125. Heterocyclic Spiro-naphthalenones. Part I: Synthesis and Reactions of some Spiro[(1 *H*-naphthalenone)-1,3'-piperidines]

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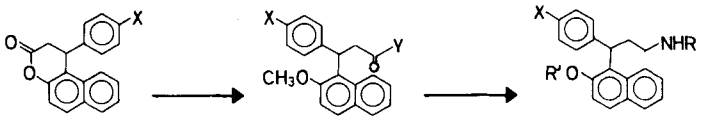
Summary

The title compounds **14**–**16** were obtained *via* an intramolecular *Mannich* condensation by treating **11**–**13** with CH_2O at RT. The unsaturated ketones **14** and **15** were reduced to the allylic alcohols **18** and **19** respectively. Ring cleavage of compound **18** on treatment with 2N HCl gave the substituted aminopropanol **20**. The allylic alcohols **18** and **19** were hydrogenated to **22** and **23** respectively. With CH_2O, the amino-alcohol **23** gave the methano-naphthoxazocine **24**, whereas **22** and **23**, on heating in polyphosphoric acid (PPA), afforded the naphthazepines **25** and **26** respectively. With organolithium compounds, the unsaturated ketones **14** and **16** gave the tertiary allylic alcohols **27**–**29**, which were hydrogenated and dehydrated to the olefins **36**–**40**; these were cyclized *via* an intramolecular alkylation to the methanodibenzo-octahydrocyclooctapyridines **41**–**43**. On heating in PPA, the allylic alcohol **29** was converted into the naphthazepine **44**. With CH_2O, the naphthol **49** gave the naphthoxazocine **50**, in equilibrium with the spiro-naphthalene-pyrrolidinone **51** in solution. Finally, in the presence of CH_2O, the naphthazepine **57** afforded the methano-naphthazepinone **58**, which, by a 4-stage degradation, was transformed to the benzisoquinoline **62**.

Introduction. – Spiro[naphthalen-1]-2-ones can be regarded as 6-spiro-cyclohexa-2,4-dienones [1] fused at the C(4)–C(5) double bond with a benzene ring. Therefore they should possess greater stability and be more readily accessible than their parent 6-spiro-cyclohexa-2,4-dienones. To our knowledge only a few examples of spiro[naphthalen-1]-2-ones have been reported in the literature[1]). We describe a very simple synthesis of some substituted spiro[1 *H*-naphthalenone)-1,3'-piperidines] (**14**, **15**, **16**) and the corresponding alcohols. Some aspects of their configuration and conformation are also presented. The alcohols, treated with acids, give rise to some interesting ring cleavages, rearrangements or cyclizations. A spiro[1*H*-naphthalenone)-1,3'-pyrrolidine] (**51**) and a related bridged naphthalen-2-one (**58**) are also included in this study.

[1]) For example [2] [3].



	X
1	H
2	Cl

	X	Y
3	H	OH
4	Cl	OH
5	H	NH CH_3
6	H	NH $CH_2C_6H_5$
7	Cl	NH CH_3

	X	R	R'
8	H	CH_3	CH_3
9	H	$CH_2C_6H_5$	CH_3
10	Cl	CH_3	CH_3
11	H	CH_3	H
12	H	$CH_2C_6H_5$	H
13	Cl	CH_3	H

Results. – 2-Naphthol and cinnamic or *p*-chlorocinnamic acid heated in a mixture of H_2SO_4 and acetic acid, gave the lactones **1** [4] or **2**. These were opened and methylated to give the carboxylic acids **3** [4] and **4**. The corresponding acid chlorides were treated with primary amines to yield the propionamides **5**, **6** and **7**, reduced with $LiAlH_4$ to **8**, **9** and **10**. The resulting methoxy-naphthylpropylamines were demethylated with BBr_3, giving the 2-naphthols **11**, **12** and **13**.

The spiro-ketones **14**, **15** and **16** were prepared by an intramolecular *Mannich* condensation which occurred almost instantaneously when the products **11**, **12** and **13** were treated with aqueous formaldehyde in ethanol at RT. The IR. spectrum of **14** showed a carbonyl band at 1660 cm^{-1}; its NMR. spectrum taken in $CDCl_3$ exhibited a doublet at δ 5.85 ppm attributable to the proton H_a and a multiplet at 9.4 assigned to H_b which seemed to interact strongly with the lone electron pair of the nitrogen atom.

In protic solvents the spiro-compound **14** was apparently in equilibrium with its readily reducible *Schiff*-base precursor; it gave on treatment with $NaBH_4$/methanol or H_2/(Pd/C)/ethanol the naphthol **17** exclusively. When the reduction was performed with $LiAlH_4$/THF the allylic alcohol **18** was obtained along with a small amount of **17**. Similarly, compound **15** was reduced with $LiAlH_4$/THF to give mainly **19**.

The presence of an intramolecular H-bridge between O and N in CH_2Cl_2 solutions of compound **18** was clearly demonstrated by a broad absorption in its IR. spectrum centered at 3150 cm^{-1} and not affected by dilution. The NMR. spectrum of **18** in $CDCl_3$ showed a sharp triplet at 3.6 ppm attributed to the equatorial proton H_c. No such sharp triplet could be observed on the NMR. spectrum of **14**, owing to the axial position of H_c.

The signal for H_b in **18** could no longer be distinguished from the multiplet for the aromatic protons which appeared at *ca.* δ 7.5 ppm, thus confirming the flipping of the piperidine ring which was maintained in the less stable conformation (axial phenyl group) by the H-bridge. Flipping back of the piperidine ring could be observed when the formation of the H-bridge was prevented by acetylation of the OH group; the signal attributed to H_b appeared again at a much lower field (δ 9.3 ppm). A shift to 8.9 ppm was also observed for H_b when the spectrum of **18** was taken in CD_3OD which promoted the cleavage of the intramolecular H-bridge.

A clear conclusion about the configuration at C(2) could not be drawn from NMR. spectroscopy. It was assumed that $LiAlH_4$ attacked the carbonyl group from the side which was not hindered by the equatorial phenyl group, thus giving the configuration indicated in formulae **18** and **19**[2]).

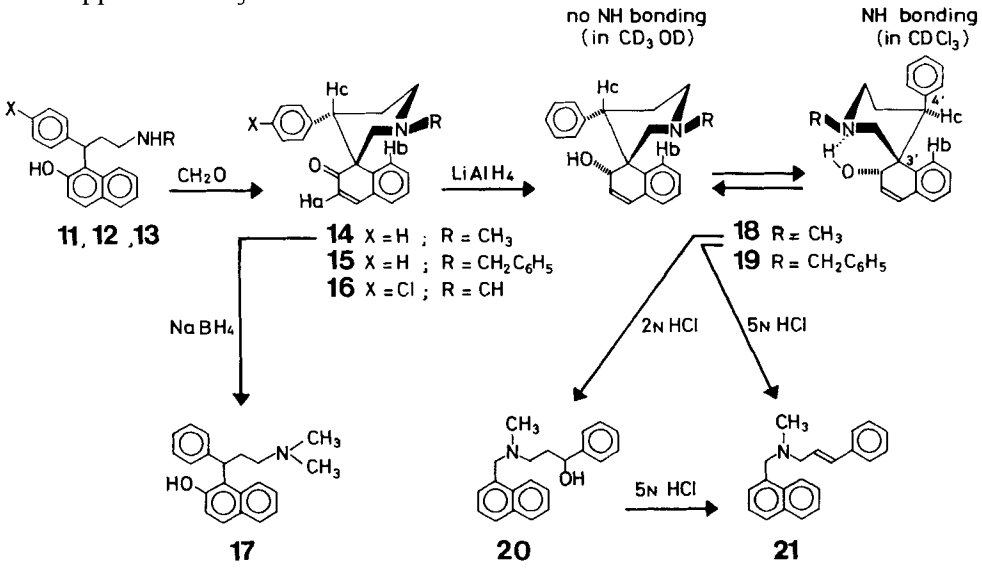
The spiro-compound **18** was readily cleaved to the aminomethyl-naphthalene **20** by mild aqueous acid treatment, or to its dehydrated form **21** under more strongly acid conditions[3]).

The allylic alcohols **18** and **19** were hydrogenated to give compounds **22** and **23** respectively which, treated with polyphosphoric acid (PPA), gave the naphthazepines **25** and **26** *via* a *Wagner-Meerwein* rearrangement. In the NMR. spectrum of **26** in C_6D_6, protons at C(2) appeared as a slightly split singlet due to a homoallylic coupling with protons at C(6).

The amino-alcohol **23** was cyclized to **24** by treatment with formaldehyde.

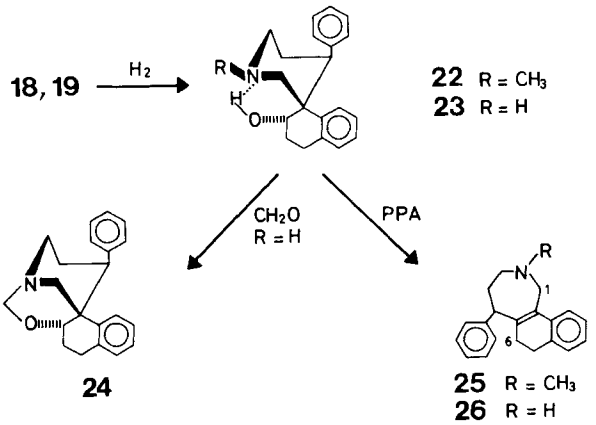
The unsaturated ketone **14** reacted with phenyllithium to give the tertiary allylic alcohol **27**, or with CH_3Li at $-20°$ to give **28**. Similarly the chlorinated spiro-ketone **16** reacted with CH_3Li to give **29**. The configuration at C(2) of compounds **27**, **28** and **29** could not be clearly deduced from NMR. data, but it was assumed that reagents such as $LiAlH_4$ selectively attacked the carbonyl group from the less hindered, side, thus forming the allylic alcohols **27**, **28** and **29**.

As reported for **18**, compounds **27**, **28** and **29** presented different conformations depending on the solvent ability to break the internal H-bridge. Both CD_3OD and ether shifted to δ 8.8 ppm the signal corresponding to H_b which appeared at *ca.* 7.5 ppm in $CDCl_3$.



[2]) The chloro-compound **16** was reduced with $LiAlH_4$ to the corresponding allylic alcohol which was submitted for X-ray crystal structure analysis. Its configuration was found to be identical with the postulated configuration of the allylic alcohols **18** and **19** [5].

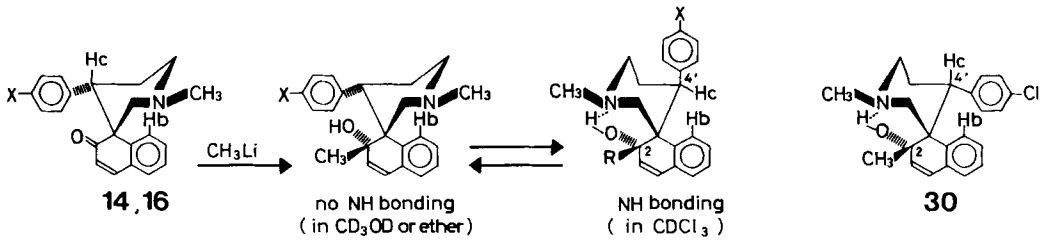
[3]) Compound **21** was also prepared by *N*-alkylation of *N*-methyl-1-naphthylamine with cinnamyl bromide.



When CH_3Li was added to the chlorinated compound **16** in boiling ether a 3:1 mixture of products **29** and **30** was obtained.

The NMR. spectrum of the isomeric tertiary allylic alcohol **30** taken in $CDCl_3$ did not show the sharp triplet appearing on the spectrum of **29** and corresponding to the equatorial H_c. This fact indicated that C(4') isomerized to the more stable configuration with the chlorophenyl group in equatorial position[4]). Only a very small proportion of isomerization could be observed when the unchlorinated compound **14** was treated with CH_3Li in boiling ether. The isomerization of the phenyl ring to a more stable configuration can be explained by the abstraction of the benzylic proton H_c by the bases present in the reaction mixture. The much higher degree of isomerization which occurred with **16** is probably the result of a lower pK_a value of H_c caused by the inductive effect of the chlorine atom.

The allylic alcohols **27** and **28** were hydrogenated to **33** and **34**. Under the same conditions chlorine was eliminated from **29** and **30** with the formation of **34** and **35**. The alcohol **33** was dehydrated by means of $SOCl_2$/pyridine to give the olefin **36**. Under similar conditions the alcohol **34** gave a 1:1 mixture of the exocyclic **37** and the endocyclic olefins **38** unseparable by thin-layer chromatography (TLC.) or by crystallization. When $POCl_3$ was used, **37** was obtained as the main product and



27 X = H ; R = C_6H_5
28 X = H ; R = CH_3
29 X = Cl ; R = CH_3

[4]) The configuration at C(2) of **30** was found by X-ray structure analysis to be identical to that of the reduction product of **16** [5] (see footnote 2).

sufficiently pure to have a clear NMR. spectrum. When the alcohol **35** was treated with $SOCl_2$/pyridine it gave a 1:1 mixture of the olefins **39** and **40** separable by TLC.

The flipping of the piperidine ring of the dehydrated products **36**, **37** and **38** was due to the disappearance of the N···H–O intramolecular H-bridge formed in $CDCl_3$ solutions of **33** and **34** and to the greater stability of the new conformation in respect of the equatorial position of the phenyl ring. The inversion of the conformation was shown in the NMR. spectra of **36** and **37** and in the spectrum of **38** in mixture with **37** (in $CDCl_3$) by the presence of the characteristic low field signal of H_b at δ 9.4 ppm. The NMR. spectrum of **37** showed also a signal at 5.35 ppm corresponding to the 2 olefinic protons H_e and H_f; no C-methyl signal was present proving the exocyclic nature of the double bond. The phenyl ring of compound **30** being equatorial, the piperidine ring should retain its stable conformation through hydrogenation and dehydration to give **39** and **40**. This assumption was supported by the NMR. spectra of **39** and **40** in $CDCl_3$ showing that H_b was not shifted by the influence of the nitrogen lone electron pair. In **39** the effect of the nitrogen was now directed on the proton H_e; its signal now appeared strongly shifted towards lower field (δ 6.5 ppm) compared with the signals of H_e and H_f both at 5.35 ppm in **37**. By contrast, the chemical shift of H_f in **39** (5.2 ppm) was very similar to that of H_e and H_f (5.35 ppm) in **37**.

The olefin **36** on treatment with PPA gave the pentacyclic compound **41**. The exocyclic olefin **37** either alone or mixed with the endocyclic olefine **38** gave **42** as the sole product when heated in PPA. Finally, both olefins **39** and **40** gave **43** on treatment with PPA[5]). The NMR. of these 3 cyclization products clearly showed the loss of one aromatic and all olefinic protons owing to the intramolecular alkylation of the phenyl group by the olefinic function. The presence of the H_b low-field NMR.-signal in both **41** and **42** (9.4 and 9.2 ppm) indicated that the N-H_b interaction was maintained; this signal was not present on the spectrum of **43**. The C-methyl signal, absent in **37** and **39**, appeared as a doublet at 1.5 and 1.15 ppm in the spectra of **42** and **43** respectively; this proves that the exocyclic double bond had migrated to the endocyclic position to give the isomers **38** and **40** prior the cyclization which occurred at C(3).

However a further migration of the double bond from C(2)–C(3) to C(3)–C(4) cannot be excluded as this could yield identical cyclized products. The absence of a signal corresponding to a diphenylmethane-like proton rules out the possibility of a cyclization at C(4). No firm conclusions could be drawn from the NMR. spectra concerning the C(15) configuration of **41**, **42** and **43**; this was thought, however, to be as shown in the *Scheme* with the new bond *cis* to the C(15) substituent, as expected in this type of cyclization.

Compound **29** on treatment with PPA gave the azocine **44**. The NMR. spectrum of the crude product suggested the presence of a small amount of the cinnamylamine **45**. No azocine was found when **18** was treated in a similar manner; here only the cinnamylamine **21** was obtained. The formation of **44** was probably due to

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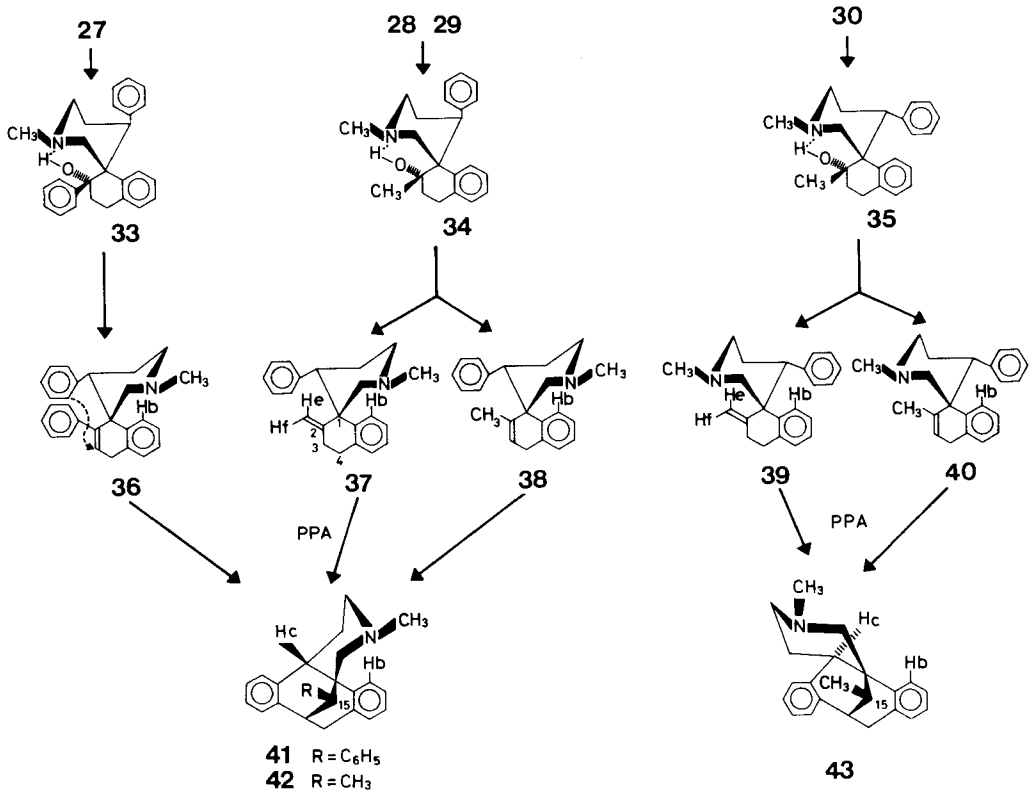
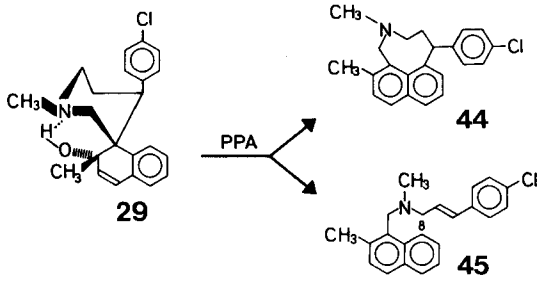
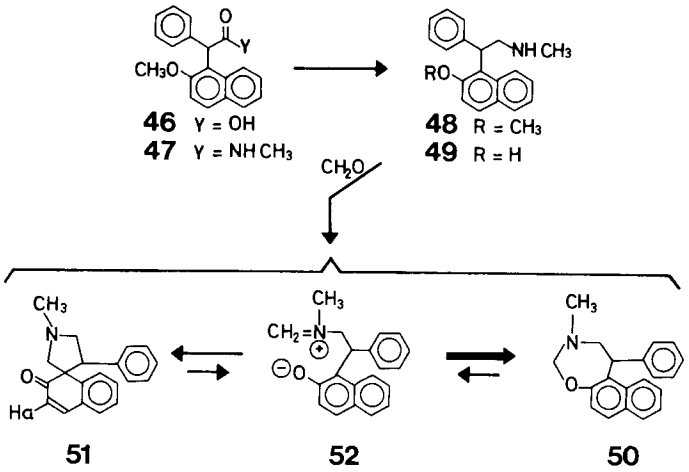
[5]) Compounds **41**, **42** and **43** can be obtained more simply by treating the alcohols **33**, **34** and **35** in PPA.

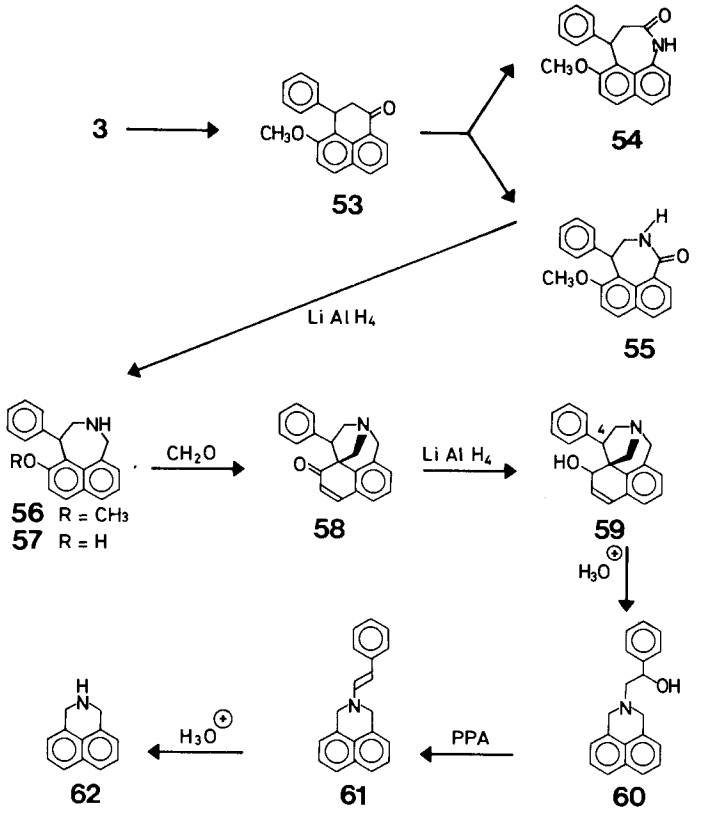


cyclization of the intermediate **45**. This cyclization would be expected to be facilitated by the 2-methyl group activating position 8 of the naphthalene nucleus.

The naphthylphenylacetic acid **46** [6] was converted to its chloride which reacted with methylamine to give the amide **47**. This was reduced with B_2H_6 to **48** which was demethylated to the β-naphthol **49**. The naphthol **49** cyclized to the oxazepine **50** with aqueous formaldehyde. Solutions of **50** exhibited a peculiar equilibrium with the spiro-compound **51**, probably through the ionic intermediate **52**. A Nujol mull of **50** showed no carbonyl band in the IR. spectrum, but when the spectra were taken in solvents a carbonyl band appeared. The amount of the tautomeric spiro-compound **51** was dependent on the solvent used. It was deter-




46 Y = OH
47 Y = NH CH3
48 R = CH3
49 R = H
CH2O
51
52
50


3
53
54
55
Li Al H4
56 R = CH3
57 R = H
CH2O
58
Li Al H4
59
H3O⊕
60
PPA
61
H3O⊕
62

mined by measuring the intensity of the NMR. absorption due to proton H_a easily visible as a doublet at δ 5.6 ppm (H_a of **14** at 5.85 ppm). In $CDCl_3$, **50** and **51** were present in a 3:1 ratio; in C_6D_6 the ratio was 6:1. The transformation of **50** to **51** was reversible. For example, when the $CDCl_3$ solution was evaporated to dryness and the residue triturated with Nujol, the carbonyl band was no longer present in the IR. spectrum.

When the formation of an oxazepine of type **50** was prevented by keeping the amino function away from the phenolic group, *e.g.* in the naphthazepine **57**, the stable 5-membered ring spiro compound **58** was formed. Compound **53** [4] was submitted to the *Schmidt* reaction giving a 3:2 mixture of **55** and **54**. The lactam **55** was reduced to the cyclic amine **56** which was demethylated to **57**. The bridged compound **58**, obtained by treating **57** with aqueous formaldehyde, was reduced with $LiAlH_4$ to the allylic alcohol **59**. No final conclusions could be drawn from spectroscopic data concerning the configuration of **58** and **59**.

In analogy to the conversion by ring cleavage of **18** into **20**, the allylic alcohol **59** was treated with 5N HCl to give the amino alcohol **60** which was dehydrated in PPA to the enamine **61**. This enamine was hydrolysed to the known benz[*d, e*]isoquinoline **62** [7].

I thank *Th. Jauner* for his excellent experimental assistance.

Experimental Part

General. – NMR. spectra were taken at 60 MHz in $CDCl_3$ unless otherwise stated, with TMS as an internal standard, using a *Varian* T-60 NMR. spectrometer. In the case of salts, a sample of the free base was prepared and used in $CDCl_3$. Abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, br. = broad; chemical shift in δ-values (ppm) coupling constants in Hz. – Analytical results obtained for the indicated elements were within ± 0.4% of the theoretical values.

1-(4-Chlorophenyl)-benzo[f]chroman-3-one (**2**). Conc. sulfuric acid (120 ml) was added to stirred glacial acetic acid (280 ml) below 60°. *p*-Chlorocinnamic acid (123.9 g, 0.682 mol, *Fluka*) and β-naphthol (98.2 g, 0.682 mol) were added and the mixture was heated 1 h under reflux then cooled to *ca.* 20°. After addition of $CHCl_3$ (500 ml), the solution was poured into ice/water (3 l). The $CHCl_3$ layer was separated, washed with 2N Na_2CO_3, dried and evaporated. The residue was crystallized from ether/petr. ether, giving 44 g (20%) of **2**, m.p. 98–100°. – $C_{19}H_{13}ClO_2$: C, H, N.

3-(4-Chlorophenyl)-3-(2-methoxy-1-naphthyl)-propanoic acid (**4**). The lactone **2** (77.8 g, 0.252 mol) was dissolved in boiling 10% NaOH (230 ml) with stirring. The solution was then cooled to 40° and dimethyl sulfate (23 ml) was added dropwise. The reaction mixture was heated for 3 min under reflux and cooled to 40°. Solid NaOH (11.5 g) and dimethyl sulfate (11.5 g) were added again, the solution was refluxed for a further 10 min, cooled to 20° and acidified with 5N HCl (200 ml). The acid **4** was extracted with $CHCl_3$ and the solution evaporated. The product crystallized from $CHCl_3$/ether giving 58.5 g (68%), m.p. 176–180°. – $C_{20}H_{17}ClO_3$: C, H, N.

Preparation of amides and lactams. – *3-(2-Methoxy-1-naphthyl)-N-methyl-3-phenylpropanamide* (**5**). The acid **3** [4] (30.6 g, 0.1 mol) was suspended in toluene (100 ml), $SOCl_2$ (13.1 g, 0.11 mol) was added and the mixture stirred at 80 to 90° until the gas evolution ceased. After distilling off about 20 ml toluene under reduced pressure, the acid chloride solution was added dropwise to a stirred solution of methylamine (18 ml) in toluene (200 ml) between −5 and 0°. The reaction mixture was washed successively with H_2O, 1N NaOH, 1N HCl, H_2O and then dried and concentrated to a volume of about 100 ml. On cooling 28.0 g (87%) of **5** crystallized, m.p. 136–139°. – $C_{21}H_{21}NO_2$: C, H, N. The following 3 compounds were prepared in the same manner as compound **5**.

N-Benzyl-3-(2-methoxy-1-naphthyl)-3-phenylpropionamide (**6**). From **3** [4] (68%), m.p. 113–115°. – $C_{27}H_{25}NO_2$: C, H, N.

3-(4-Chlorophenyl)-3-(2-methoxy-1-naphthyl)-N-methylpropionamide (**7**). From **4**, the crude product (not crystalline) was used for the next step.

2-(2-Methoxy-1-naphthyl)-N-methyl-2-phenylacetamide (**47**). From **46** [5] (57%), m.p. 134–137°. – $C_{20}H_{19}NO_2$: C, H, N.

5-Methoxy-4-phenyl-1,2,3,4-tetrahydro-naphth[1,8-c,d]azepin-1-one (**55**). During the experiment the reaction flask was flushed with N_2 to avoid concentration of HN_3 (caution! explosion hazard). The ketone **53** [4] (19.2 g, 0.066 mol) was dissolved in methanesulfonic acid containing 10% P_2O_5 (altogether 192 g of solution), and NaN_3 (5.2 g, 0.08 mol) was added in small portions with stirring. The temperature was maintained between 17 and 25°. After the addition of NaN_3, stirring was continued for 3 h and the reaction was poured into ice/water (500 ml). The products were extracted with $CHCl_3$. The organic layer was dried and evaporated. The residue crystallized from $CHCl_3$/ether, giving a mixture containing 60% of **55** and 40% of **54**. Pure lactam **55** (5.0 g, 24.7%) was isolated by fractional crystallization, m.p. 205–208°. – NMR.: 3.5 (*m*, 2 H–C(3)); 3.8 (*s*, CH_3O); 5.15 (*d*, H–C(4)); 6.4 (*t*, NH). – $C_{20}H_{17}NO_2$: C, H, N.

From the mother liquor *5-methoxy-4-phenyl-1,2,3,4-tetrahydro-naphth[1,8-b,c]azepin-2-one* (54) was separated (2.5 g, 12%), m.p. 215–225°. NMR.: 3.2 (*d*, $J=4$, 2 H–C(3)); 3.8 (*s*, CH_3O); 5.45 (*t*, $J=4$, H–C(4)); 8.65 (br. *s*, NH). – $C_{20}H_{17}NO_2$: C, H, N.

Reduction of amides or lactams. – *3-(2-Methoxy-1-naphthyl)-N-methyl-3-phenylpropylamine* (**8**). The amide **5** (12 g, 0.375 mol) was suspended in tetrahydrofuran (THF) (120 ml) and $LiAlH_4$ (3.4 g, 0.09 mol) was added. The reaction mixture was heated 1.5 h under reflux. The excess $LiAlH_4$ was destroyed by dropwise addition of a mixture of THF (90 ml) and H_2O (10 ml). The suspension was filtered and evaporated to dryness. The residue was crystallized from ether giving 8 g (70%) of **8**, m.p. 97–102°. – $C_{21}H_{23}NO$; C, H, N. – Hydrochloride, m.p. 195–197°.

The following 4 products were prepared in the same manner as **8**.

N-Benzyl-3-(2-methoxy-1-naphthyl)-3-phenylpropylamine (**9**) *hydrochloride.* From **6** (64%), m.p. 195–199°. – $C_{27}H_{28}ClNO$: C, H, N.

3-(4-Chlorophenyl)-3-(2-methoxy-1-naphthyl)-N-methylpropylamine (**10**) *naphthalene-1,5-disulfonate.* From **7** (71,8%), m.p. 260–267°. – $C_{26}H_{26}ClNO_4S$: C, H, N. For the preparation of naphthalene-1,5-disulfonates see [8].

2-(2-Methoxy-1-naphthyl)-N-methyl-2-phenylethylamine (**48**) *naphthalene-1,5-disulfonate.* From **47**, reduced with B_2H_6 (59%), m.p. 195–196°. – $C_{25}H_{25}NO_4S$: C, H, N.

5-Methoxy-4-phenyl-1,2,3,4-tetrahydro-naphth[1,8-c,d]azepine (**56**) *naphthalene-1,5-disulfonate.* From **55** (73%), m.p. 304–306°. – $C_{25}H_{23}NO_4S$: C, H, N.

Cleavage of methoxynaphthalenes to naphthols. – *1-(3-Methylamino-1-phenylpropyl)-2-naphthol* (**11**) *hydrochloride.* The amine **8** (30.5 g, 0.1 mol) dissolved in CH_2Cl_2 (300 ml) was cooled to 0–5° and a mixture of BBr_3 (50 g, 0.2 mol) in CH_2Cl_2 (500 ml) was added dropwise. After 20 min methanol (50 ml) was added cautiously and the solution was washed with 2N $KHCO_3$ (500 ml). The organic layer was dried and evaporated. The amine **11** was converted to its hydrochloride which crystallized from methanol/ether giving 20 g (61%) of product, m.p. 220–223°. – $C_{20}H_{22}ClNO$: C, H, N.

The following 4 compounds were prepared in the same manner as compound **11**.

1-(3-Benzylamino-1-phenylpropyl)-2-naphthol (**12**) *hydrochloride.* From **9** (48%), m.p. 261–263°. – $C_{26}H_{26}ClNO$: C, H, N, Cl.

1-[3-Methylamino-1-(4-chlorophenyl)propyl]-2-naphthol (**13**) *hydrochloride.* From **10** (80%), m.p. 245–251°. – $C_{20}H_{21}Cl_2NO$: C, H, N.

1-(2-Methylamino-1-phenylethyl)-2-naphthol (**49**). From **48** (67%), m.p. 138–145°. – $C_{19}H_{19}NO$: C, H, N.

4-Phenyl-1,2,3,4-tetrahydro-naphth[1,8-c,d]azepin-5-ol (**57**) *hydrobromide.* From **56** (83%), m.p. 262–272°. – $C_{19}H_{18}BrNO$: C, H, N.

Cyclizations to spiro-naphthalenones. – *Spiro[(1 H-naphthalenone)-1,3'-(trans-1'-methyl-4'-phenyl)-piperidine]* (**14**). The base of the naphthol **11**, liberated from the hydrochloride (141.8 g, 0.433 mol) was dissolved in ethanol (430 ml), a 35% aqueous solution of CH_2O (80 g, 1 mol) was added and the reaction mixture was kept for 10 min at RT. Water (5 l) was added and the product was extracted with $CHCl_3$. The organic layer was dried, evaporated and the residue crystallized from hexane giving 115.6 g (88.4%) of **14**, m.p. 96–98°. – NMR.: 2.35 (*s*, CH_3N); 5.85 (*d*, H–C(3)); 9.4 (*d*×*d*, H–C(8)). – IR.: strong 1660 cm^{-1}. – $C_{21}H_{21}NO$: C, H, N.

The following 4 products were prepared in the same manner as compound **14**.

Spiro[(1 H*-naphthalenone)-1,3'-(*trans*-1'-benzyl-4'-phenyl)piperidine]* (**15**). From **12** (89%), m.p. 109–111°. – $C_{27}H_{25}NO$: C, H, N.

Spiro[(1 H*-naphthalenone)-1,3'-(*trans*-4'-(4-chlorophenyl)-1'-methyl)piperidine]* (**16**). From **13** (86%), m.p. 112–116°. – $C_{21}H_{20}ClNO$: C, H, N, Cl.

*3-Methyl-1-phenyl-2,3,4,5-tetrahydro-naphth[1,2-*f*] [1,3]oxazepine* (**50**) and its equilibrium with *Spiro[(1* H*-naphthalenone)-1,3'-(1'-methyl-4'-phenyl)pyrrolidine]* (**51**) in solutions. From **49**, 40% of pure crystalline **50**, m.p. 98–99°. – IR. (Nujol): no carbonyl absorption; in methanol, C=O, 1660 cm^{-1}. – NMR.: Discussed in the text; ratio of **50** and **51** in $CDCl_3$ 2:1, in C_6D_6 6:1. – $C_{20}H_{19}NO$: C, H, N.

*4-Phenyl-2,4a-methano-1,2,3,4-tetrahydronaphth[1,8-*c,d*]azepin-5-one* (**58**). From **57** (65%), m.p. 153–155°. – UV. (ethanol 95%): λ_{max} 245 nm (ε 6.900). – IR. ($CHCl_3$): 1660 cm^{-1}. – NMR.: 3.8 and 4.05 (2 *d*, J_{AB} = 10, 2 H–C(3)); 4.1 and 4.6 (2 *d*, J_{AB} = 18, 2 H–C(1)); 6.0 (*d*, H–C(6)). – $C_{20}H_{17}NO$: C, H, N.

Reduction of the spiro-naphthalenones. – *1-(3-Dimethylamino-1-phenylpropyl)-2-naphthol* (**17**). The spiro-compound **14** (0.75 g, 2.5 mmol) was reduced with $NaBH_4$ (0.57 g, 15 mmol) in methanol at 10°. After the usual work-up the product was crystallized from $CHCl_3$/ether giving 0.7 g (91.7%) of **17**, m.p. 150–158°. – NMR.: 2.3 (*s*, $(CH_3)_2N$); 5.1 (*d*×*d*, *J* = 4 and 13, H–C(3')). – $C_{21}H_{23}NO$: C, H, N.

(1 RS, *2* SR, *4'* SR)*-Spiro[(1,2-dihydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**18**) *hydrochloride.* To a mixture of $LiALH_4$ (14.7 g, 0.387 mol) and THF (800 ml) the spiro compound **14** (40 g, 0.132 mol) was added portionwise and the suspension was stirred at RT. for 30 min. After the usual work-up the residual amine was converted to its hydrochloride giving 34.1 g (76%) of **18**, m.p. 234–238°. – NMR.: 2.4 (*s*, CH_3N); 3.6 (*t*, *J* = 6, H–C(4')); 4.75 (*d*×*d*, *J* = 2 and 3, H–C(2)); 5.8 (*d*×*d*, *J* = 2 and 10, 1 H olef.); 6.15 (*d*×*d*, *J* = 3 and 10, 1 H olef.). – $C_{21}H_{24}ClNO$: C, H, Cl, N.

The following 2 compounds were prepared in the same manner as compound **18**.

(1 RS, *2* SR, *4'* SR)*-Spiro[(1,2-dihydro-2-naphthol)-1,3'-(1'-benzyl-4'-phenylpiperidine)]* (**19**) *hydrochloride.* From **15** (86%), m.p. 218–224°. – $C_{27}H_{28}ClNO$: C, H, Cl, N.

*4-Phenyl-2,4a-methano-1,2,3,4,4a,5-hexahydro-naphth[1,8-*c,d*]azepin-5-ol* (**59**) *hydrochloride.* From **58** (90%), m.p. 280–290° dec. NMR.: (DMSO-d_6): 4.65 (*s*, H–C(5)); 5.5 (*s*, H–C(6), H–C(7)). – $C_{20}H_{20}ClNO$: C, H, N.

Reaction of alkyl or aryllithium with spiro-naphthalenones. – *(1* RS, *2* SR, *4'* SR)*-Spiro[(2-methyl-1,2-dihydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**28**) *hydrochloride.* To a stirred solution of **14** (15 g, 0.05 mol) in ether (150 ml) at –20°, a 2M solution of CH_3Li in ether (75 ml, 0.15 mol, *Fluka*) was added dropwise. After the addition was complete, the reaction mixture was allowed to reach RT. Water (50 ml) was added cautiously and the etheral layer was separated, dried and evaporated. The product **28** was converted to its hydrochloride giving 13.6 g (76%), m.p. 265–267°. – NMR.: 1.2 (*s*, H_3C–C(2)); 2.4 (*s*, CH_3N); 3.75 (*t*, *J* = 6, H–C(4')); 5.7 (*d*, *J* = 10, 1 H, olef.); 6.0 (*d*, *J* = 10, 1 H, olef.). – $C_{22}H_{26}ClNO$: C, H, N.

(1 RS, *2* SR, *4'* SR)*-Spiro[(2-methyl-1,2-dihydro-2-naphthol)-1,3'-(4'-chlorophenyl-1'-methylpiperidine]* (**29**) *hydrochloride.* As above, but **14** was substituted by the chlorinated product **16** (54%), m.p. 250–255°. – NMR.: 1.2 (*s*, H_3C–C(2)); 2.4 (*s*, CH_3N); 3.7 (*t*, *J* = 6, H–C(4')); 5.6 (*d*, *J* = 10, 1 H, olef.); 5.95 (*d*, *J* = 10, 1 H, olef.). – $C_{22}H_{25}Cl_2NO$: C, H, N.

(1 RS, *2* SR, *4'* RS)*-Spiro[(2-methyl-1,2-dihydro-2-naphthol)-1,3'-(4'-chlorophenyl-1'-methylpiperidine)]* (**30**). As for the preparation of **29**, but carried out in refluxing ether. The allylic alcohols **29** and **30** were present in a 3:1 ratio; first **30** crystallized from ethanol (m.p. 175–181°). – NMR.: 1.2 (*s*, H_3C–C(2)); 2.4 (*s*, CH_3N); 5.4 (*s*, 2 H olef.); 6.0 (*s*, OH). – $C_{22}H_{24}ClNO$: C, H, N.

The mother liquor was treated with HCl/ether and the main isomer **29** crystallized as HCl salt.

(1 RS, *2* SR, *4'* SR)*-Spiro[(2-phenyl-1,2-dihydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**27**). Prepared as **28**, but using phenyllithium *(Fluka)* in place of methyllithium (71%), m.p. 129–132°. – $C_{27}H_{27}NO$: C, H, N.

Ring cleavage of the allylic alcohols. – *3-[(1-Naphthylmethyl)-methylamino]-1-phenyl-1-propanol* (**20**) *hydrochloride.* Compound **18** (15 g of the hydrochloride) was dissolved in 1N HCl (300 ml) and the mixture was heated for 2 h under reflux. After cooling, the solution was made alkaline with 30% NaOH. The product was extracted with $CHCl_3$ and the organic layer was dried and evaporated. The oily amine **20** was converted to its hydrochloride giving 5.6 g (37.3%), m.p. 156–158°. – NMR.: 2.3 (*s*, CH_3N); 3.9 (*s*, NCH_2Ar); 4.8 (*t*, *J* = 5, H–C(1)). – $C_{21}H_{24}ClNO$: C, H, N.

N-Methyl-N-(1-naphthylmethyl)-3-phenylprop-2-enamine (**21**) *hydrochloride.* A solution of the hydrochloride of amino-alcohol **20** (4 g) in 5N HCl was heated for 2 h under reflux working up as above (prep. of **20**). The product was converted to its hydrochloride giving 3.6 g (95%), m.p. 173–175°. – NMR.: 2.25 (*s*, CH_3N); 3.3 (*d*, $J=5$, 2 H–C(1)); 3.95 (*s*, NCH_2Ar); 6.5 (*m*, H–C(2), H–C(3)). – $C_{21}H_{22}ClN$: C, H, N.

2-(2,5-Dihydro-1H-benz[d,e]*isoquinolin-2-yl-1-phenylethanol* (**60**) *hydrochloride.* From **59**, as for the preparation of **20** but treated with 5N instead of 1N HCl, (85%), m.p. (dec.) 225–229°. – NMR.: 2.75 (split *d*, $J=6$, 2 H–C(2); 4.0 and 4.3 (2*d*, $J_{AB}=16$, 2 H–C(1'). 2 H–C(3')); 4.95 (split *t*, $J=6$, H–C(1)). – $C_{20}H_{20}ClNO$: C, H, N.

2,5-Dihydro-1H-benz[d,e]*isoquinoline* (**62**). The hydrochloride of amino-alcohol **60** (200 mg) was dehydrated by heating in PPA (4 g) at 105° for 15 min. The mixture was poured into water and the solution boiled 15 min in order to hydrolyse the enamine **57**, cooled and made alkaline with 10% NaOH. The product was extracted with $CHCl_3$. After the usual work-up the product was crystallized from hexane yielding 130 mg of **62**, m.p. 100–105°. Lit [7] m.p. 105–106°. – $C_{12}H_{11}N$: C, H, N.

5-(4-Chlorophenyl)-2,11-dimethyl-2,3,4,5-tetrahydro-1H-naphth[1,8-c,d]azocine (**44**). The suspension of the hydrochloride of **29** (15 g) in PPA at 70° was kept 45 min between 80–90°. The solution was then poured into ice-water, made alkaline with 10% NaOH and extracted with $CHCl_3$. After the usual work-up 6.3 g (49%) of **44** were obtained, m.p. 146–152°. – NMR.: 2.5 and 2.6 (2 *s*, $ArCH_3$, NCH_3); 4.3 and 5.1 (2 *d*, $J_{AB}=14$, 2 H–C(1)); 5.8 (*d*×*d*, $J=4$ and 12, H–C(5)). – $C_{22}H_{22}ClN$: C, H, N.

Hydrogenation of the allylic alcohols. – (*1* RS, *2* SR, *4'* SR)-*Spiro[(1,2,3,4-tetrahydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**22**) *hydrochloride.* The hydrochloride of the allylic alcohol **18** (7.0 g) was dissolved in ethanol (350 ml), 5% Pd/C (1.5 g) was added and the mixture was hydrogenated. After the usual work-up, 6.1 g (86%) of **22** hydrochloride crystallized from ethanol/ether, m.p. 245–251°. – NMR.: 2.35 (*s*, CH_3N); 3.45 (*t*, $J=6$, H–C(4')); 4.0 (*t*, $J=8$, H–C(2)); 7.6 (*m*, H–C(8)). – $C_{21}H_{26}ClNO$: C, H, N.

(*1* RS, *2* SR, *4'* SR)-*Spiro[(1,2,3,4-tetrahydro-2-naphthol)-1,3'-(4'-phenylpiperidine)]* (**23**) *hydrochloride.* The hydrochloride of compound **19** was hydrogenated as **18** but in glacial acetic acid instead of ethanol, (68%), m.p. 279–287°. – $C_{20}H_{24}ClNO$: C, H, Cl, N.

(*1* RS, *2* SR, *4'* SR)-*Spiro[(2-methyl-1,2,3,4-tetrahydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**34**) *hydrochloride.* Compound **28** was hydrogenated as **18** (88%), m.p. 270–272°. – NMR.: 1.2 (*s*, $H_3C–C(2)$); 2.35 (*s*, CH_3N); 3.5 (*t*, $J=6$, H–C(4)). – $C_{22}H_{28}ClNO$: C, H, N. This product could also be obtained by hydrogenation of the chloro compound **29**, absorbing in this case 2 eq. of H_2 (38%).

(*1* RS, *2* SR, *4'* SR)-*Spiro[(2-phenyl-1,2,3,4-tetrahydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**33**) *hydrochloride.* Compound **27** was hydrogenated analogously to **18** (95%), m.p. 195–205°. – $C_{27}H_{30}ClNO$: C, H, N.

(*1* RS, *2* SR, *4'* RS)-*Spiro[(2-phenyl-1,2,3,4-tetrahydro-2-naphthol)-1,3'-(1'-methyl-4'-phenylpiperidine)]* (**35**) *hydrochloride.* Compound **30** was hydrogenated analogously to **18**. Two equivalents of H_2 were absorbed yielding 99% of **35** hydrochloride, m.p. 276–280°. – NMR.: 1.2 (*s*, $H_3C–C(2)$); 2.4 (*s*, CH_3N). – $C_{22}H_{28}ClNO$: C, H, N.

Reaction of the amino-tetrahydronaphthol 24 with formaldehyde. – (*1* RS, *4* SR, *6a* RS, *12b* SR)-*1-Phenyl-4,12b-methano-1,2,3,4,6a,7,8,12b-octahydro-naphth[1,2-g] [1,3]oxazocine* (**24**). The amino-alcohol **23** prepared from its hydrochloride (7.5 g, 0.023 mol) was dissolved in ethanol (50 ml); a 35% CH_2O solution in H_2O (5 g, 0.059 mol) was added. The mixture was left 30 min at RT., diluted with water (250 ml) and extracted with $CHCl_3$. The evaporation residue was crystallized from hexane giving 5.5 g (78.5%) of **23**, m.p. 114–116°. – NMR.: 4.7 (*s*, 2 H, OCH_2N). – $C_{21}H_{23}NO$: C, H, N.

Dehydration of tetrahydronaphthols. – *2-Methyl-5-phenyl-1,2,3,4,6,7-hexahydro-5H-naphth[1,2-c]azepine* (**25**) *naphthalene-1,5-disulfonate.* The hydrochloride of **22** (16 g) was suspended in PPA (160 g, *Fluka*) and the mixture was heated 2 min at 100°. The reaction mixture was poured into H_2O, made alkaline and then extracted with $CHCl_3$. The evaporation residue was treated with naphthalene-1,5-disulfonic acid (NDS) [8] giving 6.4 g (30%) of NDS salt, m.p. 311–313°, crystallized from dimethylformamide/H_2O/ether. – $C_{26}H_{27}NO_3S$: C, H, N.

Was prepared (as **25**): *5-Phenyl-2,3,4,6,7-hexahydro-5H-naphth[1,2-c]azepine* (26) *hydrochloride.* From the hydrochloride of **23** (38%), m.p. 232–238°. NMR. (C_6D_6): 1.35 (*s*, HN); 2.35 (split *t*, $J=6$, 2 H–C (6)); 2.9 (*t*, $J=6$, 2 H–C(7)); 3.15 (split *s*, 2 H–C(1)); 4.25 (*t*, $J=9$, H–C(5)). – $C_{20}H_{22}ClN$: C, H, N.

*Spiro[(2-phenyl-1,4-dihydronaphthalene)-1,3'-(*cis*-1'-methyl-4'-phenylpiperidine)]* (**36**) *hydrogen-maleate.* The benzyl alcohol **33** (15.6 g) was dissolved in pyridine (150 ml), and $SOCl_2$ (11 ml) was added dropwise at RT. After the addition the reaction mixture was stirred for 15 min and poured into ice/water. The product was extracted with $CHCl_3$ which was washed thoroughly with H_2O, dried and evaporated. The product **36** was isolated by means of its hydrogen-maleate which was recrystallized 3 times from ethanol/ether giving 2.45 g (12%), m.p. 165–167. – NMR.: 2.15 (*s*, CH_3N); 5.7 ($d \times d$, $J = 2$ and 6, H–C(3)); 9.4 (*m*, H–C(8)). – $C_{31}H_{31}O_4N$: C, H, N.

*Spiro[(2-methylidene-1,2,3,4-tetrahydronaphthalene)-1,3'-(*cis*-1'-methyl-4'-phenylpiperidine)]* (**37**) and *spiro[(2-methyl-1,4-dihydronaphthalene)-1,3'-(*cis*-1'-dimethyl-4'-phenylpiperidine)]* (**38**). Prepared from the alcohol **34** under conditions similar to those used for the preparation of **36**. The reaction gave a 1:1 mixture of **37** and **38** as hydrochlorides, (36%), m.p. 215–245°. The compounds were not separated. When the reaction was carried out in refluxing $POCl_3$ (20 min) instead of $SOCl_2$/pyridine at RT., **37** and **38** were obtained in a 6:1 mixture. The NMR. spectrum is discussed in the text.

*Spiro[(2-methylidene-1,2,3,4-tetrahydronaphthalene)-1,3'-(*trans*-1'-methyl-4'-phenylpiperidine)]* (**39**) and *spiro[(2-methyl-1,4-dihydronaphthalene)-1,3'-(*trans*-1'-methyl-4'-phenylpiperidine)]* (**40**) *hydrochlorides.* Conditions similar to those used for the preparation of **36**. The alcohol **35** gave a 1:1 mixture of **39** and **40** hydrochlorides (45%), m.p. 210–230°. Oily free bases were separated by preparative TLC. (1 mm Silica gel, ethanol/$CHCl_3$/heptane, 6:35:65; $R_f = 0.75$ and 0.70). The NMR. is discussed in the text.

(4a SR, *9* SR, *14b* SR, *15* SR)*-2,3,4,4a,9,10-Hexahydro-2,15-dimethyl-1*H*-9,14b-methanodibenz-[3,4:7,8]-cycloocten[1,2-c]pyridine* (**42**). The hydrochloride of compound **34** (12 g) was suspended in PPA (120 g) and heated 45 min between 80–90°. The reaction mixture was poured into ice/water, made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was dried and evaporated. The residue crystallized from $CHCl_3$/ether giving 7.6 g (67%) of **42**, m.p. 156–158°. – NMR.: 1.15 (*d*, $J = 7$, H_3C–C(15)); 2.3 (*s*, CH_3N); 9.3 (*m*, H–C(14)). – $C_{22}H_{25}N$: C, H, N.

Compound **42** was similarly prepared from the olefin **37** or **38**.

(4a RS, *9* SR, *14b* SR, *15* SR)*-2,15-Dimethyl-9,14b-methano-dibenzo*[f,j]*-1,2,3,4,4a,9,10,14b-octahydrocycloocta[1,2-c]pyridine* (**43**) *hydrochloride.* Prepared as **42**. From **35** (73%), m.p. 252–260°. – NMR.: 1.5 (*d*, $J = 7$, H_3C–C(15)); 2.3 (*s*, CH_3N); 7.7 (*m*, H–C(14)).

Compound **43** was similarly prepared from the mixture of **39** and **40**.

(4a RS, *9* SR, *14b* SR, *15* SR)*-2-Methyl-15-phenyl-9,14b-methano-dibenzo*[f,j]*-1,2,3,4,4a,9,10,14b-octahydrocycloocta[1,2-c]pyridine* (**41**) *hydrochloride.* Experimental conditions were similar to those used for the preparation of **42**. From **36** (42%), m.p. 233–253°. – NMR.: 9.4 (*m*, H–C(14)). – $C_{27}H_{27}N$: C, H, N.

Compound **41** was similarly prepared from **33** in comparable yields.

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