Benzomorphan Related Compounds. VII (1). Synthesis of Benzothienomorphans

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The synthesis of some benzo[*b*]thieno[2,3-*f*]- and [3,2-*f*]morphans by the Grewe method is described. Spectroscopic data of these compounds and of the intermediate isomeric tetrahydropyridines are included. A side-product isolated from the aluminum bromide cyclization of the 2-(2-benzothienylmethyl)tetrahydropyridine IVd is reported and a mechanism for its formation is proposed.

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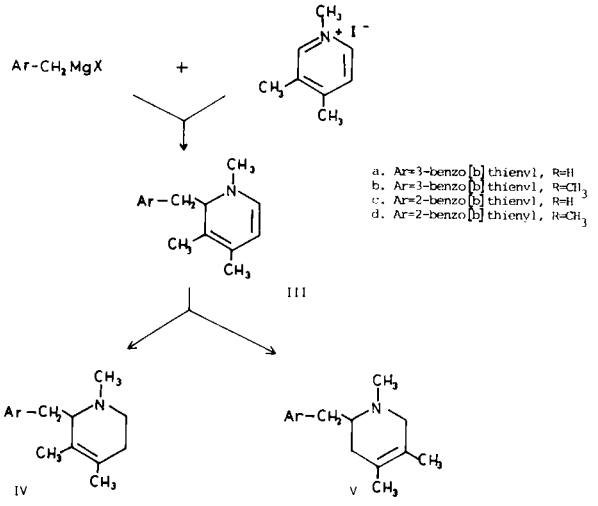
In previous papers we have reported (2) the synthesis of several heteromorphans as potential analgesics in which the benzene ring of the benzomorphans is substituted by a thiophene ring. In spite of its limitations, the Grewe method has proved to be the best synthetic route to obtain this kind of compounds. In connection with these studies we present here the preparation of some benzo[*b*]thieno-[2,3-*f*]- and [3,2-*f*]morphans by the Grewe synthesis.

Condensation of 3-benzo[*b*]thienylmethylmagnesium chloride (3), obtained under high dilution conditions in a column similar to that of the modified cyclic reactor (4), and 1,3,4-trimethylpyridinium iodide (Scheme I) gave 2-(3-benzo[*b*]thienylmethyl)-1,3,4-trimethyl-1,2-dihydropyridine (IIIb). Its nmr spectrum showed two multiplets at δ 8.07-7.75 (2H) and δ 7.60-7.30 (2H) for the benzene protons, a singlet at δ 7.12 due to the proton on the 2-position in the benzothiophene ring, a triplet at δ 3.90 due to the H_2 dihydropyridine proton, and a quartet centered at δ 3.00 due to the methylene group, thus indicating a 3-benzothienylmethyl structure and not an abnormal 3-methyl-2-benzothienyl derivative as described (3,5) in other reactions with benzo[*b*]thienylmethyl Grignard reagents (6). Other signals are two doublets (J ≃ 7.5 cps) at δ 5.91 and δ 4.77 due to the H_6 and H_5 dihydropyridine protons, respectively, and three singlets at δ 2.54, δ 1.68 and δ 1.47 due to the methyl groups.



Scheme I

Sodium borohydride reduction of IIIb afforded the tetrahydropyridine IVb.

A similar sequence from 2-benzo[*b*]thienylmethylmagnesium chloride (5) gave, besides the expected Δ^3-tetrahydropyridine IVd, a minor component (lowest tlc Rf value) (7) identified as the Δ^4-tetrahydropyridine Vd resulting from the attack of the Grignard reagent on the 6-position of the pyridinium salt. These structures were established (8) from the nmr spectral data by comparison of the *N*-methyl signals of IVd hydrochloride and Vd hydrochloride which appear (deuteriochloroform) as a doublet (NH/N-CH_3 coupling) and a broad singlet, respectively, the latter being split into an apparent triplet by addition of a drop of trifluoroacetic acid. As in the isomeric 2-(2-thienyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine and 2-(2-thenyl)-1,4,5-trimethyl-1,2,3,6-tetrahydropyridine (8), the structure of IVd and Vd cannot be discerned by comparison of the chemical shifts of the allylic C_5- (in IVd) and C_3- (in Vd) methylene protons (9) since both are found to appear approximately at the same position in the bases as in the hydrochlorides. An analogous process in which a Δ^4-tetrahydropyridine is isolated when treating a 1,3,4-trisubstituted pyridinium salt with a benzyl-type Grignard reagent has been described (10).

As expected, reaction between 2- or 3-benzo[*b*]thienylmethylmagnesium chloride and 1,4-dimethylpyridinium iodide and subsequent borohydride reduction provides mixtures of the tetrahydropyridines IVc + Vc and IVa + Va, respectively, corresponding in both cases to the Δ^3- and Δ^4-isomers.

From the IVc + Vc mixture, compound Vc (lowest tlc Rf value) (7) was separated and purified by distillation followed by recrystallization of the hydrochloride. It was not possible to isolate isomer IVc in a pure state. The assignment of the position of the double bond of Vc has been achieved from the signal of the N-CH_3 group in the nmr spectrum, which appears in its hydrochloride (deuteriochloroform) as an apparent triplet (double doublet) centered at δ 2.88, thus indicating a Δ^4-structure (8).

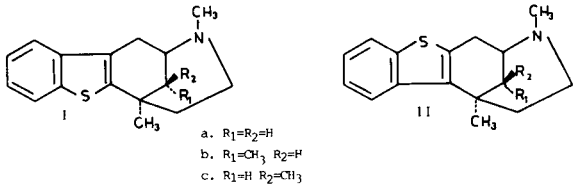
On the other hand, from the IVa + Va mixture (1:1 by nmr examination) both isomers were obtained by repeated fractional recrystallizations of their picrate salts. In this case, both isomers being available, the assignment

Table I

Compound	M.p. °C (Solvent) (a)	Yield	Formula	Analyses									
				Carbon %		Hydrogen %		Nitrogen %		Sulfur %		Chloride %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Ia·HCl	225-230 (A-E)	37% (b)	$C_{16}H_{20}ClNS \cdot \frac{1}{2}H_2O$	63.48	63.48	6.95	7.23	4.62	4.48	----	----	----	----
Ib·HCl	135-138 (A-E)	56%	$C_{17}H_{22}ClNS \cdot H_2O$	62.69	62.64	7.36	7.23	4.29	4.02	9.84	9.64	10.88	10.86
Ic·Picrate	229-231 (F)	32%	$C_{23}H_{24}N_4O_7S$	55.23	55.38	4.80	4.96	11.19	11.42	6.40	6.04	----	----
IIa·HCl	158-160 (A)	68% (b)	$C_{16}H_{19}ClNS \cdot H_2O$	61.65	61.34	7.09	7.29	4.49	4.31	----	----	----	----
IIb·HCl	255-258 (A-E)	58%	$C_{17}H_{22}ClNS \cdot H_2O$	62.69	63.01	7.36	7.36	4.29	4.29	----	----	----	----
IVa·Picrate	158-161 (F)	36% (c)	$C_{22}H_{22}N_4O_7S$	54.34	54.32	4.52	4.76	11.50	11.50	6.59	6.34	----	----
IVb·HCl	185-190 (A-E)	40%	$C_{17}H_{22}ClNS$	66.32	66.29	7.19	7.19	4.54	4.36	10.41	10.39	11.51	11.63
IVd·HCl	225-230 (A-E)	40% (d)	$C_{17}H_{22}ClNS$	66.32	66.52	7.19	7.15	4.54	4.40	10.41	10.54	11.51	11.68
Va·Picrate	162-164 (F)	36% (c)	$C_{22}H_{22}N_4O_7S$	54.34	54.21	4.52	4.84	11.50	11.39	6.59	6.33	----	----
Vc·HCl	214-218 (A)	45% (e)	$C_{16}H_{20}ClNS$	65.40	65.49	6.85	6.88	4.76	4.49	10.91	10.70	12.06	12.15
Vd·HCl	229-231 (A-E)	----	$C_{17}H_{22}ClNS$	66.32	66.21	7.19	7.44	4.54	4.62	10.41	10.29	11.51	11.67
VI	179-180 (F)	----	$C_{17}H_{21}NS$	75.27	74.90	7.74	7.98	5.16	5.39	11.82	11.53	----	----

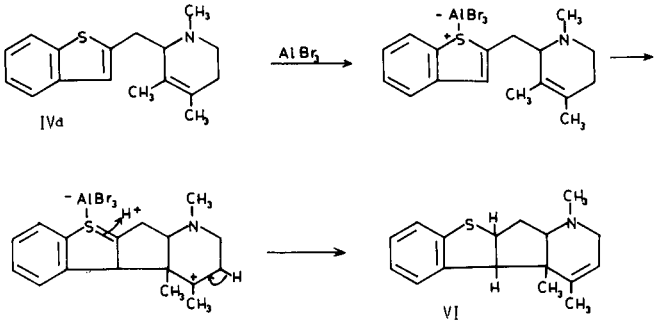
(a) Solvents: A = acetone; E = ether; F = ethanol; M = methanol. (b) Yield from a mixture of Δ^3- and Δ^4-tetrahydropyridines. (c) Yield in a mixture of IV and Va. (d) Yield in a mixture of IVd and Vd. (e) Yield in a mixture of IVc and Vc.

of the position of the double bond was achieved by comparison of the chemical shifts of the olefinic and allylic methylene protons (9) in the nmr spectra of their picrates. Thus, in the Δ^3-tetrahydropyridine IVa (highest tlc Rf value) (7), the first of these signals appears at higher field values (δ 5.30) than in the Δ^4-isomer Va, (δ 5.46), whereas the 3-CH_2 protons of Va appear at higher field values (δ 2.32-2.04) than do the 5-CH_2 protons of IVa (δ 2.54-2.20).



Scheme II

Hydrobromic acid cyclization of the isomeric mixtures IVa + Va and IVc + Vc gave the expected benzo[*b*]thienomorphans Ia and IIa, respectively. Cyclization of the tetrahydropyridine IVb, however, afforded a diastereomeric mixture (Ib + Ic) in which the major isomer was Ib (lowest tlc Rf value) when the cyclizing agent was hydrobromic acid (11), and Ic when aluminum bromide was used. Nmr spectral data of these isomers (Table III) are consistent with the ones reported in the benzomorphan series (12). Finally, from the hydrobromic acid cyclization of IVd, it was only possible to isolate the α-benzothienomorphan IIb, whereas with aluminum bromide an additional compound identified as 1,4,4a-trimethyl-1,2,4a,4b,9a,10a-hexahydro-10*H*-benzo[*b*]thieno[2',3':4,3]cyclopenta-[1,2-*b*]pyridine (VI) was obtained. The nmr spectrum of VI showed the presence of: i) a multiplet at δ 7.30-6.90 due to four aromatic protons, thus indicating a cyclized product (13); ii) a broad signal at δ 5.33 due to an olefinic proton; iii) a quartet (δ 4.27, J = 8.6 cps and J = 14 cps) and a doublet (δ 3.52, J = 8.6 cps) due to the α and β protons of the dihydrothiophene ring, respectively (14); iv) an *N*-methyl singlet; and v) two methyl signals at δ 1.35 and δ 1.29 due to the methyl groups on a double bond and on a quaternary carbon, respectively, the former



Scheme III

Table II

Tetrahydropyridines. Chemical Shifts in Deuteriochloroform (δ values) (a)

Compound	Aromatic	=C-H	$Ar-CH_2$ $N-CH_2$ N-CH	$N-CH_3$	$=C-CH_2$	$C-CH_3$
IVa•Picrate	8.02-7.67 m, 2H 7.54-7.28 m, 3H	5.30 b	4.10-3.10 m	3.02 s	2.54-2.20 b	1.77 s
IVb	7.98-7.69 m, 2H 7.50-7.22 m, 3H	-----	3.25-2.47 m	2.36 s	2.20-1.80 b	1.61 b, 6H
IVd	7.84-7.50 m, 2H 7.37-7.10 m, 2H 7.01 s, 1H (b)	-----	3.19-2.43 m	2.37 s	2.20-1.75 b	1.58 s, 6H
Va•Picrate	8.02-7.64 m, 2H 7.54-7.24 m, 3H	5.46 b	4.50-3.15 m	2.99 s	2.32-2.04 b	1.73 s
Vc	7.90-7.48 m, 2H 7.42-7.07 m, 2H 6.97 s, 1H (b)	5.34 b	3.47-2.65 m	2.39 s	2.18-1.80 b	1.61 s
Vd	7.86-7.54 m, 2H 7.40-7.15 m, 2H 7.04 s, 1H (b)	-----	3.50-2.60 m	2.42 s	2.14-1.82 b	1.57 s, 6H

(a) Abreviations: s = singlet, d = doublet, t = triplet, m = multiplet, b = broad signal. (b) Thiophene protons.

Table III

Benzo[*b*]thienomorphans. Chemical Shifts in Deuteriochloroform (δ values)

Compound	Aromatic	$N-CH_3$	C_5-CH_3	C_9-CH_3
Ia	7.88-7.19 m, 4H	2.38 s	1.41 s	-----
Ib	8.10-7.19 m, 4H	2.42 s	1.40 s	0.88 s
Ic	7,83-7.12 m, 4H	2.27 s	1.31 s	1.21 s
IIa	8.00-7.66 m, 2H 7.42-7.13 m, 2H	2.32 s	1.62 s	-----
IIb	7.97-7.67 m, 2H 7.41-7.12 m, 2H	2.35 s	1.65s	0.92 s

with J = 2 cps due to the long range coupling with the olefinic proton.

Formation of this compound may be interpreted (Scheme III) by assuming that the Lewis acid interacts with the sulphur atom, and that the electrophilic 3-position of the thiophene ring attacks on the double bond. The resulting carbocation undergoes proton elimination and the subsequent hydrolysis destroys the aluminum bromide-complex, thus yielding the dihydrobenzothiophene system VI. It is noteworthy that "normal" Grewe cyclization involves electrophilic substitution of a carbonium center on the piperidine moiety upon the nucleophilic thiophene ring, whereas the "abnormal" cyclization involves the 3-thienyl position as the electrophile, instead, adding to the nucleophilic carbon-carbon double bond of the tetrahydropyridine *i.e.*, the roles of the two reacting centers are just reversed.

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) with deuteriochloroform as a solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). Elemental analyses were performed by Instituto de Quimíca Orgánica, Barcelona.

Tetrahydropyridines.

3-Benzo[*b*]thienylmethyl chloride (15) and 2-benzo[*b*]thienylmethyl chloride (16) were converted in a modified cyclic reactor (4) into their corresponding Grignard reagents, which were allowed to react directly with the pyridinium salt, placed in the reaction flask, by a previously described method (2c). A freshly amalgamated column of magnesium turnings was prepared for each run. Thus, 0.1 mole of benzo[*b*]thienylmethyl halide in 500 ml. of dry ether were placed in a dropping funnel and 0.1 mole of the pyridinium iodide suspended in 500 ml. of dry ether were placed in the boiling flask. All operations were carried out in an atmosphere of dry nitrogen. The rate of addition of the halide was regulated to allow definite boiling in the column (about 45 mmoles of the halide per hour). When the addition was complete, the refluxing of ether in the boiling flask was continued for 2 hours. The resulting solution was poured into ice water-ammonium chloride, basified with ammonium hydroxide and extracted with ether.

The ethereal layer was extracted with 10% hydrochloric acid solution. The combined extracts were basified with ammonium hydroxide and extracted with ether. The extract was dried and evaporated to give a dihydropyridine which was used in the following reaction without purification. Thus, to a stirred solution of dihydropyridine in 70 ml. of methanol, 40 ml. of 1*N* sodium hydroxide and 0.075 mole of sodium borohydride were added and the mixture was stirred overnight at 60°. After cooling, the reaction mixture was extracted several times with ether. The dried ethereal extracts were evaporated to dryness, and the residue distilled. Tetrahydropyridines were characterized as their hydrochloride (or picrate) salts (Tables I and II).

Tetrahydropyridines IVa and Va were converted into their picrate salts. After several recrystallizations from ethanol, compound Va picrate was obtained. The initial mother liquors afforded a solid which after repeated recrystallizations from ethanol rendered pure IVa picrate.

Tetrahydropyridines IVd and Vd were separated by chromatography through a silica gel column. From 34 g. of mixture, 20.8 g. of IVd upon elution with benzene/chloroform (8:2), 2.2 g. of IVd-Vd mixture and 3.3 g. of Vd upon elution with chloroform, were obtained.

Benzo[*b*]thienomorphans.

Hydrobromic Acid Cyclizations.

Tetrahydropyridine (0.02 mole) and 60 ml. of 48% hydrobromic acid were kept at 130-135° (oil bath temperature) for 12 hours, cooled, poured into ice water, basified with concentrated ammonium hydroxide and extracted with ether. The dried ethereal extracts were evaporated at reduced pressure to give an oily material which was distilled *in vacuo* and characterized as the hydrochloride (Tables I and III).

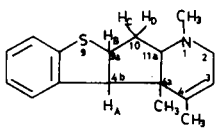
Benzo[*b*]thienomorphan IIb crystallized after distillation, m.p. 90-95° (ether).

Aluminum Bromide Cyclization of IVb.

A mixture of 0.02 mole of IVb hydrochloride, 110 ml. of carbon disulfide and 0.06 mole of aluminum bromide was refluxed for 36 hours, cooled, poured into ice water, basified with concentrated ammonium hydroxide and extracted with ether. The dried ethereal extracts were evaporated and the residue distilled at reduced pressure giving a mixture of isomers Ib and Ic, from which the β-isomer Ic was separated (32% yield) by chromatography through a silica gel column on elution with chloroform (m.p. 111-113°, ether). Separation of the α- and β-isomers can also be achieved by preparative tlc on Merck 60 F_{254} silica gel plates (2 mm) using ether/acetone/diethylamine (95:3:2) as developing agent.

Aluminum Bromide Cyclization of IVd.

Cyclization of IVd hydrochloride was carried out as described for IVb (15 hours reflux). The residue from evaporation of the dried ethereal extracts (86% yield in a IIb + VI mixture) was chromatographed on silica gel. From 9 g. of this mixture, 1.8 g. of VI on elution with benzene/chloroform (8:2), 2.6 g. of recovered mixture and 4 g. of IIb on elution with chloroform/methanol (93:7) were obtained. Compound VI was converted into its hydrochloride, m.p. 275-280° (acetone-methanol); nmr (base): 7.30-6.90 (m, 4, aromatic), 5.33 (b, 1, =C-H), 4.27 (q, 1, H_B, J_{BA} = 8.6 cps, J_{BC} = 14 cps), 3.52 (d, 1, H_A, J_{AB} = 8.6 cps) 2.94-2.71 (m, 2, N-CH_2), 2.71-1.88 (m, 3, N-CH and $^{10}CH_2$), 2.17 (s, 3, N-CH_3), 1.35 (d, 3, =C-CH_3), 1.29 (s, 3, C-CH_3); nmr (hydrochloride): 7.42-6.95 (m, 4, aromatic), 5.23 (b, 1, =C-CH), 4.88-4.30 (m, 1, H_B), 4.12-3.31 (m, 4, H_A, N-CH and N-CH_2), 2.86 (s, 3, N-CH_3), 2.63-2.16 (m, 2, $^{10}CH_2$), 1.77 (s, 3, C-CH_3), 1.05 (s, 3, C-CH_3).



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(6) We have never detected abnormal products in any of the condensations reported in this paper.

(7) In all the cases reported in this paper and in the preceding ones (1,2), the Δ^4-tetrahydropyridines have a lower tlc Rf value (silica gel plates) than the corresponding Δ^3-isomers.

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(13) This single multiplet is narrower than those in the benzothiophene series (Tables II and III), thus suggesting a partially reduced thiophene ring.

(14) These signals remain in fact unchanged in the hydrochloride, although in this case the second one is partially masked by those of the N-CH_2 and N-CH protons, paramagnetically shifted in relation to the base.

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