-acetylpyrrolidine IVa in 30 ml. of freshly distilled anhydrous tetrahydrofuran was added and the mixture was refluxed for 48 hours. The precipitate was removed by filtration and washed with ether. The combined ethereal extracts were washed with water until neutral reaction and dried. After evaporation of the solvent an oil was obtained which was chromatographed on silica gel. Elution with benzene-ether 1:1 gave 150 mg. of a mixture of unchanged ketone IVa and trace amounts (nmr, tlc) of isopropenylpyrrolidine IIa.

b).

Freshly distilled thionyl chloride (1 ml.) was added to a solution of 300 mg. (1.1 mmole) of carbinol XXVIIa in 30 ml. of freshly distilled pyridine. The reaction mixture was stirred for 15 minutes at 0° and 20 minutes at room temperature, poured into ice-water, basified with potassium carbonate and extracted with ether. The ethereal extracts were washed with water, dried and the solvent removed, giving 190 mg. (68%) of isopropenylpyrrolidine IIa, identical in all respects with the methylene derivative obtained by Stevens rearrangement of Ia (1,2).

cis-3-Isopropenyl-1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrrolidine (IIb).

Operating in the same manner from 10 ml. of thionyl chloride and 2.8 g. (8.6 mmoles) of carbinol XXVIIb in 100 ml. of pyridine, 1.7 g. (65%) of isopropenylpyrrolidine IIb were obtained. This material was identical in all respects with the methylene derivative obtained by Stevens rearrangement of Ib (1,3).

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