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A series of thieno[2,3-*f*]-, [3,2-*f*]- and [3,4-*f*]morphans prepared both by the Grewe synthesis and by the reaction of 2-cyanopyridines with 3-thienyllithium is described. Furthermore, a new synthetic route to thieno[2,3-*f*]morphans from 3-ketotetrahydrothiophene is reported. Separation and assignment of the α- and β-diastereomeric structures by means of nmr data is reported. Some side products were isolated and their structures were confirmed on the basis of their spectral data. Mechanisms for their formation are proposed.

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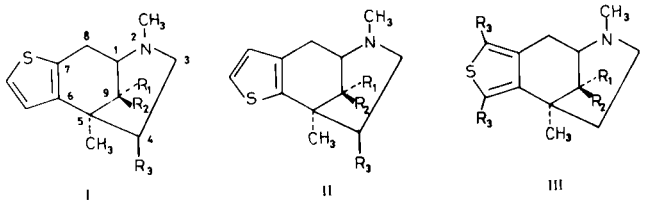
Since the first synthesis of an 6,7-benzomorphan, carried out by May (2) in 1955, a number of benzomorphan derivatives have been synthesized. Many of these show non-narcotic analgesic activity, and some are known to possess morphine antagonism activity (3). More recently, the effects of substituting the benzene ring in 6,7-benzomorphans for an heteroaromatic ring have been investigated. In this sense, the synthesis of indolo[2,3-*f*]morphans (4), of 2,5-dimethylpyrido[3,2-*f*]morphan (5), and of thienomorphans (6,7) have been described. In previous papers we have reported the preparation of α-2,5,9-trimethylthieno[3,2-*f*]morphan (Ib) by the Grewe

Scheme 1



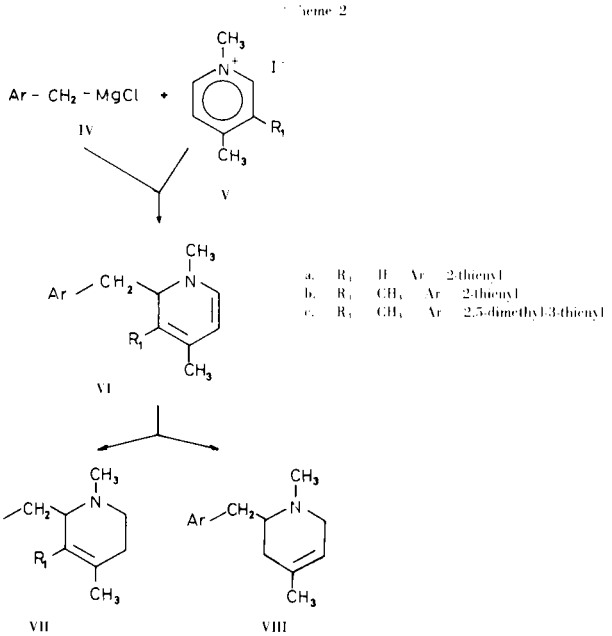
I II III

a. R_1 R_2 R_3 H
b. R_1 CH_3 R_2 R_3 H
c. R_1 R_2 H R_3 CH_3
d. R_1 R_3 H R_2 CH_3
e. R_2 H R_1 R_3 CH_3

synthesis (7a) and of thienomorphans Ia, Ib and Ic by an alternative route from 2-cyanopyridines and thienyllithium (7b). Now we wish to report the results obtained in the synthesis of some thieno[3,2-*f*]-, [2,3-*f*]- and [3,4-*f*]-morphans by the above methods and to propose another synthetic route for thieno[2,3-*f*]morphans from 3-keto-tetrahydrothiophene.

The reaction between 2-thenylmagnesium chloride (IVa), obtained under high dilution conditions in a column similar to that of the modified cyclic reactor (8), and 1,4-dimethylpyridinium iodide (Scheme 2) gave 2-(2-thenyl)-1,4-dimethyl-1,2-dihydropyridine (VIa), an unstable compound which was later reduced with sodium borohydride to a mixture of Δ^3- and Δ^4-tetrahydropyridines (VIIa and VIII, respectively) in the ratio 8:3 (by glc). The latter compounds had been previously obtained from sodium borohydride reduction of 2-(2-thenyl)-1,4-dimethylpyridinium bromide, and their cyclization had already been

Scheme 2

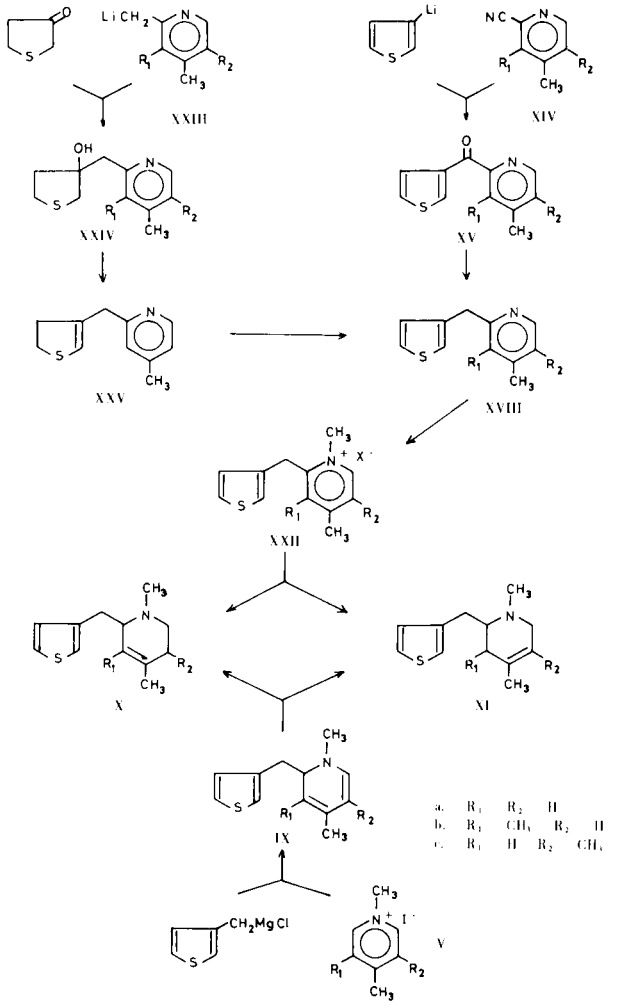


a. R_1 H Ar 2-thienyl
b. R_1 CH_3 Ar 2-thienyl
c. R_1 CH_3 Ar 2,5-dimethyl-3-thienyl

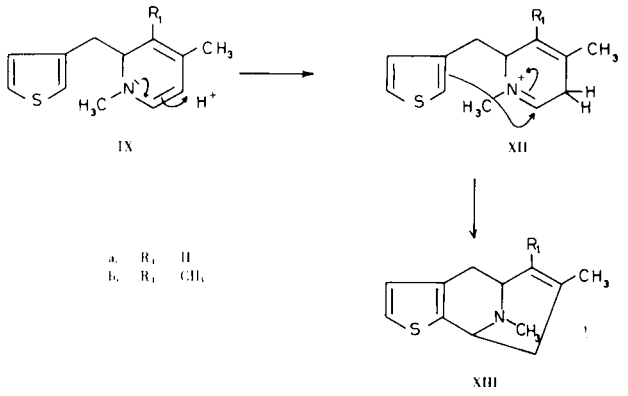
reported (7b) to yield 2,5-dimethylthieno[3,2-*f*]morphan (Ia).

On the other hand, condensation (Scheme 3) of 3-thenylmagnesium bromide (also obtained under high dilution conditions) with 1,4-dimethylpyridinium iodide and subsequent borohydride reduction provided, besides the expected tetrahydropyridines Xa and XIa, a compound identified as 7,10-dimethyl-5,9-imino-4,5,8,9-tetrahydrocycloocta[*b*]thiophene (XIIIa). An analogous sequence of reactions using 1,3,4-trimethylpyridinium iodide gave a mixture of the tetrahydropyridine Xb and the tetrahydrocycloocta[*b*]thiophene XIIIb. It is possible to rationalize the formation of compounds XIIIa and XIIIb due to the acidic treatment during the work-up of the condensation reaction. The dihydropyridines IX (Scheme 4) are transformed into their respective immonium salts XII, which act as electrophillic agents upon the 2-position of the thiophene ring to give XIII. The higher reactivity of the 2-position compared to the 3-position of the thiophene ring explains that formation of similar compounds is not observed when starting from 2-thenylmagnesium halides. Nmr spectral data of XIIIa and XIIIb showed (i) an AX pattern (J ≃ 5 cps) due to the aromatic ring protons, thus

Scheme 3

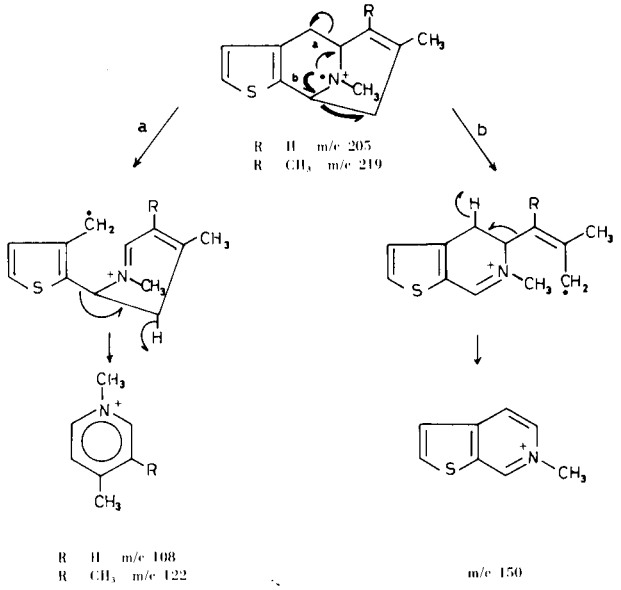


Scheme 4



indicating the presence of disubstituted thiophenes, (ii) a doublet ($J \simeq 6$ cps) at δ 3.99 and δ 3.94, respectively, due to the thenyl proton α to nitrogen atom (9), a broad signal (apparent triplet) at δ 3.45 and δ 3.15, respectively, due to the allylic proton α to the nitrogen atom, and a *N*-methyl singlet, all signals being paramagnetically shifted in the picrate salts. Furthermore, the spectrum of XIIIa showed (i) a broad signal at δ 5.39 due to the olefinic proton, and (ii) a methyl group signal on a double bond at δ 1.60. By contrast, the spectral data of XIIIb showed no proton on a double bond, and two signals due to methyl groups on a double bond at δ 1.63 and δ 1.51, thus confirming the suggested structures. The mass spectra of XIIIa and XIIIb (see Experimental) exhibited a common fragmentation pattern having peaks for the parent and for rationalizable fragmentation products, that is, the spectra indicated that upon electron impact these compounds undergo two major fragmentation processes initiated by cleavage of the activated allylic and thenyl C-C bonds β to the nitrogen atom (Scheme 5).

Scheme 5



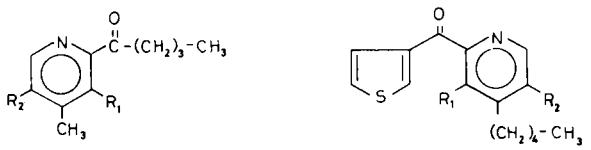
Formation of pavine in the papaverine reduction (10), transformation of 2-alkyl-1-(indol-3-ylmethyl)-1,2-dihydroisoquinolines into indolopavine derivatives (9c) and conversion of *N*-[β-(3-indolyl)-ethyl]pyridinium salts into indolo[2,3-*a*]quinolizine derivatives (11) can be considered similar processes, *i.e.*, cyclizations due to the reactivity of the intermediate dihydropyridines (or dihydroisoquinolines). In addition, the proposed mechanism is sustained by the fact that treatment of dihydropyridine IXa with diluted hydrochloric acid gave compound XIIIa in fair yield, whereas formation of XIIIb was inhibited when the dihydropyridine IXb was directly subjected to borohydride reduction, without any previous acid treatment which is usually performed after condensation in order to separate the non-aminated compounds (12).

Tetrahydropyridines Xa and XIa were obtained in the ratio 7:5 (by glc). Their separation could not be completely achieved either by column chromatography or by frac-

tional crystallization of their hydrochlorides. The position of the double bond was determined in both isomers by nmr spectral data by means of the same criteria (13) used for compounds VIIa and VIII (7b). Thus, the Δ^3-tetrahydropyridine (Xa) (major component, lowest glc retention time, and identical to that obtained by another procedure (14)) showed a broad signal at δ 5.17 due to the olefinic proton, whereas in the Δ^4-isomer (XIa) (minor component, longest glc retention time, and identical to the one obtained below), the signal appeared at lower field value, δ 5.37. Furthermore, the *N*-methyl signal in the hydrochloride spectrum of Xa appeared as a singlet (both in deuteriochloroform and deuterium oxide), supporting a Δ^3-tetrahydropyridine structure, whereas it appeared as an apparent triplet (in deuteriochloroform) or a doublet (in deuterium oxide) in the XIa hydrochloride spectrum, in accordance with a Δ^4-structure existing as a mixture of two epimers (13b). In the above reactions between thenylmagnesium halides and pyridinium salts, formation of abnormal products was never detected, in spite of the tendency of benzyl-type Grignard reagents to give this kind of side reactions (8) (15).

Tetrahydropyridines X and XI have also been obtained from 2-cyanopyridines (XIV). Thus, condensation of XIV with 3-thienyllithium (Scheme 3) led to ketones XV along with small amounts of the respective butyl ketones XVI (formed by the attack of butyllithium on cyanopyridines XIV) from which they could be separated by column chromatography. In the preparation of XVb, ketone XVIIb was also obtained. Its formation can be explained

Scheme 6

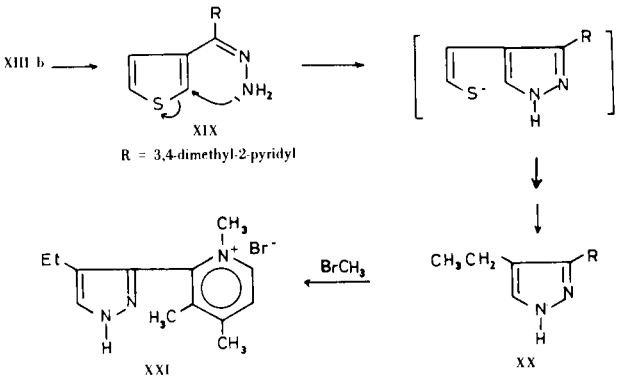


XVI XVII

a. R_1 R_2 H
b. R_1 CH_3 R_2 H
c. R_1 H R_2 CH_3

by metallation of the 4-methyl group of the pyridine ring, followed by its reaction with the butyl bromide present in the medium (formed in the halogen-metal exchange reaction during 3-thienyllithium formation), and could be minimized by addition of the 3-thienyllithium solution to the cyanopyridine XIV at -70°. The above compounds had nmr spectra and analyses consistent with the proposed structures. Wolff-Kishner reduction of ketones XVa and XVc afforded, in acceptable yields, the thenylpyridines XVIIIa and XVIIIc, respectively. Similar reduction of XVb, however, appeared to give, besides the expected ketone XVIIIb (17% yield) a compound which was identified as 4-ethyl-3-(3,4-dimethyl-2-pyridyl)pyrazole (XX) and characterized as its methobromide XXI. The nmr

Scheme 7



XIX

R = 3,4-dimethyl-2-pyridyl

XXI XX

spectrum of XX showed two doublets at δ 8.32 and δ 7.00 and two singlets at δ 2.25 and δ 2.10 due to the protons and the methyl groups, respectively, on the pyridine ring, a singlet at δ 7.28 due to the proton on the 5-position in the pyrazole ring, a quadruplet at δ 2.41 and a triplet at δ 1.03 due to the ethyl group. It seems reasonable to assume that in the conversion of XVb into XX by hydrazine treatment during the Wolff-Kishner reduction, the hydrazone XIX is formed as an intermediate (Scheme 7). An intramolecular attack of the amino group on the 2-position of the thiophene ring causes its opening and the simultaneous formation of the pyrazole ring whose lateral chain is further converted by reduction to the 4-ethyl group. Such a ring closure is not without precedent; as in our case, similar processes in which a pyrazole is isolated when treating different pentagonal heterocycles with a carbonyl group in β-position under Wolff-Kishner reduction conditions have been described (16).

Finally, the reaction of thenylpyridines (XVIII) with methyl bromide followed by sodium borohydride reduction in methanolic solution of the resulting methobromides (XXII) gave the tetrahydropyridines X and XI. Thus, reduction of XXIIa gave a mixture of two compounds in the ratio 5:1 (by glc), which corresponds to the isomeric 1,2,3,6- and 1,2,5,6-tetrahydropyridines (XIa and Xa, respectively), identical to those obtained by the Grewe method. Separation and purification of the Δ^4-isomer XIa was achieved by fractional crystallization of the hydrochloride of the mixture. Similarly, reduction of XXIIb and XXIIc afforded the tetrahydropyridine bases Xb and XIc, respectively, the former being also identical to the one obtained by the Grewe synthesis. The *N*-methyl signal in the nmr spectrum of Xb hydrochloride appeared as a doublet in deuteriochloroform (due to the NH/N-CH_3 coupling) and as a singlet in deuterium oxide (due to the interchange of the acidic proton for deuterium), whereas in the XIc hydrochloride spectrum it appeared as a triplet in deuteriochloroform (two epimers interconverting and interchanging their acidic protons slowly) and as a doublet in deuterium oxide. These results gave additional support

Table I

Compound	M.p. °C (Solvent) (a)	Yield	Formula	Analyses									
				Carbon %		Hydrogen %		Nitrogen %		Sulfur %		Halide %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Ia hydrochloride	203-204 (A-E)	49%	$C_{12}H_{18}ClNS$	59.11	58.87	7.44	7.68	5.74	5.57	13.15	12.86	14.54	14.86
Ib	78-79 (A)	45%	$C_{13}H_{19}NS$	70.55	70.42	8.65	8.71	6.33	6.45	14.46	14.35		
Id hydrochloride	207-210 (A-E)		$C_{13}H_{20}ClNS$	60.57	60.65	7.81	7.99	5.43	5.22	12.44	12.59	13.75	13.88
IIa hydrochloride	259-262 (M-E)	64%	$C_{12}H_{18}ClNS$	59.11	59.39	7.44	7.80	5.74	5.74	13.15	13.15	14.54	14.68
IIb hydrochloride	198-200 (A-E)	74%	$C_{13}H_{20}ClNS$	60.57	60.28	7.81	7.88	5.43	5.45	12.44	12.42	13.75	14.03
IIc hydrochloride	189-191 (A)	60%	$C_{13}H_{20}ClNS \cdot H_2O$	56.64	56.23	7.98	8.26	5.08	5.10				
IId hydrochloride	250-253 (A-E)		$C_{13}H_{20}ClNS$	60.57	60.39	7.81	7.81	5.43	5.32			13.75	13.85
IIIb hydrochloride	215-220 (A-E)		$C_{13}H_{20}ClNS \cdot H_2O$	56.64	56.94	7.98	8.36	5.08	5.09				
IIId hydrochloride	305-308 (A-M)		$C_{13}H_{20}ClNS$	60.57	60.86	7.81	7.80	5.43	5.48	12.44	12.61	13.75	13.48
IIIe·Picrate	217-220 (F)	30%	$C_{21}H_{26}N_4O_7S$	52.74	53.08	5.43	5.46	11.71	11.93				
VIIa hydrochloride	108-109 (A-E)	30% (b)	$C_{12}H_{18}ClNS \cdot 0.5\ H_2O$	57.01	57.34	7.57	7.57	5.54	5.56			14.04	14.05
VIIc·Picrate	126-129 (F)	16%	$C_{21}H_{26}N_4O_7S$	52.74	52.93	5.43	5.23	11.71	11.38	6.70	6.49		
VIII hydrochloride	137-139 (A-E)	30% (b)	$C_{12}H_{18}ClNS$	59.11	58.90	7.44	7.57	5.74	5.50				
Xb hydrochloride	117-122 (A-E)	54% (c)	$C_{13}H_{20}ClNS$	60.57	60.64	7.81	7.82	5.43	5.31	12.44	12.35	13.75	13.86
		37% (d)											
XIa hydrochloride	144-145 (A-E)	46% (e)	$C_{12}H_{18}ClNS$	59.11	58.82	7.44	7.72	5.74	5.52	13.15	13.25	14.54	14.58
		68% (f)											
XIc hydrochloride	153-155 (A)	49% (d)	$C_{13}H_{20}ClNS$	60.57	60.37	7.81	8.09	5.43	5.40	12.44	12.32	13.75	14.17
XIIIa·Picrate	165-170 (F)	38%	$C_{18}H_{18}N_4SO_7$	49.76	49.59	4.14	4.31	12.90	12.78	7.37	7.66		
XIIIb·Picrate	200-203 (F)		$C_{19}H_{20}N_4SO_7$	50.91	50.71	4.46	4.60	12.15	12.43	7.15	7.06		
XVa	94-95 (M)	52%	$C_{11}H_9NOS$	65.02	64.93	4.46	4.40	6.89	6.92	15.74	15.75		
XVb hydrochloride	198-200 (A)	53%	$C_{12}H_{12}ClNOS$	56.80	56.81	4.76	4.93	5.51	5.28	12.63	12.88	13.97	13.80
XVc	69-70 (E)	63%	$C_{12}H_{11}NOS$	66.37	66.56	5.10	5.25	6.45	6.22	14.75	14.80		
XVIa·Picrate	109-110 (F)		$C_{17}H_{18}N_4O_8$	50.24	50.34	4.47	4.37	13.79	13.78				
XVIb hydrochloride	127-128 (A)		$C_{12}H_{18}ClNO \cdot C_3H_6O$	63.03	63.13	8.46	8.49	4.90	4.85			12.40	12.60
XVIIb hydrochloride	145-148 (A)		$C_{16}H_{20}ClNOS$	62.02	61.75	6.50	6.83	4.52	4.65	10.35	10.01		
XVIIIa hydrochloride	185-187 (A)	54% (g)	$C_{11}H_{12}ClNS$	58.48	58.51	5.36	5.42	6.20	6.08	14.20	14.43	15.70	15.90
		20% (h)											
XVIIIb hydrochloride	158-159 (A)	23%	$C_{12}H_{14}ClNS$	60.11	59.91	5.89	5.92	5.85	5.55				
XVIIIc hydrochloride	186-187 (A)	67%	$C_{12}H_{14}ClNS$	60.11	59.87	5.89	6.18	5.85	5.93	13.37	13.47	14.79	15.06
XXI	220-222 (A-F)	10%	$C_{13}H_{18}BrN_3$	52.71	52.40	6.12	6.39	14.18	14.50			26.97	26.61
XXIIa	202-204 (A-M)	78%	$C_{12}H_{14}BrNS$	50.70	50.64	4.96	5.03	4.92	4.83	11.28	11.17		
XXIIb	200-201 (A-M)	65%	$C_{13}H_{16}BrNS \cdot H_2O$	49.37	49.77	5.74	5.39	4.43	4.15	10.14	10.51	25.26	25.12
XXIIc	205-206 (A-M)	68%	$C_{13}H_{16}BrNS$	52.35	51.72	5.41	5.59	4.70	4.58	10.75	10.78		
XXIVa	83-85 (E)	39%	$C_{11}H_{15}NOS$	63.14	63.14	7.23	7.28	6.69	6.47	15.28	15.34		
XXIVb hydrochloride	144-146 (A)	18%	$C_{12}H_{18}ClNOS$	55.58	55.77	6.59	7.10	5.40	5.40	12.35	12.50	13.62	13.40

(a) Solvents: A = acetone; E = ether; F = ethanol; M = methanol. (b) Yield in a mixture of VIIa and VIII. (c) Yield by Grewe synthesis. (d) Yield from the appropriate methiodide, XXII. (e) Yield in a mixture of Xa and XIa by Grewe synthesis. (f) Yield in a mixture of Xa and XIa from the methiodide XXIIa. (g) Yield from ketone XVa. (h) Yield from carbinol XXIVa.

Table II

Thienomorphans: Chemical Shifts in Deuteriochloroform (δ values)

Compound	Thiophene H_α (a)	Thiophene H_β (a)	N-CH_3	C_5-CH_3	C_9-CH_3	Other CH_3
Ia (b)	6.92 d	6.70 d	2.27 s	1.30 s		
Ib	7.06 d	6.79 d	2.36 s	1.32 s	0.84 d	
Id	7.04 d	6.82 d	2.33 s	1.28 s	1.21 d	
IIa	7.04 d	6.78 d	2.36 s	1.38 s		
IIb (b)	6.95 d	6.67 d	2.25 s	1.33 s	0.82 d	
IIc	7.09 d	6.81 d	2.36 s	1.34 s		0.73 d (C_4-CH_3)
IId	7.06 d	6.77 d	2.30 s	1.31 s	1.21 d	
IIIb	6.90 (s, 2H)		2.37 s	1.34 s	0.79 d	
IIId	6.93 (d, H_2) (c)		2.32 s	1.30 s	1.21 d	
	6.84 (d, H_5) (c)					
IIIc			2.20 s	1.42 s	0.82 d	2.50 s (Ar-CH_3)

(a) $J_{H_\alpha\text{-}H_\beta}$ = 5 ppm unless otherwise indicated. (b) In carbon tetrachloride. (c) J = 2.4 cps.

to our previously described criterion for the structural determination of Δ^3- and Δ^4-tetrahydropyridines by nmr (13b).

Thenylpyridine XVIIIa was also prepared by an alternative synthetic route. The lithium derivatives (XXIII) of 2,4-lutidine and 2,3,4-trimethylpyridine, obtained by metallation of the pyridine bases with phenyllithium (17), were condensed with 3-ketotetrahydrothiophene (18), giving the tertiary alcohols XXIVa and XXIVb, respectively. Spectral data and analyses are consistent with the suggested structures. Attempts to dehydrate XXIVa with *p*-toluenesulfonic acid or by previously described methods (19) (sulfuric acid, potassium hydrogen sulfate) for the dehydration of other 3-hydroxytetrahydrothiophenes were unsuccessful. Unaltered carbinol XXIVa was recovered in all cases, and also a certain amount of the aromatization product, 2-(3-thenyl)-4-methylpyridine (XVIIIa) was obtained. Nevertheless, thionyl chloride treatment of XXIVa in dry benzene gave a mixture mainly formed, according to nrm analysis, of a dihydrothiophene, probably XXV (δ 3.61, s, pyridine-CH_2), along with XVIIIa. This mixture, without further purification, was converted into the thenylpyridine XVIIIa (identical to the one obtained from 2-cyano-4-methylpyridine) by sulfur dehydrogenation.

The preparation of thieno[3,2-*f*]morphans Ia-c by cyclization of the appropriate tetrahydropyridines with 48% hydrobromic acid (20) was recently reported (7a,b). In compound Ib nmr spectral data showed evidence for an α-diastereomer in which the 5- and 9-methyl groups were in a *cis* orientation respect to the hydroaromatic ring, whereas in Ic the 4- and 5-methyl groups were in a *trans* orientation with respect to the piperidine ring, *i.e.*, with the 9- (in Ib) and 4- (in Ic) substituents away from the lone pair of the nitrogen atom (21). By contrast, when the cyclization of VIIb was carried out with aluminum bromide, a mixture of α- and β-diastereomers (Ib and Id, respectively) was obtained, in which Id was predominant. Separation of the mixture was achieved either by chromatography through a silica gel column, or by preparative tlc. The nmr spectrum of Id showed: (i) two doublets ($J \simeq 5$ cps) in the aromatic region indicating an AX system formed by protons of the thiophene ring; (ii) a singlet at δ 1.28 due to the methyl group in the 5-position; and (iii) a doublet at δ 1.21 due to the 9-methyl group. Such a downfield chemical shift, in contrast with the δ 0.84 observed in the α-compound (Ib), showed evidence for a β-diastereomer (Id) (21). This result is similar to the one obtained by aluminum bromide cyclization in the benzomorphan series (22). Similarly, hydrobromic acid cyclization of the tetrahydropyridines Xa (or XIa), Xb and XIc gave the expected thieno[2,3-*f*]morphans IIa, IIb and IIc, respectively (20). Sterochemistry at the C_4- and C_9-centers was established in the same way as in the [3,2-*f*] series: the nmr spectra of IIb and IIc showed doublets at δ 0.82 and δ 0.73, respectively, thus indicating α-diastereomers (21). Furthermore, in the aromatic region, two doublets (AX type) with a coupling constant $J \simeq 5$ cps appeared in all cases according to the expected coupling constant between the 2- and 3-thiophene protons in a thieno[2,3-*f*]morphan structure (II). This indicated that cyclization had taken place on the 2-position of the thiophene ring.

Treatment of tetrahydropyridine Xb with aluminum bromide, however, was found to yield a four-component mixture in the ratio 3:1:1:1 (23). Separation of this mixture, partly achieved by chromatography through a silica gel column (24), gave two fractions. The first one was a mixture of β-2,5,9-trimethylthieno[2,3-*f*]morphan (IId) (major component in the original mixture) and β-2,5,9-trimethylthieno[3,4-*f*]morphan (IIId), from which isomer IIId was separated by fractional recrystallization of its hydrochloride salt. The resultant mother liquors (mainly IId) were reconverted into the free base, distilled and purified as the hydrochloride salt, affording IId hydrochloride. The second fraction was a mixture of α-2,5,9-trimethylthieno[2,3-*f*]morphan (IIb) and α-2,5,9-trimethylthieno[3,4-*f*]morphan (IIIb), the former being identical to the compound obtained in the hydrobromic acid cycli-

Table III

Chemical Shifts in Deuteriochloroform (δ values) (a)

Compound	Thiophene	H_α-Pyr	H_β-Pyr	=C-H	Ar-CH_2	N-CH_3	=C-CH_2	C-CH_3
VIa	7.26-6.75 m	5.95 d				2.42 s		1.64 s
VIIa	7.17-6.80 m			5.27 b	3.50-2.50 (m, 5H) (b)	2.42 s	2.25-1.85 m	1.66 s
VIIc	7.4 s				3.10-2.50 (m, 5H) (b)	2.28 s	2.12-1.86 b	1.62 s
	2.36 (s, 6H, Ar-CH_3)							1.54 s
VIII	7.20-6.74 m			5.37 b	3.30-2.65 (m, 5H) (b)	2.41 s	2.06-1.80 b	1.64 s
IXb	7.30-6.83 m	5.83 d	4.63 d		2.84-2.63 q	2.63 s		1.67 s
						3.78 t (c)		1.53 s
Xa	7.33-6.84 m			5.17 b	3.20-2.31 (m, 5H) (b)	2.40 s	2.25-1.78 m	1.64 s
Xb	7.27-6.99 m				2.97-2.42 (m, 5H) (b)	2.35 s	2.12-1.72 b	1.60 (s, 6H)
XIa	7.40-6.80 m			5.37 b	3.20-2.45 (m, 5H) (b)	2.41 s	2.10-1.75 b	1.62 s
XIc	7.30-6.79 m				3.22-2.50 (m, 5H) (b)	2.39 s	2.00-1.70 b	1.58 (s, 6H)
XVa	8.78 (dd, H_2)	8.52 d	8.76 (s, H_3)					2.40 s
	7.81 (dd, H_4)		7.45-7.13 (H_5)					
	7.45-7.13 (H_5)							
XVb (d)	8.02 (dd, H_2)	7.07 d	8.25 d					2.27 (s, 6H)
	7.61 (d, H_4)							
	7.22 (dd, H_5)							
XVc	8.83 (dd, H_2)	8.43 s	7.90 s					2.32 (s, 6H)
	7.87 (d, H_4)							
	7.31 (dd, H_5)							
XVIIIa	7.29-6.79 m	8.35 d	7.29-6.79 m		4.02 s			2.19 s
XVIIIb	7.35-6.75 m	8.27 d	6.93 d		4.17 s			2.21 s
								2.15 s
XVIIIc	7.50-6.85 m	8.20 s	6.84 s		4.01 s			2.10 (s, 6H)
XXIIa	7.49-6.97 m	9.42 d	7.85-7.49 (m, 2H)		4.73 s	4.55 s		2.55 s
XXIIb	7.43-6.90 m	9.31 d	7.81 d		4.68 s	4.49 s		2.60 s
								2.47 s
XXIIc (e)	7.47-6.92 m	9.04 s	7.51 s		4.53 s	4.35 s		2.41 s
								2.47 s

(a) Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal, dd = double doublet. (b) Signal due to the Ar-CH_2, N-CH_2 and N-CH groups. (c) Signal due to the N-CH group. (d) In carbon tetrachloride. (e) In deuteriochloroform-deuteriomethanol.

zation of Xb. Compound IIIb was separated by fractional recrystallization of its hydrochloride salt from acetone-ether in which IIb is much more soluble. The above isomeric structures were established from nmr spectral data. Nmr spectra of IId and IIId showed thereby a doublet at δ 1.21 as opposed to doublets at higher field values for IIb (δ 0.82) and IIIb (δ 0.79), providing evidence for β- and α-isomers, respectively. On the other hand, in compound IId the aromatic protons appeared as doublets with a coupling constant of J = 5 cps, both in the base (δ 7.06, and δ 6.77) and in the hydrochloride (δ 7.26 and δ 6.92). Similar results were obtained with compound IIb. In compound IIId, however, the aromatic protons appeared as a singlet (δ 7.14) in the hydrochloride, which was split in the free base into a doublet (H_2, δ 6.93) with a coupling constant of J = 2.4 cps (the one expected for a thieno[3,4-*f*]morphan structure) and a double doublet (H_5, δ 6.84) with J = 2.4 cps and J = 1.2 cps, the latter due to the long range coupling with a thenyl proton. Similarly, in the IIIb hydrochloride spectrum, a singlet appeared at δ 7.07 which remains (δ 6.90) in the free base.

Finally, we h ve synthesized unambiguously another thieno[3,4-*f*]morphan structure by the Grewe synthesis from 3-chloromethyl-2,5-dimethylthiophene (25) and 1,3,4-trimethylpyridinium iodide (Scheme 2). Borohydride reduction of the dihydropyridine VIc and hydrobromic acid cyclization of the resulting tetrahydropyridine VIIc on the singlet non-substituted position of the thiophene ring, gave the α-2,5,9-trimethyl-2′,5′-dimethylthieno-[3,4-*f*]morphan (IIIe). Its nmr spectrum revealed the absence of aromatic protons and showed a doublet at δ 0.82 due to C_9-methyl group.

Tests for analgesic activity of the above compounds are in progress, and interesting results have been found in some of them.

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 solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). The glc were run isothermally at 140° 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. The mass spectrum was determined on an AEI (model MS-902 S) mass spectrometer. Preparative tlc was run on Merck 60 F_{254} silica gel plates (2 mm). The developing solvent was ether/acetone/diethylamine: 95/3/2. Elemental analyses were performed by Instituto de Química Orgánica, Barcelona.

A. Tetrahydropyridines by the Grewe Synthesis.

2-Thenyl chloride, 3-thenyl bromide and 3-chloromethyl-2,5-dimethylthiophene (25) were converted in a modified cyclic reactor (8) to their corresponding Grignard reagents, which were allowed to react directly with the pyridinium salt (V) placed in the reaction flask. A freshly amalgamated column of magnesium turnings was prepared for each run. Thus, 0.4 mole of thenyl halide in 1 l. of dry ether were placed in a dropping funnel and 0.4 mole of the pyridinium iodide V, suspended in 1200 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 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 (A) 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 0.22 mole of dihydropyridine in 250 ml. of methanol, 150 ml. of 1 *N* sodium hydroxide and 0.3 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.

Tetrahydropyridines VIIa and VIII were separated and purified by fractional recrystallization of their hydrochlorides. Thus, crystallization from acetone-ether gave VIIa hydrochloride. The filtrate was concentrated yielding a small amount of VIII hydrochloride.

Tetrahydropyridines Xa and XIa could not be completely separated either by column chromatography or by fractional crystallization of their hydrochlorides. From the crude reaction mixture (Xa, XIa and XIIIa), compound XIIIa were separated by chromatography through a silica gel column on elution with benzene/chloroform: 1/1.

Tetrahydropyridine Xb was obtained by the above procedure together with variable amounts of XIIIb. Separation of Xb and XIIIb was carried out by chromatography through a silica gel column on elution with chloroform and chloroform/methanol: 9/1, respectively. Some of the major peaks in the mass spectrum of XIIIb were (m/e, relative intensity): 219 (98, parent ion), 218 (49), 204 (46), 173 (13), 150 (32) and 122 (100).

The formation of XIIIb can be avoided as follows: the dihydropyridine ethereal solution (A) was evaporated and the residue reduced as above. After cooling, the reduced reaction mixture was extracted several times 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 organic layer was dried and the solvent removed giving the tetrahydropyridine Xb which was purified by distillation.

7,10-Dimethyl-5,9-imino-4,5,8,9-tetrahydrocycloocta[*b*]thiophene (XIIIa).

3-Thenylmagnesium bromide was allowed to react with 1,4-dimethylpyridinium iodide in the cyclic reactor. 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 and the aqueous solution was refluxed for 1 hour. After cooling, the reaction mixture was made basic with ammonium hydroxide and extracted with ether. The ether layer was dried and the solvent was removed giving an oily residue identified as XIIIa. Some of the major peaks in the mass spectrum of XIIIa were (m/e, relative intensity): 205 (100, parent ion), 204 (56), 190 (45), 175 (11),

174 (11), 173 (13), 150 (57), 149 (12), 147 (10), 109 (11) and 108 (98); metastable ions were noted at m/e 110 (205→150) and 57 (205→108).

B. Tetrahydropyridines from 2-Cyanopyridines.

3-Thienyl Pyridyl Ketones (XV).

A solution of 74.2 g. (0.455 mole) of 3-bromothiophene in 400 ml. of dry ether was added dropwise to an ethereal butyllithium solution (540 ml., 1.18 *N*), keeping the temperature at -70°. The resulting mixture was stirred for 10 minutes under nitrogen and was slowly added at -70° to a solution of cyanopyridine XIV (0.28 mole) in dry benzene. When the addition was complete the mixture was maintained at -70° for 2 hours and then refluxed for 30 minutes. The resulting solution was hydrolyzed with 30% hydrochloric acid. The aqueous acidic layer was refluxed for 2 hours, rendered basic with 50% sodium hydroxide solution and extracted with chloroform. The organic layer was dried and the solvent removed, giving a residue which was purified by chromatography through a silica gel column. On elution with benzene, ketones XV were obtained.

n-Butyl 4-Methyl-2-pyridyl Ketone (XVIa).

This compound was obtained by chromatography of the XVa crude reaction mixture on elution with hexane/benzene:1/1; nmr: 8.54 (d, 1, C_6-H), 7.86 (s, 1, C_3-H), 7.27 (d, 1, C_5-H), 3.20 (t, 2, $COCH_2$), 2.39 (s, 3, C_4-CH_3), 0.94 (t, 3, CH_3).

n-Butyl 3,4-Dimethyl-2-pyridyl Ketone (XVIb).

This compound was obtained by chromatography of the XVb crude reaction mixture on elution with hexane/benzene:1/1; nmr (hydrochloride): 8.70 (d, 1, C_6-H), 7.97 (d, 1, C_5-H), 3.40 (t, 2, $COCH_2$), 2.64 (s, 3, C_4-CH_3), 2.42 (s, 3, C_3-CH_3), 2.15 (s, 6, acetone), 0.93 (t, 3, CH_3).

3-Thienyl 3-Methyl-4-pentyl-2-pyridyl Ketone (XVIIb).

This compound was obtained by chromatography of the XVb crude reaction mixture on elution with hexane/benzene:1/1; nmr (carbon tetrachloride): 8.22 (d, 1, C_6-pyridine), 7.96 (dd, 1, C_2-H thiophene), 7.53 (dd, 1, C_5-H thiophene), 7.14 (dd, 1, C_4-H thiophene), 7.02 (d, 1, C_5-H pyridine), 2.58 (t, 2, C_4-CH_2), 2.27 (s, 3, N-CH_3), 2.00-0.65 (broad signal, 9, $(CH_2)_3$-CH_3).

3-Thenylpyridines (XVIII).

To a solution of 21.6 g. of potassium hydroxide in 140 ml. of diethyleneglycol, 0.11 mole of XV and 17.9 g. of 85% hydrazine hydrate were added. The resulting mixture was refluxed for 1 hour and then enough water and excess hydrazine hydrate was distilled to raise the temperature to 170°, and the remaining solution was refluxed for 4 hours. The reaction mixture was poured over 200 g. of ice and extracted several times with ether. The ethereal layer was washed with water, dried and the solvent removed.

Thenylpyridine XVIIIa was obtained by distillation of the resulting oily residue.

Thenylpyridine XVIIIc was purified by chromatography through a silica gel column on elution with benzene.

The crude thenylpyridine XVIIIb was partly dissolved in benzene, and purified by chromatography through a silica gel column on elution with chloroform. The insoluble residue (m.p. 124-126°) was identified as 4-ethyl-3-(3,4-dimethyl-2-pyridyl)-pyrazole (XX); nmr: 1.03 (t, 3, CH_2CH_3), 2.10 (s, 3, C_4-CH_3), 2.25 (s, 3, C_3-CH_3), 2.41 (c, 2, CH_2), 7.00 (d, 1, C_5-H), 7.28 (s, 1, C-H pyrazole), 8.32 (d, 1, C_6-H). It was characterized as its methobromide (XXI), m.p. 220-222°; nmr: 1.07 (t, 3, CH_2CH_3), 2.15 (s, 3, C_3-CH_3), 2.25 (c, 2, CH_2), 2.66 (s, 3, C_4-CH_3), 4.12 (s, 3, N-CH_3), 7.80 (s, 1, C-H pyrazole), 7.97 (d, 1, C_5-H), 9.65 (d, 1, C_6-H). A similar result was obtained when the Wolff-Kishner reduction was performed in ethyleneglycol at 130°.

N-Methylpyridinium Salts (XXII).

Excess methyl bromide (27.8 g.) was passed through a cool stirred solution of XVIII (13.9 g.) in 75 ml. of acetone-benzene (3:1). The mixture was stirred at 0° for 30 minutes and then refluxed for 4 hours. By cooling, the methobromides (XXII) were obtained.

2-(3-Thenyl)-tetrahydropyridines.

Sodium borohydride (0.052 mole) was added portionwise in the cold to a stirred solution of 0.037 mole of methobromide (XXII) in 100 ml. of methanol. The mixture was gently refluxed for 6 hours, cooled, diluted with cold water and extracted with ether. Solvent was removed from the dried extract leaving the crude tetrahydropyridines as an oil which was purified by distillation *in vacuo*.

C. 2-(3-Thenyl)-4-methylpyridine (XVIIIa) from 3-Ketotetrahydrothiophene.

2-(3-Hydroxy-3-tetrahydrothienylmethyl)-4-methylpyridine (XXIVa).

An ethereal phenyllithium solution (920 ml., 1.3 *N*) was added dropwise under nitrogen to 150 ml. (2.4 moles) of 2,4-lutidine in 150 ml. of dry ether (temperature between 0-10°). When the addition was complete the mixture was stirred for 30 minutes at room temperature. Then, 92 g. (0.9 mole) of 3-ketotetrahydrothiophene (18) in 125 ml. of dry ether were added dropwise during 3 hours (temperature 0°). After 90 minutes at room temperature, the resulting mixture was poured into cold water and the aqueous layer was extracted with chloroform. The combined organic solutions were extracted with 10% hydrochloric acid. The acidic solution was rendered basic with 10% sodium hydroxide solution and extracted with chloroform. The organic phase was washed with water, dried and the solvent and excess of 2,4-lutidine removed by distillation *in vacuo*. Crystallization of the residue from ether-petroleum ether afforded 70 g. of XXIVa; nmr (carbon tetrachloride): 8.27 (d, 1, C_6-H pyridine), 6.92 (b, 2, C_3- and C_5-H pyridine), 5.45 (b, 1, OH), 2.99 (s, 2, pyridine-CH_2), 2.97-2.66 (m, 2, S-CH_2), 2.59 (s, 2, S-CH_2), 2.32 (s, 3, CH_3), 1.91 (t, 2, CH_2).

2-(3-Hydroxy-3-tetrahydrothienylmethyl)-3,4-dimethylpyridine (XXIVb).

In a similar way as described for XXIVa, 185 ml. of phenyllithium 0.9 *N*, 20 g. (0.165 mole) of 2,3,4-trimethylpyridine (26) and 12 g. (0.11 mole) of 3-ketotetrahydrothiophene gave 21 g. of an oily residue which was steam distilled to eliminate excess of 2,3,4-trimethylpyridine, and then purified by chromatography through a silica gel column. On elution with benzene/chloroform: 9/1, 5 g. (18% yield) of XXIVb was obtained which was characterized as its hydrochloride; nmr (hydrochloride): 8.44 (d, 1, C_6-H pyridine), 7.63 (d, 1, C_5-H pyridine), 3.70 (s, 2, pyridine-CH_2), 3.17-2.75 (m, 4, CH_2-S-CH_2), 2.56 (s, 3, C_4-CH_3), 2.47 (s, 3, C_3-CH_3), 2.23-1.86 (m, 2, CH_2).

2-(3-Thenyl)-4-methylpyridine (XVIIIa).

Thionyl chloride (16 ml., 0.22 mole) in 50 ml. of dry benzene was added slowly with stirring to a solution of 30 g. (0.144 mole) of XXIVa in 350 ml. of dry benzene cooled to 0°. When the addition was complete the mixture was refluxed for 1 hour, cooled and poured into ice water. The aqueous layer was made basic with 10% sodium hydroxide solution and extracted with ether. Evaporation of the dried ether extracts left an oil (24 g.) which was inti-

mately mixed with 4 g. of sulfur and heated at 140-145° for 2 hours. The cooled residue was extracted thrice with ether and thrice with benzene. The combined dried organic extracts were evaporated leaving a residue (20 g.) which was purified through a silica gel column. On elution with benzene 5.6 g. (20% yield) of thenylpyridine XVIIa were obtained. The base was distilled and converted into its hydrochloride, identical to the one obtained by Wolff-Kishner reduction of XVa.

Thienomorphans.

Hydrobromic Acid Cyclizations.

Tetrahydropyridine (0.02 mole) and 60 ml. of 48% hydrobromic acid were kept at 130-135° (oil bath temperature) for 4 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 hydrochlorides.

Aluminum Bromide Cyclization of VIIb.

A mixture of 0.02 mole of VIIb hydrochloride, 100 ml. of carbon disulfide, and 0.06 mole of aluminum bromide was refluxed for 17 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 (51% yield) a mixture of isomers, Ib and Id, which were separated by chromatography through a silica gel column. From 2.96 g. of mixture, 1.11 g. of Id on elution with benzene/chloroform: 1/9, and 0.72 g. of Ib on elution with chloroform/methanol: 9/1, were obtained.

Aluminum Bromide Cyclization of Xb.

Cyclization of Xb hydrochloride was carried out as described for VIIb. The residue from evaporation of the dried ethereal extracts was distilled at reduced pressure to give (76% yield) a mixture of isomers (IIb, IId, IIIb and IIId) which were partly separated by chromatography through a silica gel column. From 3.44 g. of mixture, 2.15 g. of a IId-IIId mixture on elution with benzene/chloroform: 2/8, and 1.23 g. of a IIb-IIIb mixture on elution with chloroform/methanol: 6/4, were obtained. The IId-IIId mixture was distilled *in vacuo* and converted into the hydrochloride. By fractional recrystallizations from acetone-methanol, isomer IIId was obtained as its hydrochloride. From the mother liquors the free base was liberated once again, distilled and reconverted in its hydrochloride salt. On recrystallization from acetone-ether, IId hydrochloride was obtained. Similar treatment of the IIb-IIIb mixture afforded IIIb hydrochloride (acetone-ether).

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