

Benzomorphan Related Compounds. IV (1). The Stevens Rearrangement of a Trimethoxybenzyl-1,2,5,6-tetrahydropyridinium Salt

J. Bosch, J. Canals and R. Granados

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

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The potassium hydroxide-induced (Stevens) rearrangement of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (I) gives the desired 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (III) and the Hofmann elimination product, *N*-methyl-*N*-(3,4,5-trimethoxybenzyl)-2,3-dimethyl-2,4-pentadienamine (II). In the presence of ethereal phenyllithium, the salt I undergoes rearrangement giving the expected tetrahydropyridine III in about 17% yield and four other products, *N*-(3,4,5-trimethoxybenzyl)methylamine (VI), 1,3,4-trimethyl-2-(6-methyl-2,3,4-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine (IV), 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (V) and 1,3,4-trimethyl-4-(3,4,5-trimethoxybenzyl)-1,4,5,6-tetrahydropyridine (VII), the latter being the 1,4-Stevens rearrangement product which cyclizes easily to β -2',3',4'-trimethoxy-2,5,9-trimethyl-7,8-benzomorphan (VIII). Their structures have been proved both by analytical and spectral data. A possible route for VIII and its stereochemical aspects are discussed.

The Stevens rearrangement of 1-benzyl-1,2,5,6-tetrahydropyridinium salts has been widely used for the preparation of the useful synthetic intermediates Δ^3 -tetrahydropyridines (2) whose cyclization leads to 6,7-benzomorphans, which are pharmacologically interesting for their analgesic activity.

In a previous paper (3) we reported the preparation of 2-(3,4,5-trimethoxybenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (III) by treatment of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (I) under Stevens rearrangement conditions, either with powdered potassium hydroxide in refluxing benzene, or with ethereal phenyllithium solution. The reaction led in both cases, however, to a complex mixture of products, the separation, purification and identification of which is discussed in this paper.

Our starting material was the quaternary ammonium salt I which was readily obtained, as a stable hydrate, by treating 1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (2) with 3,4,5-trimethoxybenzyl chloride (4) in acetone.

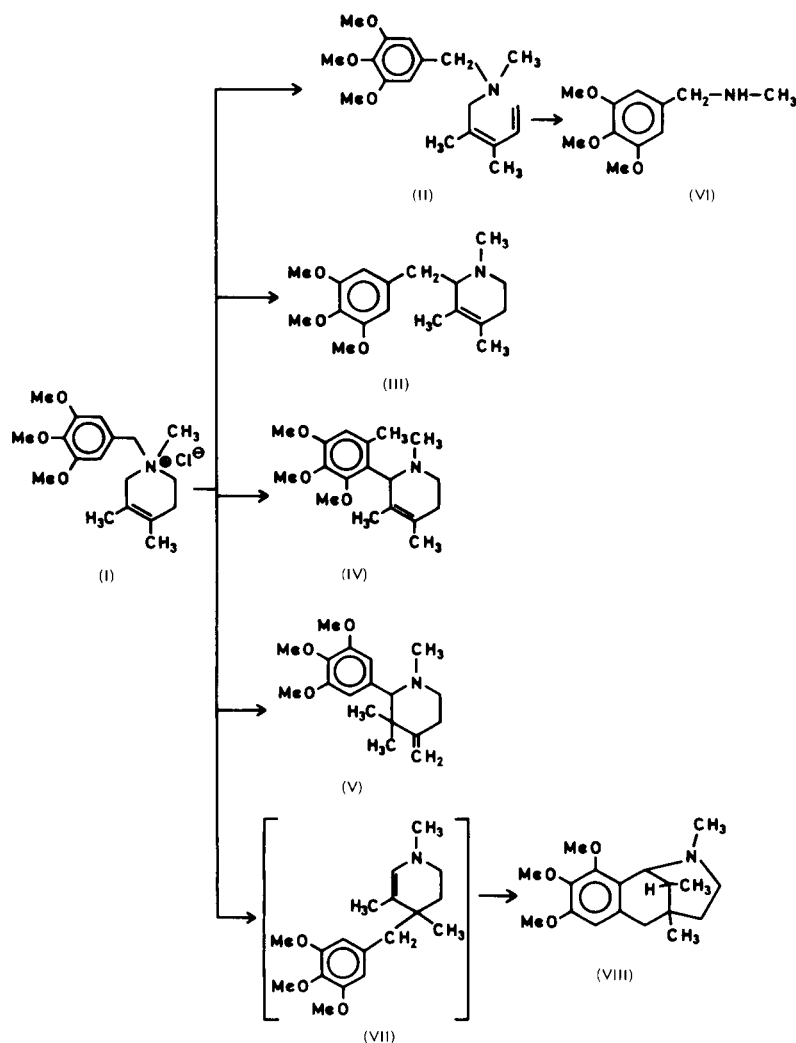
Treatment of I with powdered potassium hydroxide-anhydrous benzene gave a four component mixture in the ratio 1:2:2:1 (glc). The two main components were separated by chromatography through a silica gel column and identified as *N*-methyl-*N*-(3,4,5-trimethoxybenzyl)-2,3-dimethyl-2,4-pentadienamine (II), (5) and 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (III), (6).

The structure of II, a Hofmann elimination product of I, was elucidated from spectral and analytical data. The infrared spectrum showed bands at 1630 and 900 cm^{-1} thus indicating the presence of a conjugated $\text{C}=\text{CH}_2$ group. The nmr spectrum showed an ABX pattern and all the other signals were consistent with those expected for that structure. Thus, three singlets due to the three methyl groups appeared at δ 2.14, δ 1.87 and δ 1.80, and two singlets due to the benzylic and allylic methylenes at δ 3.35 and δ 3.06, respectively. The yield in the Hofmann elimination product (II) was higher than that reported by Block and Clarke (7) for analogous cases. On the other hand, when the ammonium salt I was treated with refluxing aqueous potassium hydroxide solution, II was the only resulting product (72% yield).

The structure of III was confirmed by its nmr spectrum and was found to be identical with the product obtained by unambiguous synthesis achieved by sodium borohydride reduction of 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)pyridinium iodide (3). The free base III showed a singlet at δ 1.60 due to the methyl groups on the double bond, and a singlet at δ 2.37 due to the *N*-methyl group. Furthermore, the nmr spectrum of III·HCl differed from that of the isomeric 1,4,5-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine hydrochloride salt (X) obtained by another synthetic route (1).

Treatment of I with excess ethereal phenyllithium produced a mixture, whose glc examination showed four

Scheme 1



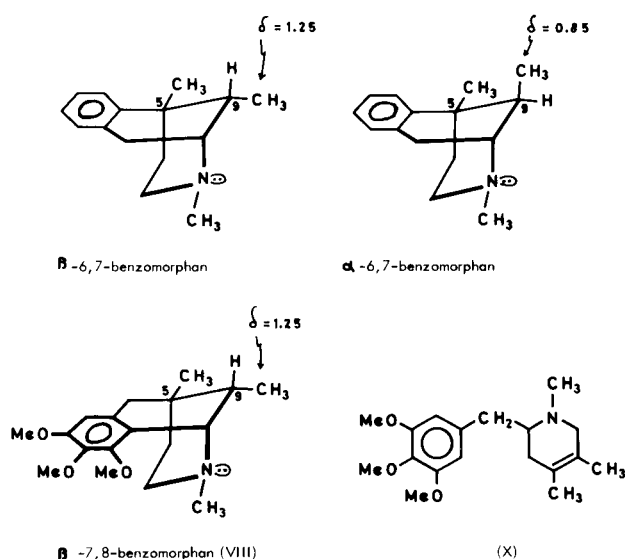
main components in 3:2:7:5 ratio (increasing retention time order). Neither the Hofmann elimination product (II) nor the Δ^4 -tetrahydropyridine (X) were detected. The main product was found to be identical with the known tetrahydropyridine (III), *i.e.*, the expected product of the rearrangement. Separation of the mixture, achieved by fractional distillation through a spinning-band column, gave three fractions. The first one (lowest b.p.) was mainly composed of the two components with lowest

retention time in glc. The intermediate fraction was almost identical with the initial mixture and was separated by further distillation. The third fraction (highest b.p.), was fundamentally composed of 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (III). Redistillation of the first fraction afforded three compounds, namely *N*-(3,4,5-trimethoxybenzyl)methylamine (VI), 1,3,4-trimethyl-2-(6-methyl-2,3,4-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine (IV) and 1,3,3-trimethyl-2-

Table. Analyses

Compound	M.p. °C	Formula	Carbon %		Hydrogen %		Nitrogen %		Chlorine %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
I	149-152	$C_{18}H_{28}ClNO_3 \cdot H_2O$	60.07	59.90	8.40	8.38	3.89	3.85	9.85	10.02
II·HCl	207-208	$C_{18}H_{28}ClNO_3$	63.24	63.09	8.26	8.27	4.09	4.12	10.37	10.09
III·HCl	221-223	$C_{18}H_{28}ClNO_3$	63.24	63.18	8.26	8.45	4.09	4.26	10.37	10.12
IV·HCl	196-197	$C_{18}H_{28}ClNO_3$	63.24	63.33	8.26	8.60	4.09	4.06	10.37	10.67
V·HCl	208-210	$C_{18}H_{28}ClNO_3$	63.24	63.56	8.26	8.70	4.09	4.17	10.37	10.40
VIII	96-98	$C_{18}H_{27}NO_3$	70.79	71.10	8.91	9.23	4.59	4.58	---	---

Scheme 2



(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (V).

Compound VI (8), which had the lowest boiling point of this mixture, was isolated in a very small amount (undetected by glc in the original mixture), and identified by both spectral data and the melting point of its hydrochloride salt (9). The formation of an analogous compound in the Stevens rearrangement of a related tetrahydropyridinium salt has been reported and interpreted (10).

Compound IV, resulting from a Sommelet rearrangement of 1, had the lowest glc retention time (3.3 minutes) among the four main components in the original mixture and was purified as its hydrochloride salt. An analogous compound has been isolated from the reaction of 1-*p*-methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride with phenyllithium (11). The structure of IV was established from the nmr spectral data. The integration of its nmr spectrum showed the presence of an aromatic proton in front of three methoxy groups, thus indicating a pentasubstituted benzene. On the other hand, the presence of an aromatic methyl singlet at δ 2.28 as well as a broad singlet at δ 4.15 due to a benzylic proton α to a nitrogen atom, which is paramagnetically shifted to δ 4.98 (deuterium oxide) in the hydrochloride salt, supported this structure. Such a downfield signal showed evidence for an allylic proton, thus implying that the aromatic ring was attached to a 2-position of the tetrahydropyridine, and not to a 6-position (12). Further support for structure IV was provided by the very different field values (δ 1.27 and δ 1.66) of the double bond methyl groups, one of them being affected by the vicinal aromatic ring.

Compound V, (13) which had a higher boiling point,

was purified as its hydrochloride salt, and its structure was also established from spectral data. The ir spectrum showed absorptions at 1630 and 900 cm^{-1} due to a terminal methylene group. The nmr spectrum of V clearly indicated the presence of: i) two identical aromatic protons, ii) a two-proton singlet at δ 4.71 due to the terminal methylene group, iii) an *N*-methyl singlet and iv) a singlet due to a *gem*-dimethyl group on a quaternary carbon atom. In contrast with compound IV whose α to nitrogen benzylic proton appeared at δ 4.15, a singlet at δ 2.87 was observed for the same proton in compound V. In the nmr spectrum of V·HCl the *gem*-dimethyl group appeared as two singlets. A similar effect has been reported for an analogous compound (14).

Finally, from the third fraction of the distillation of the original mixture the expected rearrangement product (III) was obtained in its hydrochloride salt in 17% yield. The resultant mother liquors were reconverted into the free base and the residues of several combined preparations distilled again through a spinning-band column. From the different fractions two minor compounds could be isolated and purified though only one of them has been identified. Thus, from the lowest boiling point fraction, a compound with empirical formula $\text{C}_{18}\text{H}_{27}\text{NO}_3$, isomeric with the above ones, was obtained by crystallization. The nmr spectrum showed: i) only one aromatic proton in front of three methoxy groups, ii) a methyl group on a quaternary carbon atom, iii) a methyl group as a doublet at δ 1.25 ($J = 6$ cps), iv) a *N*- CH_3 group, and v) a two proton singlet at δ 2.60 due to a methylene group adjacent to an aromatic ring. In the hydrochloride this last signal was insignificantly shifted to lower fields, thus indicating that it was only slightly affected by the nitrogen atom. Finally, a broad signal at δ 4.45 due to a benzylic proton α to nitrogen, which was masked in the free base spectrum by that of the methoxy groups (δ 3.8-3.9), was also observed. This downfield chemical shift has also been found in analogous structures (15). No signal due to methyl groups on a double bond was detected. These data suggested a tricyclic structure, namely 2',3',4'-trimethoxy-2,5,9-trimethyl-7,8-benzomorphan (VIII) (16) for this compound, and showed evidence for the β -diastereomer, in which methyl groups in positions 5 and 9 are in a *trans* orientation, i.e., with the 9-methyl group equatorial to the hydroaromatic ring and next to the lone pair of the nitrogen atom. This 9-methyl group may be compared from a stereochemical point of view to that in the same position in the β -6,7-benzomorphan series (17), since their relative position in regard to the aromatic ring and the nitrogen lone pair is in both cases identical.

It is possible to rationalize the formation of this compound during the acidic treatment in the work-up of the

reaction, by cyclization of the 1,4-Stevens rearrangement product (VII). This was confirmed by heating under reflux in acetone the hydrochloride salts of the crude original mixture and reconverting them into the free bases. An oil, whose glc examination showed a significant decrease in the proportion of the fourth component of the original mixture (i.e., the only one which could not be isolated), was obtained. Simultaneously, the presence of VIII, non-existent in the former mixture, was detected (glc). This result supported the formation of the 7,8-benzomorphan (VIII) through the initially formed 1,4-Stevens rearrangement product, namely 1,3,4-trimethyl-4-(3,4,5-trimethoxybenzyl)-1,4,5,6-tetrahydropyridine (VII), the latter being the unidentified component of the original mixture. The easy cyclization of this tetrahydropyridine (VII) in acidic medium may be interpreted through the protonation of the enaminic system leading to an immonium salt, which acts as an electrophilic agent upon the aromatic ring.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12 Spectrometer (60 MHz, tetramethylsilane at δ 0.0 ppm as the internal standard) with deuteriochloroform as the solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). Ir spectra were recorded with a Perkin-Elmer 457, spectrophotometer. The glc were run isothermally at 195° on a Carlo Erba (Fractovap Mod. GT) chromatograph with a flame ionization detector. A 2 m glass column, 4 mm in diameter was used, packed with 6% XE-60 on 80-100 mesh Chromosorb P silanized. Carrier gas: 40 ml./min. helium. The mass spectrum was determined on an AEI (model MS-902S) mass spectrometer.

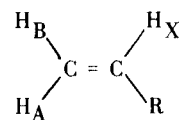
1,3,4-Trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (I).

To a solution of 30 g. (0.24 mole) of 1,3,4-trimethyl-1,2,5,6-tetrahydropyridine in 100 ml. of acetone, 55 g. (0.25 mole) of 3,4,5-trimethoxybenzyl chloride in 200 ml. of acetone were added. The mixture was stirred under reflux for 4 hours. On cooling, 80 g. of the product (I) was obtained (92%). Recrystallization from acetone-absolute ethanol gave white crystals, m.p. 149-152°; nmr: 1.65 (s broad, 6, =C-CH₃), 3.22 (s, 3, N-CH₃), 3.36 (s, 2, =C-CH₂-N), 3.82 (s, 3, OCH₃), 3.87 (s, 6, OCH₃), 5.05 (s, 2, Ar-CH₂), 7.03 (s, 2, Ar-H).

N-Methyl-*N*-(3,4,5-trimethoxybenzyl)-2,3-dimethyl-2,4-pentadienamine (II).

A mixture of 16.2 g. (0.045 mole) of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (I), 25.2 g. (0.45 mole) of potassium hydroxide and 145 ml. of water was kept under reflux 33 hours. An organic layer separated and was extracted with ether. After 45 hours of additional reflux the aqueous layer was extracted with ether. From the combined ethereal solutions, previously dried with anhydrous sodium sulphate, the hydrochloride salt of II was obtained (11.1 g., 72% yield). It was recrystallized from acetone-absolute ethanol, m.p. 207-208°; nmr (base): 1.80 (s, 3, C-CH₃), 1.87 (s, 3, C-CH₃),

2.14 (s, 3, N-CH₃), 3.06 (s, 2, =C-CH₂), 3.35 (s, 2, Ar-CH₂), 3.79 (s, 9, OCH₃), 6.59 (s, 2, Ar-H), 4.96 (d, 1, H_B, J_{BX} = 10 cps), 5.12 (d, 1, H_A, J_{AX} = 16 cps), 7.00 (c, 1, H_X, J_{BX} = 10 cps, J_{AX} = 16 cps).



Stevens Rearrangement of 1,3,4-Trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (I).

a) Using Potassium Hydroxide/Benzene.

A mixture of 8 g. (0.023 mole) of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (I) and 1.8 g. of powdered reagent 85% potassium hydroxide in 70 ml. of anhydrous benzene was refluxed under nitrogen for 10 hours. During this time, 0.8 ml. of water was collected in a Dean-Stark separator. The cooled mixture was washed with water, dried and concentrated to give a brown oil (7 g.). The crude base was shown to be a four-component mixture in the ratio 1:2:2:1 (glc). It was converted into its hydrochloride salt and, after several recrystallizations from acetone, a mixture of the two predominant components, namely *N*-methyl-*N*-(3,4,5-trimethoxybenzyl)-2,3-dimethyl-2,4-pentadienamine (II) and 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (III), was obtained. No further improvement in separation was achieved by successive recrystallizations of this mixture. The two main compounds were separated by chromatography through a silica gel (130 g.) column. The original mixture (4.5 g.) afforded 1.5 g. of a colorless oil identified as II (5) on elution with benzene/chloroform: 7/3, and 0.7 g. of III (6) with chloroform/methanol: 8/2, the latter being further converted into its hydrochloride, m.p. 221-223° (acetone); nmr: 1.61 (s, 3, C-CH₃), 1.73 (s, 3, C-CH₃), 2.04-2.27 (broad, 2, =C-CH₂), 2.81 (d, 3, N-CH₃), 3.79 (s, 3, OCH₃), 3.84 (s, 6, OCH₃), 6.26 (s, 2, Ar-H); nmr (base): 1.61 (s, 6, C-CH₃), 1.80-2.20 (broad, 2, =C-CH₂), 2.37 (s, 3, N-CH₃), 3.81 (s, 9, OCH₃), 6.51 (s, 2, Ar-H); hydrobromide, m.p. = 213-214° (acetone).

b) Using Ethereal Phenyllithium Solution.

A mixture of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride (I) (60 g., 0.167 mole) was suspended in ether (200 ml.) and a phenyllithium solution (600 ml., 1M) was added rapidly with vigorous stirring. The mixture was refluxed with stirring under nitrogen for 8 hours, poured into cold water (500 ml.), and the aqueous layer was extracted with ether. The combined ethereal solution was extracted with dilute hydrochloric acid. The acidic solution was cooled in ice, rendered basic with concentrated ammonium hydroxide and extracted with ether. The ethereal phase was dried with magnesium sulphate and evaporated to give 46 g. of a brown oil. The glc of the product showed it to be a mixture of four main components in the ratio 3:2:7:5 (retention time: 3.3, 4.2, 8.5 and 9.8 minutes, respectively). The oil was distilled at 0.02 mm Hg through a spinning-band column and three fractions were collected. The first fraction (8.1 g., b.p. 104-142°) was found by glc to be *N*-(3,4,5-trimethoxybenzyl)methylamine (VI) (retention time 2.2 minutes, undetected in the original mixture), 1,3,4-trimethyl-2-(6-methyl-2,3,4-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine (IV) and 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine (V). The second fraction, (3.7 g., b.p. 142-160°), was found to be a

mixture fundamentally identical with the original one and was recovered in further distillations. The third fraction (16.2 g., b.p. 160-177°), was found to be 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (III), and 1,3,4-trimethyl-4-(3,4,5-trimethoxybenzyl)-1,4,5,6-tetrahydropyridine (VII).

The first fraction was redistilled. From the fraction with the lowest b.p. *N*-(3,4,5-trimethoxybenzyl)methylamine (VI) was obtained and identified as its hydrochloride, m.p. 177-179° (acetone-absolute ethanol) Lit. (9) 178°; nmr (deuterium oxide): 1.34 (s, 3, C-CH₃), 1.83 (s, 3, C-CH₃), 2.41 (s, 3, Ar-CH₃), 2.80 (s, 3, N-CH₃), 3.75 (s, 3, OCH₃), 3.84 (s, 3, OCH₃), 3.88 (s, 3, OCH₃), 4.98 (broad, 1, benzylic proton), 6.82 (s, 1, Ar-H). The free base liberated from this hydrochloride had a m.p. 50-52° (retention time 3.3 minutes); nmr: 1.27 (s, 3, C-CH₃), 1.66 (s, 3, C-CH₃), 2.08 (s, 3, N-CH₃), 2.28 (s, 3, Ar-CH₃), 3.81 (s, 6, OCH₃), 3.87 (s, 3, OCH₃), 4.15 (s, 1 benzylic proton), 6.42 (s, 1, Ar-H). Compound V, 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-methylenepiperidine, was the predominant component in the last fractions and was purified as its hydrochloride, m.p. 208-210° (acetone); nmr: 1.18 (s, 3, C-CH₃), 1.22 (s, 3, C-CH₃), 2.81 (d, 3, N-CH₃), 3.83-3.90 (9, OCH₃), 4.00 (s, 1, benzylic proton), 5.18 (d, 2, =CH₂), 6.94 (d, 2, Ar-H). The free base liberated from this hydrochloride had a m.p. 52-53° (retention time 4.2 minutes); nmr: 1.24 (s, 6, C-CH₃), 2.19 (s, 3, N-CH₃), 2.87 (s, 1, benzylic proton), 3.82 (s, 9, OCH₃), 4.71 (s, 2, =CH₂), 6.51 (s, 2, Ar-H).

The third fraction of the initial distillation was converted into the hydrochloride and was crystallized from acetone, giving 1,3,4-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridine (III) (17% yield, m.p. 221-223°, retention time 8.5 minutes). From the mother liquors the free base was liberated once again and distilled through a spinning-band column. The fraction with the lowest b.p. was dissolved in ether and compound VIII, β -2',3',4'-trimethoxy-2,5,9-trimethyl-7,8-benzomorphan, crystallized, m.p. 96-98° (ether) (retention time 4.9 minutes); nmr: 0.94 (s, 3, C₅-CH₃), 1.25 (d, 3, C₉-CH₃), 2.07 (s, 3, N-CH₃), 2.60 (s, 2, Ar-CH₂), 3.80 (s, 9, OCH₃), 6.38 (s, 1, Ar-H); hydrochloride, m.p. 183-186° (acetone-ether); nmr: 1.06 (s, 3, C₅-CH₃) 1.60 (d, 3, C₉-CH₃), 2.56 (s, 2, Ar-CH₂), 2.82 (s, 3, N-CH₃), 3.80

(s, 3, OCH₃), 3.84 (s, 3, OCH₃), 3.89 (s, 3, OCH₃), 4.46 (s, 1, benzylic proton), 6.48 (s, 1, Ar-H). The higher b.p. fractions were converted into their hydrochlorides, leading to an unidentified compound, m.p. 206-208° (acetone-ether), m.p. of the free base 61-63° (retention time 7.0 minutes). Analysis and mass spectrum were correct for C₁₉H₃₀ClNO₃.

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