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Synthesis of the Antidepressant Zimelidine and Related 3-(4-Bromophenyl)-3-(3-pyridyl)allylamines. Correlation of their Configurations

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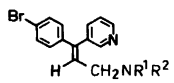
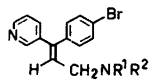
Various methods for the synthesis of the antidepressant (*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine, zimelidine, are described. In addition, syntheses of the analogous secondary and primary amines, as well as the corresponding tertiary, secondary and primary *E*-isomers are shown. The steric interrelations of these amines are discussed on the basis of chemical and spectral evidence (NMR, UV).

(*Z*)-3-(4-Bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)-allylamine (*1*), zimelidine, is a new antidepressant with secured clinical effect.[1,2] In connection with the evaluation of this drug, the investigation was extended to the corresponding secondary *3* and primary *5* amines as well as to the *E*-isomers *2*, *4* and *6*, see Fig. 1. This paper describes various synthetic routes to these compounds.

Originally *1* was prepared from the acetophenone *7* *via* the Mannich base *8* and the amino-alcohol *9* (Scheme 1).[3,4] Dehydration of *9* yielded a mixture of the diastereomers *1* and *2* in a ratio of 3:1. The separation of *1* and *2* was effectively achieved by utilizing the differing solubilities of their hydrochlorides. Precipitation in acetone gave the hydrochloride of *1* in high purity and good yield, and from the mother liquor *2* was isolated as the oxalate.





Z-Isomers			*E*-Isomers		
No.	R^1	R^2	No.	R^1	R^2
1	CH_3	CH_3	*2*	CH_3	CH_3
3	CH_3	H	*4*	CH_3	H
5	H	H	*6*	H	H

Fig. 1. Stereoisomers of the 3-(4-bromophenyl)-3-(3-pyridyl)allylamines discussed in this paper.

It was of interest to develop other more general routes to zimelidine, which could also be applied for synthesis of the secondary and primary amines *3*–*6*. A key intermediate, the ketone *10*, was prepared essentially as previously described.[5]

As shown in Scheme 1, a Reformatsky reaction of *10* gave the hydroxy-ester *11*, which was subsequently reduced to the diol *12*. A mixture of isomeric allylic bromides *13* was obtained either by treating *12* with phosphorus tribromide or by bromination of the isomer mixture *14*. The latter was formed in a Wittig reaction, which gave a *Z*–*E*-ratio of 1:1, while the bromination of *12* gave an isomer ratio of 4:1. The bromides were treated *in situ* with dimethylamine or with methylamine giving mixtures of *1* and *2* or of *3* and *4*, respectively, (Schemes 1 and 2). A mixture of *1* and *2* was also formed directly from the ketone *10*, using the ylide from 2-(dimethylamino)ethyltriphenylphosphonium bromide.[6] This reaction, carried out in tetrahydrofuran, gave the isomers *1* and *2* in a ratio of 3:2.

Furthermore, the hydroxy-ester *11* was used in a reaction sequence, leading *via* the amide *17* and the amino-alcohol *18* to the secondary amines *3* and *4* (Scheme 2). These were formed as a mixture in approximately the same *Z*–*E*-ratio as were *1* and *2* in the dehydration of *9*. The separation of *3* and *4* was achieved by precipitation of their oxalates

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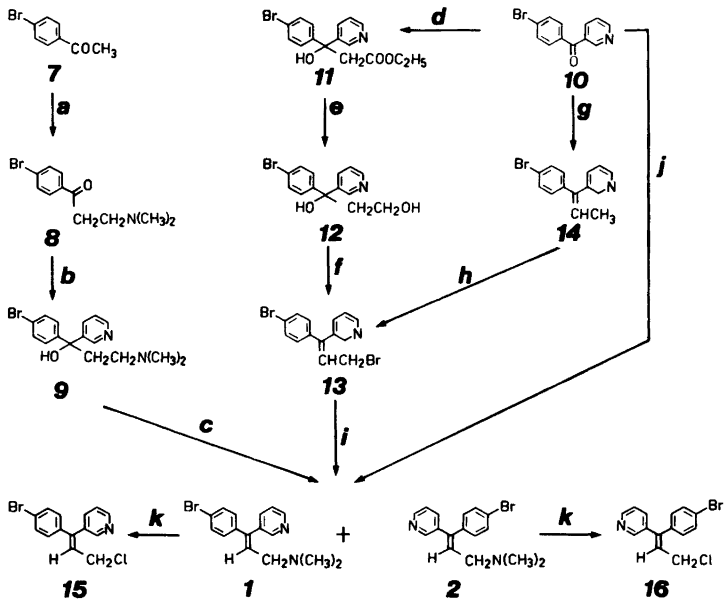
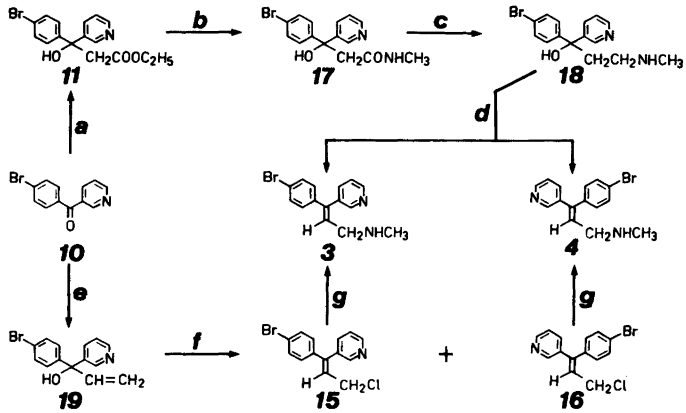


Scheme 1. Syntheses of the tertiary amines *1* and *2*. [a] HCHO, $HNMe_2 \cdot HCl$, EtOH. [b] 3-Lithiopyridine, Et_2O. [c] H_2SO_4, Ac_2O. [d] Zn, $BrCH_2COOEt$, C_6H_6. [e] $LiAlH_4$, Et_2O. [f] PBr_3, CH_2Cl_2. [g] $Ph_3P{=}CHCH_3$, DMSO, THF. [h] NBS, AIBN, CCl_4. [i] $HNMe_2$, CH_2Cl_2. [j] $Ph_3P{=}CHCH_2NMe_2$, THF. [k] $ClCOOCH_2CCl_3$, C_6H_6.

from different solvents.

As the isomerically pure tertiary amines *1* and *2* had become available from large scale preparations, they were attractive as starting materials for the synthesis of *3* and *4*. Thus, dealkylation experiments with various chloroformates were performed. No secondary amines were isolated, but when using trichloroethyl chloroformate, *1* and *2* gave the allylic chlorides *15* and *16*, respectively, in good yields (Scheme 1). No *cis*–*trans*-isomerization was observed. These findings are in agreement with independent results of others, published after the completion of this part of our work.[7] The allylic chlorides were isolated as crystalline and stable



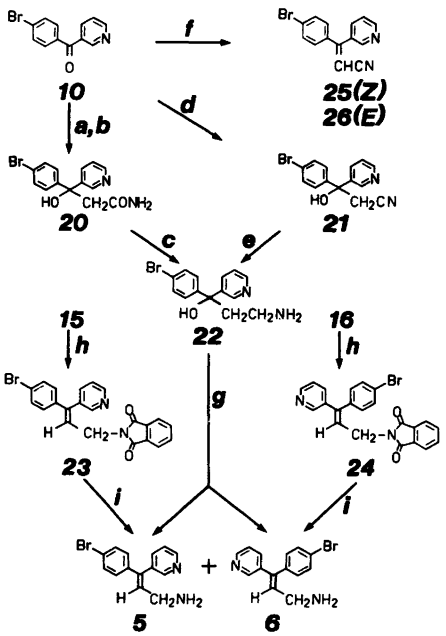
Scheme 2. Syntheses of the secondary amines *3* and *4*. [a] Zn, $BrCH_2COOEt$, C_6H_6. [b] H_2NMe (30% aq.). [c] $NaBH_4$, $BF_3 \cdot Et_2O$. [d] H_2SO_4 (75% aq.). [e] $CH_2{=}CHMgBr$, THF. [f] PCl_5, CH_2Cl_2. [g] H_2NMe, EtOH.

hydrochlorides. Each chloride (*15*, *16*) gave the corresponding secondary amine (*3*, *4*) upon treatment with methylamine (Scheme 2).

Another way of obtaining the allylic halides has been found in the acidic rearrangement of the tertiary allylic alcohol *19*. Treatment of *19* with phosphorus pentachloride afforded predominantly the isomer *15*.[8] This constitutes a convenient route to the *Z*-isomers of amines such as *1* and *3*.[8,9]

The tertiary and secondary amines *1*–*4* could all be obtained by dehydration of the appropriate alcohols. Thus, in order to synthesize the primary amines *5* and *6*, the amino-alcohol *22* was prepared as shown in Scheme *3*. Dehydration of *22* gave a mixture of *5* and *6*, but only *5*, formed in slight excess, could be isolated. The isomer *6* was obtained from the allylic chloride *16* using the Gabriel reaction. By this method amine *5* was also obtained, starting with *15*.

Another route to the primary amines was investigated *via* the nitriles *25* and *26*, which could easily be prepared and separated (Scheme *3*). However, reduction to the primary amines *5* and *6* could not be achieved using a mixture of lithium aluminium hydride and aluminium chloride or lithium aluminium hydride alone.



Scheme 3. Syntheses of the primary amines *5* and *6*. [a] Zn, $BrCH_2COOEt$, C_6H_6. [b] NH_3 (conc.), EtOH. [c] $NaBH_4$, $BF_3.Et_2O$. [d] $LiCH_2CN$, THF, −50 °C. [e] $LiAlH_4$, THF, −30 °C. [f] $(EtO)_2P(O)=CHCN$, DMSO, THF. [g] H_2SO_4 (70 % aq.). [h] Potassium phtalimide, DMF. [i] $H_2NNH_2.H_2O$, MeOH.

STRUCTURAL RELATIONSHIPS

The steric correlations between the amines depicted in Fig. 1 reside on chemical as well as spectral evidence. Chemically, the three amines *1*, *3* and *5* are interrelated *via* the allylic chloride *15*, and the amines *2*, *4* and *6* *via* the chloride *16* (*cf.* Schemes 1–3). From each of these reactions only one isomer was detected indicating that no isomerization occurred. Furthermore, *3* was converted to *1* on *N*-methylation, giving a closed reaction sequence (*1*–*15*–*3*–*1*).

In the ^1H NMR spectra there are easily recognizable features which permit the isomeric amines to be divided into two series. Firstly, the triplet of the olefinic proton appears at a field slightly lower for *1*, *3* and *5* than for *2*, *4* and *6*, respectively. The amine mixtures show two well-resolved triplets, useful in determination of the ratio of the isomers. Secondly, in the low field part of the aromatic region, the signals of the 2- and 6-pyridyl protons are separated in the first series, while overlapping in the second. These shift differences give rise to characteristic patterns as shown in Fig. 2. Thirdly, the width of the AA'BB' spin system of the *p*-bromophenyl protons is *ca.* 0.15 ppm smaller in the former series than in the latter (*cf.* Ref. 4).

The same distinction could be made on the basis of UV-spectra. In hydrochloric acid solution *1*,

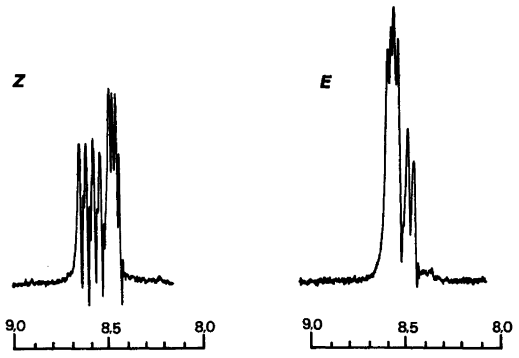


Fig. 2. The NMR-pattern of the 2- and 6-pyridyl protons of the *Z*- and *E*-isomers, exemplified by compounds *3* and *4*.

Table 1. Europium-induced shift in NMR spectra of compounds *25* and *26*. Values in ppm from TMS, measured in $CDCl_3$ at 37 °C.

	25		*26*	
	vinyl	2-py	vinyl	2-py
Plain compound[a]	5.87	8.65	5.77	8.57
With $Eu(fod)_3$[b]	6.42	12.75	6.85	13.68
LIS	0.55	4.10	1.08	5.11
LIS-ratio	0.13		0.21	
Standard compound	*1*		*2*	
LIS-ratio[c]	0.15		0.23	

[a] Concentration *ca.* 0.4 M. [b] [$Eu(fod)_3$]/[nitrile] *ca.* 0.2. [c] Calculated from figures in Ref. 11.

3 and *5* have a λ_{max} at about 250 nm and *2*, *4* and *6* at about 220 nm.

The configuration of zimelidine (*1*) has been established to be *Z* by an X-ray single-crystal analysis.[10] Furthermore, the configuration of both *1* and *2* have been determined by the use of lanthanide shift reagents, the LIS-technique.[11] These results together with the correlations above give the configurations shown in Fig. 1 for the amines *1*–*6*.

The allylic chlorides *15* and *16* give spectral data in parallel with those of the amines (NMR and especially UV). Isomer *15* belongs to the *Z*-, and *16* to the *E*-series, thus confirming the chemical evidence.

The nitriles *25* and *26* have conjugated systems differing from those of the amines and, as a consequence, the UV and simple NMR spectra do not give reliable steric information. A similar ambiguous situation has been described for the corresponding carboxylic acids and aldehydes.[4] Nevertheless, a correlation with the amines *1* and *2* has been possible using the LIS-technique and observing the vinyl and the 2-pyridyl protons. $Eu(fod)_3$ was used as the shift reagent and it was assumed that a one to one complex with the pyridine nitrogen atom is determining the LIS. It was recently shown that this is true for the complexes of *1* and *2*.[11] Good additional evidence for the validity of this assumption is that the LIS-ratios found for *25* and *26* are very close to those for *1* and *2*. According to these results *25* has the *Z*- and *26* has the *E*-configuration.

The steric division of the amines *1*–*6* into two groups is also reflected in their biological effects. One well recognized screening method for potential antidepressants measures the inhibition of the neuronal uptake of biogenic amines. *In vitro*, each of the *Z*-isomers, *1*, *3* and *5*, inhibits the uptake of 5-hydroxytryptamine more strongly than the corresponding *E*-isomer, *2*, *4* or *6*. For noradrenaline the selectivity is reversed.*

EXPERIMENTAL

If not otherwise stated the following applies. Melting points are uncorrected. Elemental analyses gave figures within ±0.4 % from the calculated values. Spectra were recorded on the following instruments and are reported in the following way (significant peaks only). Mass: LKB 9000 (purified salt, direct inlet, 70 eV), MS: *m/e* (rel. int. %). Ultraviolet: Zeiss DMR 21 (in 0.1 M HCl), UV: λ nm(ε). Proton magnetic resonance: Varian T 60 (free amine recovered from the purified salt, solvent $CDCl_3$, internal TMS), NMR: δ (multiplicity).

(Z)-3-(4-Bromophenyl)-N,N-*dimethyl-3-(3-pyridyl)allylamine (1).* (a) *Dehydration of* 9. Concentrated H_2SO_4 (6 ml) was added dropwise to *9* (14.5 g, 43 mmol) dissolved in 125 ml acetic anhydride. The solution was heated under reflux for 30 min, cooled and poured into 250 ml ice-water. The solution was made alkaline with 500 ml 5 M NaOH and extracted with 3 × 250 ml ether. The ether layer was treated with charcoal, dried (Na_2SO_4) and the solvent evaporated to give 13.8 g crude amine as an oil containing *1* and *2* in a ratio of 3:1. The amine mixture was dissolved in acetone and concentrated HCl (75 mmol) was added, giving a solid precipitate.

Recrystallization from aqueous ethanol gave 9.6 g (55 %) of the dihydrochloride monohydrate of *1*. M.p. 195–198 °C. Anal. $C_{16}H_{17}BrN_2.2HCl.H_2O$: C, H, Br, Cl, N, O. MS: 318/316 (29/29, M), 58 (100). UV: 250 (19700, max), 225 (14000, min). NMR: 8.60 (dd, 1, 6-pyridyl), 8.46 (m, 1, 2-pyridyl), 7.42, 7.08, 7.6–7.3 (AA'BB'+m, 6, C_6H_4+4,5-pyridyl), 6.30 (t, 1, CH), 2.98 (d, 2, CH_2), 2.23 (s, 6, CH_3).

(b) *Bromination of* 14 *to* 13 *and amination of crude* 13. The olefin mixture *14* (1.0 g, 3.5 mmol) and *N*-bromosuccinimide (0.62 g, 3.5 mmol) in 180 ml carbon tetrachloride were heated with stirring and azoisobutyronitrile (0.1 g) was added at 70 °C. After heating under reflux for about 2 h the mixture was cooled and the succinimide formed was filtered off. The resulting solution of crude *13* was stirred at room temperature with aqueous dimethylamine

*Concentration of amines *1*–*6* (μM) giving 50% inhibition of the neuronal uptake in mouse brain slices *in vitro*: 5-Hydroxytryptamine: *1* (1.7), *2* (6.1), *3* (0.10), *4* (2.5), *5* (2,4), *6* (6.0). Noradrenaline: *1* (>24), *2* (6.1), *3* (1.52), *4*(0.8), *5* (>24), *6* (3.0).[12]

(43 %, 10 ml, 100 mmol) for 4 h and then extracted with 3 × 75 ml 0.5 M HCl. The aqueous layers were made alkaline with 30 % NaOH and extracted with 2 × 100 ml dichloromethane. Drying ($MgSO_4$) and evaporation gave 0.65 g (59 %) of an oil consisting of *1* and *2* in a ratio of about 1:1 according to NMR.

(c) *From the propanediol* 12. The diol *12* (0.92 g, 3.0 mmol) and PBr_3 (1.62 g, 6.0 mmol) in 60 ml dichloromethane were heated under reflux overnight. After cooling in an ice-bath a solution of dimethylamine (4.5 g, 100 mmol in 5 ml CH_2Cl_2) was added and the mixture was then stirred at room temperature for 1 h. Alkalization with 50 ml 2 M NaOH, extraction with dichloromethane, washing with water, drying ($MgSO_4$), and evaporation gave a mixture of *1* and *2* as an oil, 0.81 g (85 %), in the ratio 82:18 (GLC, OV-17 on Chromosorb, 2 m column, 200 °C). The dihydrochloride of *1* was precipitated from acetone and crystallized from aqueous 2-propanol, giving 0.50 g (41 %) dihydrochloride monohydrate. M.p. 191–195 °C, ≤0.5 % of *2* (GLC).

(d) *Wittig reaction of* 10. Butyllithium (10 mmol) in hexane was added to 2-(dimethylamino)ethyltriphenylphosphonium bromide (4.14 g, 10 mmol) in 30 ml dry tetrahydrofuran at ambient temperature during 1 min. After stirring for 30 min a suspension of *10* (2.62 g, 10 mmol in 15 ml THF) was added to the solution of the dark red ylide. The mixture was heated at 60 °C for 5 h and after cooling 25 ml 2 M HCl were added. The solvent was evaporated *in vacuo* after addition of toluene to the mixture. Additional 2 M HCl was added and the aqueous phase was washed twice with toluene, filtered, made alkaline and extracted twice with ether. Drying ($MgSO_4$) and evaporation gave 2.2 g (69 %) of amines as a yellow oil. Integration of an Eu $(fod)_3$-shifted NMR showed *1* and *2* in a ratio of 62:38. Concentrated HCl (1 ml, 11 mmol) was added to a solution of 1.2 g of the amine mixture in acetone. After heating to reflux the mixture was cooled and the acetone was decanted from the smeary precipitate. Crystallization from aqueous 2-propanol gave 1.20 g (30 %) of the dihydrochloride monohydrate of *1*. M.p. 192–194 °C.

(e) *Eschweiler-Clarke methylation of* 3. A mixture of *3* (0.6 g, 1.8 mmol), formic acid (0.6 g, 13 mmol) and formalin (0.4 ml 36 % aqueous solution, 4.8 mmol) was heated on a steam bath for 3 h. GLC (as in procedure (c)) revealed a complete conversion of *3* to *1*. Precipitation of the dihydrochloride from acetone and recrystallization twice from aqueous 2-propanol gave 0.33 g (45 %) dihydrochloride monohydrate. M.p. 192–200 °C. No melting point depression was found on admixture with a sample of *1* from procedure (a).

(E)-3-(4-Bromophenyl)-N,N-*dimethyl-3-(3-pyridyl)allylamine (2)*. The mother liquor from the precipitation of the hydrochloride of *1*, method (a), was concentrated *in vacuo*. The oily residue was dissolved in water, made alkaline, and extracted with ether, Washing with water, drying (Na_2SO_4), and evaporation gave a colourless oil. To an ice-cooled solution of this oil in dry acetone an equivalent amount of oxalic acid in dry acetone was added dropwise. The formed crystalline precipitate was washed with cold acetone, dried *in vacuo*, and recrystallized three times from methanol. M.p. 174–176 °C. The analyses showed the compound to be the "sesquioxalate" of *2*. Anal. $C_{16}H_{17}BrN_2.1.5\ C_2H_2O_4$: C, H, Br, N, O. MS: identical with *1*. UV: 237 (18100, shoulder), 219 (21900, max). NMR: 8.53 (m, 1, 2-pyridyl), 8.50 (dd, partly concealed, 1, 6-pyridyl), 7.55, 7.05, 7.6–7.0 (AA'BB'+m, 6, C_6H_4+4,5-pyridyl), 6.27 (t, 1, CH), 3.01 (d, 2, CH_2), 2.23 (s, 6, CH_3).

(Z)-3-(4-Bromophenyl)-N-*methyl-3-(3-pyridyl)-allylamine (3)*. (a) *Dehydration of* 18. The aminopropanol *18* (1.1 g, 3.4 mmol) was dissolved in H_2SO_4 (75 %, 12 ml) and the solution heated with stirring on a steam bath for 25 min. After cooling, ice and NaOH (2 M, *ca.* 130 ml) were added to pH 10. The mixture was extracted with 3 × 75 ml ether. The combined ether layers were extracted with 3 × 100 ml 1 M HCl. After alkalization (30 % NaOH) extraction with methylene chloride, drying ($MgSO_4$) and evaporation, a mixture of *3* and *4* in a ratio of 3:1 was obtained. A hot solution of the amine mixture (0.58 g, 1.9 mmol) and oxalic acid (0.20 g, 2.2 mmol) in ethanol gave the oxalate of *3* on cooling. The salt was recrystallized from aqueous ethanol (93 %) giving 0.58 g (44 %). M.p. 206–208 °C. The dihydrochloride monohydrate of *3* was prepared from a solution of the free amine (12 g) in 100 ml ethanol by adding 6.5 ml concentrated HCl giving 8.3 g. M.p. 155–158 °C. Anal. $C_{15}H_{15}BrN_2.2\ HCl.H_2O$: C, H, Br, Cl, N, O. MS: 304/302 (94/100, M), 44 (84). UV: 248 (19200, max), 224 (12500, min). NMR: 8.61 (dd, 1, 6-pyridyl), 8.47 (m, 1, 2-pyridyl), 7.43, 7.08, 7.5–7.3 (AA'BB'+m, 6, C_6H_4+4,5-pyridyl), 6.28 (t, 1, CH), 3.26, (d, 2, CH_2), 2.39 (s, 3, CH_3), 1.38 (s, 1, NH).

(b) *Amination of* 15. The hydrochloride of *15* (13.8 g, 40.0 mmol) was stirred with methylamine (12 ml, 240 mmol) in 1200 ml ethanol at room temperature for 24 h. After concentration *in vacuo* 50 ml 2 M HCl was added. The mixture was washed with ether, made alkaline with 2 M NaOH and extracted with dichloromethane. Drying and evaporation gave 12 g of *3* as an oil, ≥95 % purity by NMR.

(E)-3-(4-Bromophenyl)-N-*methyl-3-(3-pyridyl)-allylamine (4)*. (a) *Dehydration of* 18. The residue from precipitation of the oxalate of *3* (procedure (a)) contains *3* and *4* in the ratio 2:3. A solution of this amine mixture (2.7 g, 8.8 mmol) and oxalic acid

(0.81 g, 8.9 mmol) in 90 ml warm aqueous acetonitrile (85 %) gave on cooling 1.9 g oxalate of *4*. Recrystallization (aq. CH_3CN) gave 1.1 g. M.p. 198 – 201 °C. Anal $C_{15}H_{15}BrN_2.C_2H_2O_4$: C, H, Br, N, O. MS: 304/302 (90/100, M), 147 (57), 44 (46). UV: 236 (18800, shoulder), 220 (20800, max). NMR: 8.54 (m, 1, 2-pyridyl), 8.48 (dd, partly concealed, 1, 6-pyridyl), 7.55, 7.05, 7.6 – 7.0 (AA'BB' + m, 6, C_6H_4 + 4,5-pyridyl), 6.23 (t, 1, CH), 3.28 (d, 2, CH_2), 2.40 (s, 3, CH_3), 1.31 (s, 1, NH).

(b) *Amination of* 16. Compound *4* was prepared from the hydrochloride of *16* (7.0 g, 23 mmol), as described for compound *3* method (b). The oxalate of *4* was prepared (6.0 g, 86 %). M.p. 195 – 197 °C. Anal. $C_{15}H_{15}BrN_2.C_2H_2O_4$: C, H, Br, N, O.

(Z)-3-(4-Bromophenyl)-3-(3-pyridyl)allylamine (5). (a) *Dehydration of* 22. The amino-propanol *22* (4.7 g, 16 mmol) was mixed with 12 ml 70 % H_2SO_4 and the solution was heated at 80 °C for 30 min. Ice-water was added and then 35 ml of 30 % NaOH. The reaction mixture was extracted with ether. Drying (Na_2SO_4) and evaporation gave 4.5 g of an oil. This was dissolved in 50 ml methanol and oxalic acid (2.0 g, 16 mmol) in 25 ml 2-propanol and 5 ml water was added giving 2.5 g of crystals. Recrystallization (55 ml MeOH – 2-PrOH – H_2O, 5:5:1) gave 1.8 g (30 %) of the oxalate of *5* containing one mol equiv. of methanol. M.p. 160 – 162 °C. Anal. $C_{14}H_{13}BrN_2.C_2H_2O_4.CH_4O$: C, H, Br, N, O. UV: 247 (19600, max), 224 (12700, min). NMR: 8.55 (dd, 1, 6-pyridyl), 8.42 (m, 1, 2-pyridyl), 7.35, 7.01, 7.5 – 7.2 (AA'BB' + m, 6, C_6H_4 + 4,5-pyridyl), 6.19 (t, 1, CH), 3.31 (d, 2, CH_2).

(b) *Hydrazinolysis of* 23. The pthalimide *23* (2.8 g, 6.7 mmol) was dissolved in 95 ml methanol and a solution of hydrazine hydrate (0.8 ml, 16 mmol) in 5 ml methanol was added dropwise with stirring at 40 °C. The solution was heated at 60 °C for 5 h, and then concentrated *in vacuo*. The residue, combined with 100 ml 2M NaOH was extracted with ether and this extract with diluted HCl. The aqueous layer was made alkaline with 30 % NaOH, and extracted with dichloromethane. Drying and evaporation gave 1.25 g of an oil. A warm solution of this oil and and oxalic acid dihydrate (0.63 g, 5.0 mmol) in 50 ml acetonitrile gave on cooling 1.61 g (63 %) of the oxalate of *5*. M.p. 162 – 164 °C, undepressed on admixture with a sample prepared by method (a).

(E)-3-(4-Bromophenyl)-3-(3-pyridyl)allylamine (6). The pthalimide *24* (1.6 g, 3.8 mmol), treated as described in method (b) for preparation of 5, gave 1.3 g (90 %) of the oxalate of *6*. Analytical sample, m.p. 169 – 171 °C (MeOH – CH_3CN, 8:1). Anal. $C_{14}H_{13}BrN_2.\frac{1}{2}C_2H_2O_4$: C, H, Br, N, O. UV: 237 (15400, shoulder), 221 (17500, max), 214 (17000, min). NMR: 8.45 (m, 1, 2-pyridyl), 8.41 (dd, partly concealed, 1, 6-pyridyl), 7.44, 6.96, 7.6 – 6.9 (AA'BB' + m, 6, C_6H_4 + 4,5-pyridyl), 6.13 (t, 1, CH), 3.30 (d, 2, CH_2).

1-(4-Bromophenyl)-3-dimethylamino-1-propanone (8). From 4-bromoacetophenone (*7*) compound *8* was obtained according to Ref. 13. Yield 73 % of the hydrochloride. M.p. 191 – 193 °C (lit.[13] 196 °C). The free amine *8* was prepared and recrystallized from hexane – ethanol. M.p. 66 – 68 °C.

1-(4-Bromophenyl)-3-(dimethylamino)-1-(3-pyridyl)propan-1-ol (9). 3-Bromopyridine (118 g, 0.78 mol) in 100 ml dry ether was added dropwise under nitrogen at −60 °C during 45 min to a solution of butyllithium (1.00 mol) in 425 ml hexane mixed with 200 ml ether. After stirring for another 15 min, a solution of *8* (102 g, 0.40 mol, free amine) in 600 ml ether was added dropwise at −40 to −30 °C during 50 min. The mixture was stirred for 2.5 h while the temperature was allowed to rise to ambient and then poured into 1500 g ice and 150 ml conc. HCl. The water layer was separated, the pH was adjusted to 4, washed with dichloromethane, made alkaline and extracted with ether three times. The ether layer was treated with charcoal, dried (Na_2SO_4) and concentrated. The residue was triturated with hexane and then recrystallized from 2-propanol to give 68.3 g (51 %) of *9*. M.p. 123 – 125 °C. Anal. $C_{16}H_{19}BrN_2O$: C, H, Br, N, O. NMR: 2.42 (s, 4, CH_2CH_2), 2.25 (s, 6, CH_3).

4-Bromophenyl 3-pyridyl ketone (10). This compound was prepared according to Ref. 5.

Ethyl 3-(4-bromophenyl)-3-hydroxy-3-(3-pyridyl)-propionate (11). A mixture of *10* (100 g, 0.38 mol) and zinc (50 g, 0.76 mol) in 200 ml dry benzene was refluxed under nitrogen, while ethyl bromoacetate (112 g, 0.70 mol) in 100 ml benzene was slowly added during 30 min. The mixture was further refluxed for 4 h, cooled and diluted with 600 ml benzene. The solution was washed three times with 10 % aqueous acetic acid. Ether (400 ml) was added and the hydrochloride of *11* was formed as an oil after addition of 10 % HCl. The salt was made alkaline and the amine extracted with benzene. The hydrochloride of *11* was precipitated by addition of HCl in ether to give 135 g (92 %). M.p. 177 – 182 °C (2-propanol). Anal. $C_{16}H_{16}BrNO_3.HCl$: C, H, Br, Cl, N, O. NMR: 4.03 (q, 2, CH_2O), 3.21 (s, 2, CH_2CO).

1-(4-Bromophenyl)-1-(3-pyridyl)-1,3-propanediol (12). A solution of *11* (9.5 g, 27 mmol, free amine) in 50 ml ether was added dropwise to an ice-cold mixture of $LiAlH_4$ (1.0 g, 27 mmol) and 150 ml ether. The reaction mixture was heated under reflux for 5 h, cooled and a saturated Na_2SO_4 solution was added. Filtration and evaporation gave a residue which was crystallized from chloroform to give 6.3 g (76 %) of *12*. M.p. 130 – 132 °C. Anal. $C_{14}H_{14}BrNO_2$: C, H, Br, O. NMR: 3.80 (t, 2, CH_2O), 2.50 (t, 2, CH_2).

3-(4-Bromophenyl)-3-(3-pyridyl)allyl bromide

(13). Compound 13 was not isolated. See preparation of *1* method (b) and (c).

1-(4-Bromophenyl)-1-(3-pyridyl)propene (14). Sodium hydride (3.0 g, 50 % in oil, 63 mmol) was heated in 100 ml anhydrous dimethyl sulfoxide at 85 °C for 30 min under nitrogen. After cooling to room temperature a solution of ethyltriphenylphosphonium iodide (26 g, 62 mmol, in 100 ml DMSO) was added with stirring. After 30 min a deep red colour had developed, and a solution of *10* (11.2 g, 42 mmol) in 100 ml tetrahydrofuran was added at room temperature. After another hour the mixture was poured into 1.5 l of ice-water. Extraction with 3 × 250 ml ether, washing with water, drying (Na_2SO_4) and evaporation gave 27.2 g of a semicrystalline residue. On trituration with ether–isopropylether (200 ml 1:1) at −5 °C for 1 h a solid was formed, which was filtered off. The filtrate was concentrated and distilled to give 10.8 g (90 %) of *14*. B.p. 110–120 °C/1–2 Pa, n_D^{25} 1.6272, *E*–*Z* ratio 1:1 (from NMR).

(Z)-3-(4-Bromophenyl)-3-(3-pyridyl)allyl chloride (15). A solution of 2,2,2-trichloroethyl chloroformate (24.8 g, 117 mmol) in 200 ml dry benzene was added dropwise to a stirred solution of *1* (20.0 g, 63 mmol, free amine) in 900 ml dry benzene. The reaction mixture was refluxed for 2 h, cooled, filtered and the solvent evaporated. Recrystallization from acetone gave 13.6 g (70 %) of the hydrochloride of *15*. M.p. 190–192 °C. Anal. $C_{14}H_{11}BrClN.HCl$: C, H, Br, Cl, N. UV: 251 (19900, max), 226 (12400, min). NMR (hydrochloride in $CDCl_3$): 9.06 (dq, 1, 6-pyridyl), 8.68 (m, 1, 2-pyridyl), 8.4–8.0 (m, 2, 4,5-pyridyl), 7.47, 7.01 (AA′BB′, 4, C_6H_4), 6.49 (t, 1, CH), 4.05 (d, 2, CH_2).

(E)-3-(4-Bromophenyl)-3-(3-pyridyl)allyl chloride (16). The hydrochloride of *16* was prepared from *2* in analogy with *15*. Yield 57 %. M.p. 208–210 °C (acetone). Anal. $C_{14}H_{11}BrClN.HCl$: C, H, Br, Cl, N. UV: 240 (18700, shoulder), 224 (20500, max). NMR (hydrochloride in $CDCl_3$): 8.84 (dm, 1, 6-pyridyl), 8.65 (m, 1, 2-pyridyl), 8.4–7.8 (m, 2, 4,5-pyridyl), 7.61, 7.09 (AA′BB′, 4, C_6H_4), 6.56 (t, 1, CH), 4.09 (d, 2, CH_2).

3-(4-Bromophenyl)-3-hydroxy-N-methyl-3-(3-pyridyl)propionamide (17). The hydrochloride of *11* (19.4 g, 50 mmol) was dissolved in a mixture of aqueous methylamine (40 %, 200 ml) and 30 ml ethanol. After stirring for 24 h at room temperature a precipitate had formed. It was collected and recrystallized from 150 ml 2-propanol, giving 13.2 g (79 %) of *17*. M.p. 188–191 °C. Analytical sample, m.p. 190–191 °C (2-PrOH). Anal. $C_{15}H_{15}BrN_2O_2$: C, H, Br, N, O. NMR: 3.42 (s, 1, OH), 3.20 (s, 2, CH_2), 2.57 (d, 3, CH_3).

1-(4-Bromophenyl)-3-(methylamino)-1-(3-pyridyl)propan-1-ol (18). To a mixture of *17* (5.0 g, 15 mmol) and $NaBH_4$ (4.0 g, 106 mmol) in 300 ml dry tetrahydrofuran, boron trifluoride etherate (23 ml, 183 mmol, in 100 ml THF) was added slowly at 0 °C. After 7 h at 0 °C another 4.0 g of $NaBH_4$ and boron trifluoride etherate (23 ml) were added as above and the mixture stirred for 50 h at room temperature. Water was then added slowly followed by 2 M NaOH to pH 11 and the mixture extracted with ether. Washing with water, drying (Na_2SO_4) and evaporation gave 15 g of a solid, which was treated with 50 ml 50 % H_2SO_4 at 110 °C for 10 min. After neutralization with saturated Na_2CO_3, extraction with ether gave 5.1 g of an oil. A warm solution of this oil and oxalic acid (1.4 g, 16 mmol) in 200 ml acetone gave on cooling the oxalate of *18*. Recrystallization from 250 ml ethanol gave 2.3 g (38 %). M.p. 179–182 °C. Anal. $C_{15}H_{17}BrN_2O.C_2H_2O_4$: C, H, Br, N, O. NMR: 4.67 (broad, 2, OH, NH), 2.62 (m, 2, CH_2), 2.32, 2.25 (m + s, 5, $CH_2 + CH_3$).

1-(4-Bromophenyl)-1-(3-pyridyl)-2-propen-1-ol (19). This compound was prepared according to Ref. 8.

3-(4-Bromophenyl)-3-hydroxy-3-(3-pyridyl)propionamide (20). The hydroxy-ester *11* (0.8 g, 2.5 mmol) was dissolved in 10 ml ethanol, concentrated NH_3 (50 ml) was added and the mixture was stirred at room temperature for 24 h. The precipitate formed was collected and recrystallized from 2-propanol. Yield 0.45 g (56 %) M.p. 213–214 °C. Anal. $C_{14}H_{13}BrN_2O_2$: H, Br, N, O. Found: C 51.9 Calc.: C 52.4. NMR: 3.16 (s, 2, CH_2).

3-(4-Bromophenyl)-3-hydroxy-3-(3-pyridyl)propionitrile (21). Acetonitrile (6.5 g, 0.16 mol) in 50 ml dry tetrahydrofuran was added dropwise under nitrogen at −50 °C to a mixture of butyllithium in hexane (100 ml, 1.5 M) and 50 ml tetrahydrofuran and allowed to react for 35 min. A solution of *10* (36.5 g, 0.14 mol, in 250 ml THF) was added at −50 °C and the mixture was set aside to reach room temperature and then poured into 500 g ice-water and 500 ml dichloromethane. The aqueous layer was further extracted with 2 × 200 ml dichloromethane. Washing with water, drying and evaporation gave 39.7 g of an oil. It was dissolved in 500 ml warm 2-propanol and 35 ml 4 M HCl-ether (0.14 mol) in 100 ml 2-propanol was added. Cooling gave 34.6 g (74 %) of the hydrochloride of *21*. M.p. 163–165 °C. Anal. $C_{14}H_{13}BrN_2O.HCl$: C, H, Br, N. Found: O 5.35. Calc.: O 4.71. NMR: 3.18 (s, 2, CH_2).

3-Amino-1-(4-bromophenyl)-1-(3-pyridyl)propan-1-ol (22). (a) *From hydroxy-nitrile* 21. A solution of *21* (17.2 g, 56 mmol) in 175 ml tetrahydrofuran was diluted with 200 ml ether. After cooling to −35 °C $LiAlH_4$ (4.0 g, 112 mmol) was added in portions under nitrogen. The mixture was kept at 0 °C for 2 h and then at 15 °C for 2 h. The reaction was quenched by slow addition of 20 ml saturated

Na_2SO_4. After stirring for 1/2 h, the inorganic salts were filtered off and extracted with 2 × 100 ml ether. Washing, drying and evaporation gave 14.7 g of an oil. This was dissolved in 500 ml warm 2-propanol and a solution of oxalic acid (4.3 g, 48 mmol) in 300 ml 2-propanol was added. After cooling overnight 11.8 g (53 %) crystals were collected. M.p. 98–105 °C. The free amine *22* was isolated and recrystallized from 2-propanol. M.p. 118–120 °C. MS: 308/306 (28/28, M), 106 (68), 30 (100). NMR: 2.90 (m, 2, CH_2), 2.33 (m, 2, CH_2).

(b) *From hydroxy-amide* 20. To a mixture of *20* (5.7 g, 17 mmol) and $NaBH_4$ (3.8 g, 100 mmol) in 200 ml tetrahydrofuran, boron trifluoride etherate (18.4 g, 130 mmol, in 50 ml THF) was added slowly under nitrogen at 0 °C. After stirring for 48 h at room temperature the mixture was made alkaline with 2M NaOH and extracted with chloroform. Evaporation gave 4 g of an oil, which crystallized on treatment with ether–hexane, yielding 2.3 g (63 %) of *22*. M.p. 95–115 °C. NMR: As for (a).

(Z)-1-(4-Bromophenyl)-3-pthalimido-1-(3-pyridyl)propene (23). Potassium pthalimide (4.7 g, 25 mmol) was added to a solution of the hydrochloride of *15* (5.2 g, 17 mmol) in 60 ml dimethylformamide and the mixture was heated with stirring at 80 °C for 3 h. Addition of ice-water, extraction with ether, drying and evaporation gave 5.8 g of a crystalline residue. Recrystallization from 140 ml methanol gave 2.9 g (41 %) of *23*. M.p. 136–140 °C. Anal. $C_{22}H_{15}BrN_2O_2$: C, H, Br, N, O.

(E)-1-(4-Bromophenyl)-3-pthalimido-1-(3-pyridyl)propene (24). Using the procedure described for compound *23*, the hydrochloride of *16* (5.2 g) gave 1.9 g (35 %) of *24*. M.p. 136–137 °C. Anal. $C_{22}H_{15}BrN_2O_2$: C, H, Br, N, O. NMR: 8.47 (m, 2, 2,6-pyridyl), 7.72, 7.55, 7.19, 7.9–7.0 (d + AA'BB' + m, 10, phthalimido + C_6H_4 + 4,5-pyridyl), 6.11 (t, 1, CH), 4.38 (d, 2, CH_2).

(Z)-3-(4-Bromophenyl)-3-(3-pyridyl)acrylonitrile (25). A mixture of NaH (20 g, 50 % in oil, 0.40 mol) and 200 ml dry dimethyl sulfoxide was heated at 80 °C for 40 min with stirring under nitrogen. After cooling a solution of diethyl cyanomethylphosphonate (53 g, 0.30 mol, in 150 ml DMSO) was slowly added and the mixture was stirred for 1.5 h at room temperature. A solution of *10* (60 g, 0.23 mol) in 350 ml tetrahydrofuran was slowly added at 23 °C. Stirring was continued for 1 h. The reaction mixture was poured into 1000 ml of ice-water. Extraction with 5 × 150 ml ether, washing of each portion with 100 ml water, drying of the combined extracts and evaporation of the solvent gave 73 g of an oil. This was dissolved in 200 ml benzene and separated on 800 g silica (0.063–0.200 mm) in benzene. When 2 l eluate had been collected, the solvent was changed to methanol–isopropylether–benzene (1:10:10). Subsequent fractions gave 19.6 g of compound *25*, 5.7 g of a mixture of *25* and *26*, and 1.9 g of *26*. TLC using methanol–isopropylether (1:25) showed R_F 0.36 for *25* and R_F 0.18 for *26*. The 19.6 g *25* was recrystallized from 60 ml ethanol giving 11.3 g. M.p. 122–123 °C. Anal. $C_{14}H_9BrN_2$: C, H, Br, N. MS: 286/284 (58/62), 205 (100). NMR: 5.87 (s, 1, CH).

(E)-3-(4-Bromophenyl)-3-(3-pyridyl)acrylonitrile (26). Fractions from the preparation of *25*, which contained *26*, were combined and recrystallized from isopropylether giving pure *26*. M.p. 93–94 °C. Anal. $C_{14}H_9BrN_2$: C, H, Br, N. MS: 286/284 (66/68), 205 (100). NMR: 5.77 (s, 1, CH). The hydrochloride was prepared and crystallized from acetone. M.p. 116–120 °C. Anal. $C_{14}H_9BrN_2$.HCl: C, H, N.

Stereostructure of the nitriles 25 and 26. Dry solutions of *25* and *26*, respectively, in deuteriochloroform (Merck Uvasol) were prepared. Solid $Eu(fod)_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium, (Ciba-Geigy, used as purchased) was added in portions until each solution showed an easily observable induced shift difference (LIS). The figures found are shown in Table *1*.

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