A Reinvestigation of the Stevens Rearrangement of 1,3,4-Trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium Chloride

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1,3,3-Trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (XI) is prepared in an unambiguous way which involves the Refortmatsky reaction followed by ethanolysis on the *N*-(3,4,5-trimethoxybenzylidene)methylamine, later treatment of the resulting aminoester with ethyl acrylate, ring closure by Dieckmann reaction with decarbalkoxylation and, finally, a Wittig reaction on the piperidone obtained. The resulting methylenepiperidine XI differs in its physical and spectroscopic data from the methylene derivative IIIa obtained by the Stevens rearrangement of the 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride, whose structure must be reviewed.

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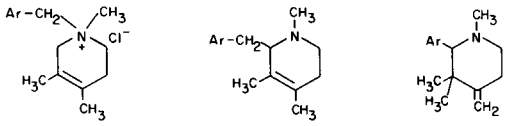
In a previous work (1) we studied the products obtained by the Stevens rearrangement of the 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (Ia). The expected 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (IIa) was isolated and identified as well as other compounds, one of which was identified, by elemental analysis and spectroscopic data as 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (IIIa). A compound of similar structure relationship, identified as 2-*p*-chlorophenyl-1,3,3-trimethyl-4-methylenepiperidine (IIIb), had been previously reported by Jacobson (2) as a by-product of the Stevens rearrangement of 1-*p*-chlorobenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium chloride (Ib).

Figure 1



I II III

a, Ar = 3,4,5-trimethoxyphenyl

b, Ar = p-chlorophenyl

Since compound IIIa was of interest for later studies, its synthesis was planned in a more advantageous way that overcame the low yields and the tedious separation of the rearrangement products. Scheme I shows the synthetic route by which 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (XI) was unequivocally obtained. Surprisingly, physical and spectroscopic data did not coincide with those of compound IIIa obtained by the rearrangement reaction.

The *N*-(3,4,5-trimethoxybenzylidene)methylamine (IV) was obtained by adding 3,4,5-trimethoxybenzaldehyde to a solution of methylamine in anhydrous benzene in accordance with a similar procedure used for analogous aldehydes (3); this method improves previous preparations of IV (4). The aminoester VI was prepared by the Reformatsky reaction on the Schiff base IV, followed by alcoholysis of the resulting 2-azetidinone V. The Reformatsky reaction on imines is a good method to prepare 2-azetidinones (5), and the cyclization of the initially formed anionic species occurs in the reaction media in all but a few isolated cases and conditions (6). Nevertheless, this does not present any problems since alcoholysis of 2-azetidinones (7) occurs without difficulty giving the product with an optimum yield. In our case, the reaction of IV with zinc and ethyl 2-bromo-2-methylpropionate gave the β-lactam V and from this, upon heating in absolute ethanol saturated with dry hydrogen chloride, the aminoester VI with a 75% overall yield was obtained. The ir spectrum of the β-lactam V shows a strong absorption at 1763 cm^{-1}, while in the nmr spectrum the most characteristic signals observed are three singlets at δ 4.19, δ 1.49 and δ 0.83 for the methine proton and the methyl group *cis* and *trans* to it, respectively (8). The ir spectrum of compound VI shows a carbonyl absorption characteristic of an ester group at 1725 cm^{-1}, and in the nmr spectrum a singlet at δ 3.61 appears for the methine proton as well as two singlets at δ 1.02 and δ 1.10 (δ 1.20 and δ 1.60 in the hydrochloride) for the *gem*-dimethyl group as a result of its diastereotopic character.

The aminodiester VII was only obtained by treatment of VI with ethyl acrylate in the presence of glacial acetic acid (9). Other procedures described for the incorporation of a β-carbethoxyethyl-type chain to an amine were unsuccessful. So, after prolonged heating of VI with ethyl acrylate in the absence of solvent and catalyst (10) the initial material was recovered. The use of ethanol as the

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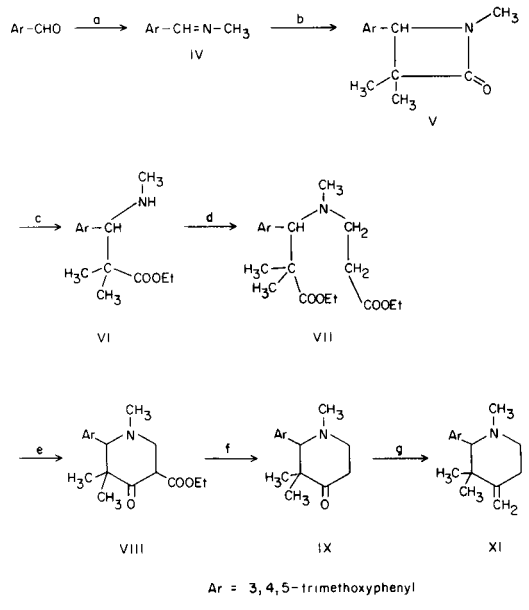
Scheme I



Reagents: a, CH_3NH_2/dry benzene; b, $(CH_3)_2$—$CBrCO_2Et$/Zn/methylat; c, EtOH/dry HCl; d, CH_2=CH-CO_2Et/AcOH; e, NaH/dry benzene; f, HCl 50%, heat; g, $(C_6H_5)_3P$=CH_2.

solvent at room temperature (11), at reflux, or under pressure in a sealed tube at several temperatures yielded only small amounts of the aminodiester VII. When boron trifluoride-etherate was used as a catalyst at reflux temperature for an extended period of time (12), partial decomposition of VI took place, and the isolated products were imine IV, 3,4,5-trimethoxybenzaldehyde, and small amounts of aminodiester VII. Finally, the reactions of VI with ethyl 3-bromopropionate in the presence of potassium carbonate and xylene (13) or with sodium acetate without solvent (14), yielded unsatisfactory results. The ir spectrum of the aminodiester VII shows only one carbonyl absorption centered at 1740 cm^{-1}, although the nmr spectrum shows different signals for the two ethyl groups. The *gem*-dimethyl group appears again as two singlets at δ 0.90 and δ 1.27, whose difference of chemical shifts increases in the hydrochloride (δ 0.90 and δ 1.73).

The Dieckmann cyclization of the aminodiester VII using sodium hydride in anhydrous benzene (15) gave the β-keto ester VIII with a 61% yield. Its decarbalkoxylation, by boiling with 6*N* hydrochloric acid, yielded the piperidone IX. The 2-(4-hydroxy-3,5-dimethoxyphenyl)-1,3,3-trimethyl-4-piperidone (X), was also isolated as a result of the demethylation of one of the methoxy groups during the acid treatment. The piperidone IX shows an absorption at 1705 cm^{-1} in the ir spectrum due to the carbonyl group. In its nmr spectrum singlets are observed at δ 2.89, δ 1.24 and δ 0.95 for the proton in the 2-position and the axial and the equatorial methyl groups (16), respectively, in the 3-position of the heterocyclic ring.

Finally, the Wittig reaction of the piperidone IX with triphenylmethylenephosphorane gave 1,3,3-trimethyl-2-3,4,5-trimethoxyphenyl)-4-methylenepiperidine (XI) with a 92% yield. Its hydrochloride showed a melting point, 249-251°, different from the previously reported (208-210°) for the compound IIIa obtained in the Stevens rearrangement (1). Their spectroscopic data are also dissimilar, showing no coincidence with those of the rearrangement product. Thus, in the ir spectrum of XI the absorption of the exocyclic double bond is observed at 1645 cm^{-1} (IIIa, 1630 cm^{-1}) (1). The nmr spectrum shows, as characteristic signals, a singlet at δ 4.67 for the terminal methylene protons, a singlet at δ 2.56 for the proton in the 2-position of the heterocyclic ring (displaced paramagnetically at δ 3.67 in the hydrochloride), and two singlets at δ 1.09 and δ 0.90 for the axial and equatorial methyl groups, respectively, in the 3-position (16) (δ 1.52 and δ 1.05 in the hydrochloride). The mass spectrum of XI exhibited a molecular peak at m/e 305 and a parent peak at m/e 181 for a tropylium ion $(C_{10}H_{13}O_3)^+$ by contrast to those of transposition product IIIa (M^+ 305; m/e 222, parent ion 100%).

The above results oblige us to look again at the structure of the methylene derivative IIIa (1) and IIIb (2), probably, obtained in the Stevens rearrangement of the tetrahydropyridinium salts Ia and Ib, respectively. At this moment we are investigating as indicated and we will shortly present the results obtained.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-12 Spectrometer (60 MHz, tetramethylsilane at δ 0.0 ppm as internal standard). Chemical shifts are reported as δ values in parts per million (ppm). Infrared spectra were determined on a Perkin-Elmer model 457 Spectrometer. The mass spectrum was determined on an AEI (model MS-902 S) mass spectrometer. Elemental analyses were performed by Instituto de Química Orgánica Aplicada de Cataluña, Barcelona.

N-(3,4,5-Trimethoxybenzylidene)methylamine (IV).

In a flask fitted with a stirrer and a gas condenser, 150 ml. of anhydrous benzene was placed; an excess of methylamine was bubbled in and 50 g. of 3,4,5-trimethoxybenzaldehyde, dissolved in the minimum amount of anhydrous benzene, was added. The mixture was stirred for 4 hours; then the gas condenser was replaced by a Dean-Stark trap, and the reaction mixture was refluxed until 4.6 ml. of water distilled. After removing the solvent an oil was obtained which gave 52.9 g. (99% yield) of IV by distillation (b.p. 117-127°/0.15 mm); ir (sodium chloride): 1648 cm^{-1}; nmr (deuteriochloroform): 3.38 (d, 3H, J = 2 Hz, N-CH_3), 3.76 (s, 9H, O-CH_3), 6.92 (s, 2H, Ar-H), 8.02 (c, 1H, J = 2 Hz, =CH).

Table

Analyses

Compound	M.p. °C (Solvent) (a)	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found	Chlorine % Calcd.	Chlorine % Found
V	100-101 (P)	$C_{15}H_{21}NO_4$	64.49	64.24	7.58	7.80	5.01	5.15	–	–
VI HCl	210-211 (A-E)	$C_{17}H_{28}ClNO_5$	56.42	56.18	7.80	7.83	3.87	3.97	9.79	9.96
VII HCl	156-157 (A)	$C_{22}H_{36}ClNO_7$	57.19	57.16	7.85	7.90	3.03	2.97	7.67	7.84
VIII HCl	184-186 (A-E)	$C_{20}H_{30}ClNO_6$	57.75	57.80	7.27	7.30	3.36	3.30	8.52	8.75
IX HCl	246-247 (A-F)	$C_{17}H_{26}ClNO_4$	59.38	59.42	7.62	7.59	4.07	4.02	10.31	10.03
X HCl	210-211 (A-E)	$C_{16}H_{24}ClNO_4 \cdot H_2O$	55.24	55.65	7.53	7.20	4.02	4.01	–	–
XI HCl	249-251 (A)	$C_{18}H_{28}ClNO_3$	63.24	63.25	8.20	8.38	4.09	4.07	10.37	10.08

(a) Solvents: A = acetone; E = ether; F = ethanol; P = petroleum ether.

1,3,3-Trimethyl-4-(3,4,5-trimethoxyphenyl)-2-azetidinone (V).

In a flask with a stirrer was placed 40.4 g. (618 mmoles) of zinc in small pieces, covered with the minimum possible amount of anhydrous methanol-free methylal. Several drops of ethyl 2-bromo-2-methylpropionate are added refluxing simultaneously under a nitrogen atmosphere. After the reaction starts, the boiling was maintained and 60.2 g. (302 mmoles) of ethyl 2-bromo-2-methylpropionate dissolved in 200 ml. of anhydrous methylal was added in one hour. After the addition, the heating was prolonged for 45 minutes and 51.7 g. (247 mmoles) of IV in 50 ml. of anhydrous methylal was slowly added. The reaction mixture was stirred for 48 hours at room temperature. After this time, 450 ml. of 1.33*N* hydrochloric acid was added, the mixture stirred for 12 hours, basified and filtered. The resulting solution was extracted several times with ether. The ethereal extracts were dried and evaporated to dryness. The residue obtained was crystallized from anhydrous ether giving 55.7 g. (81% yield) of V; ir (potassium bromide): 1763 cm^{-1} (C=O); nmr (deuteriochloroform): 0.83 (s, 3H, C-CH_3), 1.41 (s, 3H, C-CH_3), 2.84 (s, 3H, N-CH_3), 3.84 (s, 9H, O-CH_3), 4.19 (s, 1H, C-CH), 6.39 (s, 2H, Ar-H).

Ethyl 3-Methylamino-3-(3,4,5-trimethoxyphenyl)-2,2-dimethylpropionate (VI).

Dry hydrogen chloride was bubbled intermittently for 24 hours through a solution of 33 g. (118 mmoles) of V in 300 ml. of absolute ethanol heated to 55-60°. The solvent was removed and the solid residue was dissolved into 500 ml. of water; this solution was extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and extracted with ether. This last ethereal extract was dried and the ether removed; 36.2 g. (94% yield) of VI are obtained, m.p. 69-70° (petroleum ether); ir (chloroform): 1725 cm^{-1} (C=O); nmr (carbon tetrachloride): 1.02 (s, 3H, C-CH_3), 1.10 (s, 3H, C-CH_3), 1.25 (t, 3H, J = 7.3 Hz, CH_3 ester), 2.20 (s, 3H, N-CH_3), 3.61 (s, 1H, CH), 3.76 (s, 3H, O-CH_3), 3.84 (s, 6H, O-CH_3), 4.13 (c, 2H, J = 7.3 Hz, CH_2 ester), 6.54 (s, 2H, Ar-H).

Ethyl 3-(β-Carbethoxyethylmethylamino)-3-(3,4,5-trimethoxyphenyl)-2,2-dimethylpropionate (VII).

A mixture of 8.65 g. (26.6 mmoles) of VI, 4 g. (40.0 mmoles) of ethyl acrylate and 0.3 ml. of glacial acetic acid was heated under inert atmosphere at 100° for 16 hours. The resulting residue was dissolved in ether and extracted several times with dilute hydrochloric acid. The aqueous solution was basified and extracted with chloroform. The organic layer was dried and the solvent removed *in vacuo*, affording 8.19 g. of an oil which by distillation yielded 4.78 g. of starting material VI (170-185°/0.08 mm) and 3.02 g. of aminodiester VII (b.p. 220-240°/0.06 mm), yield (with reference to consumed aminoester): 71%; ir (chloroform): 1740 cm^{-1} (C=O); nmr (carbon tetrachloride): 0.90 (s, 3H, C-CH_3), 1.17 (t, 3H, J = 7.3 Hz, CH_3 ester), 1.23 (t, 3H, J = 7.3 Hz, CH_3 ester), 1.27 (s, 3H, C-CH_3), 2.18 (s, 3H, N-CH_3), 2.1-2.6 (broad, 4H, CH_2), 3.76 (s, 3H, O-CH_3), 3.84 (s, 6H, O-CH_3), 3.65-3.95 (s, 1H, CH), 4.08 (c, 2H, J = 7.3 Hz, CH_2 ester), 4.13 (c, 2H, J = 7.3 Hz, CH_2 ester), 6.58 (s, 2H, Ar-H).

5-Carbethoxy-1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (VIII).

A solution of 2.87 g. (6.75 mmoles) of aminodiester VII in 8 ml. of anhydrous benzene was slowly added, under nitrogen atmosphere, over a suspension of 0.36 g. (15.2 mmoles) of paraffin-free sodium hydride in 10 ml. of anhydrous benzene. A few drops of absolute ethanol was added and, when the reaction starts, the mixture was refluxed for 4 hours, cooled, and 0.91 g. of glacial acetic acid and water was added and the mixture filtered. The resulting benzene solution was dried over anhydrous potassium carbonate and the solvent removed *in vacuo*, obtaining 1.56 g. (61% yield) of VIII; ir (sodium chloride): 1740, 1715, 1660 and 1620 cm^{-1}. The ferric chloride/methanol test was positive.

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

A solution of 1.56 g. (4.1 mmoles) of β-keto ester VIII and 40 ml. of 50% hydrochloric acid was refluxed for 2 hours 30 minutes, basified with concentrated sodium hydroxide, extracted with ether, dried and the solvent removed, 0.42 g. (22% yield) of piperidone IX, m.p. 120-122°, was obtained; ir (sodium chloride): 1705 cm^{-1} (C=O); nmr (deuteriochloroform): 0.93 (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, CH), 3.85 (s, 9H, O-CH_3), 6.54 (s, 2H, Ar-H).

The mother liquors of the hydrolysis were acidified with 2*N* hydrochloric acid, basified with ammonium hydroxide and extracted with ether; after drying and removing the solvent 0.31 g. of an oil, which solidifies on cooling, was obtained which corresponds to the phenol X; ir (chloroform): 3540 cm^{-1} (O-H), 1705 cm^{-1} (C=O); nmr (carbon tetrachloride): 0.86 (s, 3H, C-CH_3), 1.07 (s, 3H, C-CH_3), 2.03 (s, 3H, N-CH_3), 3.81 (s, 6H, O-CH_3), 6.43 (s, 2H, Ar-H).

1,3,3-Trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (XI).

Triphenylmethylphosphonium bromide (7.7 g., 20.0 mmoles) was slowly added, under nitrogen atmosphere, over a mixture of 12.2 ml. (20.0 mmoles) of 1.64*M* ethereal *n*-butyllithium and 50 ml. of anhydrous ether, and the resulting mixture was stirred for 3 hours at room temperature. A solution of 6.5 g. (20.0 mmoles) of the piperidone IX in 80 ml. of freshly distilled tetrahydrofuran was added and the mixture was refluxed for 24 hours. The white precipitate which appears was removed by filtration and washed with ether; the ethereal extracts were collected, 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 benzene-ether 9/1, 6 g. (92% yield) of XI was obtained; ir (sodium chloride): 1645 cm^{-1} ($C=CH_2$); nmr (deuteriochloroform): 0.90 (s, 3H, C-CH_3 eq), 1.09 (s, 3H, C-CH_3 ax), 1.80 (s, 3H, N-CH_3), 2.56 (s, 1H, CH), 3.81 (s, 9H, O-CH_3), 4,67 (s, 2H, $C=CH_2$), 6.51 (s, 2H, Ar-H). Some of the major peaks in the mass spectrum of XI were (m/e, relative intensity): 305 (73), 290 (27), 262 (23), 247 (11), 231 (40), 194 (86), 181 (100), 179 (20), 138 (62), and 124 (20).

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