

215. Synthesis of Phenyl- and Benzyl-Substituted Pyrrolidines and of a Piperidine by Intramolecular C-Alkylation. Synthons for Tricyclic Skeletons¹⁾

by Roland Achini

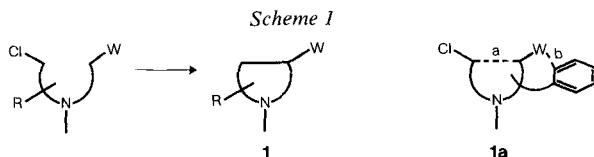
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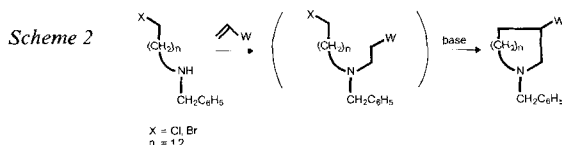
Summary

The construction of new or novel functionalized annulated and bridged tricyclic compounds by two consecutive C,C-bond formations (a and b in **1a**, Scheme 1) is described. In a first step, chloroalkyl-substituted aminonitriles yielded pyrrolidines **8**, **15a**, **15b**, **23**, **25** and piperidine **18** by carbanionic ring closure (Schemes 5, 6, 7 and 8). Subsequent *Friedel-Crafts* cyclization transformed the β -aminonitriles **8**, **15a**, **15b** and **18** either directly or via their carboxylic acid derivatives to the indeno [1,2-*c*]pyrrole, 2,5-methano-3-benzazocine, benz [f]isoindoline and 1,4-ethano-2-benzazepine skeletons **11**, **16a**, **16b** and **21**, respectively (Schemes 5, 6 and 7). By classical ring expansion reactions the pyrrolo [3,4-*c*]isoquinoline and benzopyrano [3,4-*c*]pyrrole skeletons **28** resp. **31** were obtained from **11** (Scheme 9).

A few years ago we published a new synthesis of pyrrolidines based on the intramolecular opening of an epoxide by a carbanion [1]. Because of our interest in a general, versatile and efficient synthesis of tricyclic compounds we studied the preparation of new types of pyrrolidines and piperidines using similar methodology but with chlorine as the leaving group instead of the epoxide ring (Scheme 1)²⁾.



- 1) Presented at the Autumn Meeting of the Swiss Chemical Society in Berne, Switzerland, October 19, 1979.
- 2) In this connection it is interesting to note the 'Michael-alkylation ring synthesis' of *Dolfini & Dolfini* [2] (Scheme 2). The preparation of pyrrolidines ($n = 1$), however, is restricted to strong electrophilic Michael acceptors ($W = \text{COCH}_3$, not CN , COOC_2H_5) on account of the deactivated aminohalides.



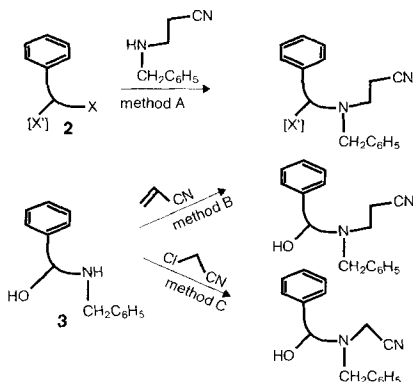
As is well known such compounds can be used as synthons for the construction of tricyclic skeletons when R contains an aromatic nucleus and W is a group that can function as a *Friedel-Crafts* type electrophile (**1a**). This paper describes our experience in constructing tricyclic compounds by two consecutive C,C-bond formations using W both as an activating group in carbanionic ring closures (a) and as an electrophile in *Friedel-Crafts* cyclizations (b).

1. Preparation of the starting materials. – The nitrile group was used as an activating group for the intramolecular C-alkylations since its α -carbanion is a powerful nucleophile. We preferred the N-atom in its basic form since the carbanion derived from *N*-acylated amino nitriles frequently led to poor results, at least partly due to *retro-Michael* reactions (in the case of R–CO–N–CH₂–CH₂–CN) or β -eliminations (in the case of tosyl–N–CH₂–CN). Three methods were used to introduce the nitrile group (*Scheme 3*): (i) *N*-alkylation of 3-(benzylamino)propionitriles by an alkylating agent (**2**) containing an additional leaving group (X') in a latent form for the subsequent cyclization (*method A*); suitable alkylating agents were epoxides and α -haloketones; (ii) *N*-Alkylation of amino alcohols (**3**) by either acrylonitrile (*method B*), or (iii) by chloroacetonitrile (*method C*), using the hydroxyl group of **3** as a latent leaving group.

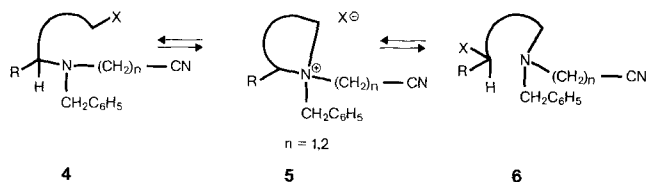
2. The rearrangement problem. – Because of the basic nature of the amino group we had to be especially careful about the rearrangement of the aminohalides (*Scheme 4*). Here, a quaternary ammonium compound **5** can be formed during the preparation of the aminohalide or under the conditions of the carbanionic cyclization, which may either revert to the starting material **4** or rearrange to a new aminohalide **6** [3]. The factor governing the quaternization will be the ring size of **5**. Cyclization of the carbanion derived from **5** by an intramolecular S_N2-type attack of the nucleophile – the mechanism postulated for intermolecular cases [3a, b] – would be disfavoured according to *Baldwin's* rules [4].

3. β -Aminohalides. – The β -chloroalkylamines **7** were prepared in three simple steps from phenacyl bromides (*Scheme 5*). In general, the β -halogenoalkylamines are very labile since they readily rearrange by a β -group participation *via* aziridi-

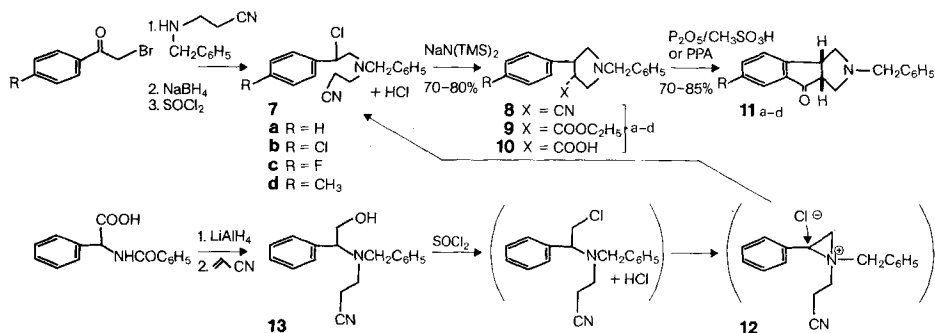
Scheme 3



Scheme 4



Scheme 5



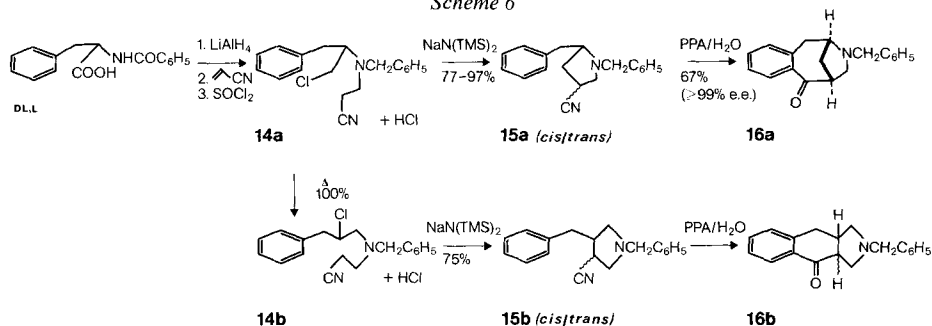
nium intermediates, either when heated or treated with nucleophiles [3a,c,d] (*cf.* Scheme 4). However, we did not observe any rearrangement with compounds **7** because the chloride anion would open the possible aziridinium salt **12** by an S_N1 -type mechanism *via* benzylic and therefore more stable carbenium ion to give the original β -chloroalkylamines **7**. This was confirmed by an alternative synthesis of the same secondary chloride **7a**, but starting from the primary alcohol **13**, involving a rearrangement as indicated in Scheme 5. Treatment of **7** with sodium hexamethyldisilazane led to the *trans*-substituted phenylpyrrolidines **8** under thermodynamic control of the stereochemistry (see exper. part), which were solvolyzed to amino esters **9** and amino acids **10** and then cyclized by a *Friedel-Crafts*-type reaction to the *cis*-indeno [1,2-*c*]pyrroles **11**.

In the case of the labile primary chloride **14a** (Scheme 6), which we prepared in 3 steps from DL- and L-N-benzoyl-phenylalanine, we were able to limit the rearrangement to **14b** to a maximum of 20–25% by choosing appropriate reaction conditions (see exper. part). By carbanionic ring closure of **14a** to the pyrrolidines **15a** and direct *Friedel-Crafts* reaction of the nitriles an efficient synthesis of the previously unknown 2,5-methano-3-benzazocine skeleton (**16a**³) was achieved, which could be carried out easily on a kilogram scale⁴). Since **14a**, separated from its by-product **14b** by crystallization, gave **15a** contaminated only by 1% of **15b** in 97% yield, rearrangement *via* an aziridinium intermediate does not play a significant role in the carbanionic cyclization process (*cf.* Sect. 2). Separation of the *cis*- and

³) Recently the synthesis of the 2,5-methano-3-benzazocine and 1,4-ethano-2-benzazepine skeletons in poor yield has been reported [5].

⁴) We thank Dr. H. Braunschweiger, head of our kilogram laboratory, for synthesizing the tricyclic compounds mentioned in this paper on a kilogram scale.

Scheme 6

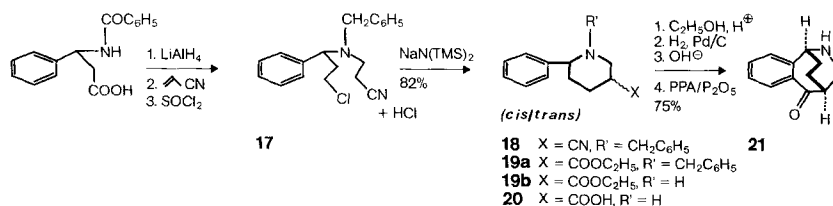


trans-isomers of **15a** by chromatography was possible but unnecessary for the construction of **16a**, since only the *cis*-isomer can be cyclized and the *trans*-isomer is epimerized under the conditions of the *Friedel-Crafts* reaction. For this reason, we were able to convert the cheap L-*N*-benzoyl-phenylalanine into a single, diastereomerically and enantiomerically pure **16a** with two centers of chirality. On the other hand the chloride **14a** could be transformed quantitatively to **14b** by heating at 140° . This was then cyclized to an epimeric mixture of pyrrolidines **15b**⁵⁾ and finally converted to an epimeric mixture of benz[*f*]isoindoline derivatives **16b**⁵⁾.

4. γ -Aminohalides. – The γ -chloroalkylamines seemed to be more stable than their β -analogs, and rearrangements involving azetidinium intermediates could be suppressed for the most part under our reaction conditions (see exper. part). The synthesis of the previously unknown 1,4-ethano-2-benzazepine skeleton **21**³⁾ starting from 3-benzoylamino-3-phenylpropionic acid via chloride **17** and piperidine derivatives **18–20** (Scheme 7) was perfectly straightforward. Again separation of the *cis*-/*trans*-mixture of **18** was possible but unnecessary as explained above.

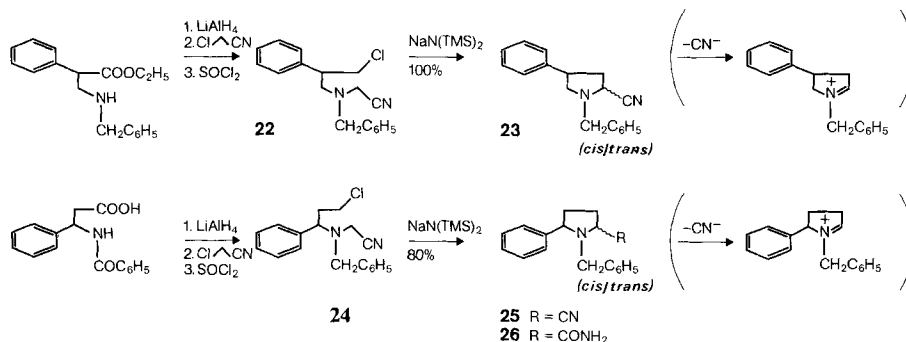
The cyclization of the α -amino nitriles **22** and **24** (Scheme 8), of which the carbanions correspond to a formyl synthon with inversed polarity [7], provided in good to excellent yield the phenylpyrrolidines **23** and **25** respectively as a mixture of the *cis*- and *trans*-isomers. However, α -*t*-amino-nitriles are very labile compounds: loss of cyanide anion results in iminium salts [8], which, as is well known, can combine intramolecularly with nucleophilic centers to cyclization products [9] or are cleaved to carbonyl compounds under hydrolytic conditions [10]. On the

Scheme 7



⁵⁾ Identical with samples prepared in *Sandoz Ltd.* via an independent route [6] (*cf.* exper. part).

Scheme 8



other hand, enamines can be formed either by elimination of HCN or by proton abstraction from the iminium salts. Direct treatment of either **23** or **25** with polyphosphoric acid led to complex mixtures which seemed to contain, at least partially, iminium salts and their secondary products. The nitrile **25** could be hydrolyzed in quantitative yield to the *cis*-/*trans*-mixture of carboxamide **26**, from which one pure isomer could be isolated by crystallization. However, we were unable to transform **23** or **25** into either the corresponding acid or ester in acceptable yields.

5. Structural assignments. – The structures of the labile aminohalides and their resulting cyclization products were assigned by ^1H -NMR.-spectroscopy. The main arguments are:

Aminohalides. As depicted in Scheme 4 primary halides **4** have a methine proton of the type $\text{CH}-\text{N}^6$ which is transformed to a methine proton of the type $\text{CH}-\text{X}$ ($\text{X} = \text{Cl}$) during the rearrangement of **4** to secondary halides **6**. This is recognizable by a significant downfield shift (Table).

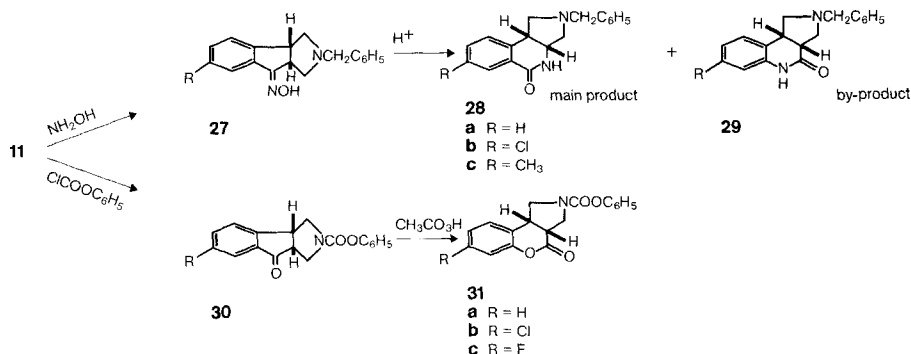
Pyrrolidines, piperidines and tricyclic compounds. Those cyclic structures derived from primary halides exhibit a new aliphatic ($\text{C}-\text{CH}_2-\text{C}$)-methylene group resulting from ring closure between $\text{C}-\text{CH}_2-\text{Cl}$ and $^-\text{C}-\text{CN}$. This group with a characteristic signal at high field (around $\delta = 2$ ppm) is lacking in structures derived from secondary halides.

Table. ^1H -NMR. data of methine protons of aminohalides of type **4** and **6** (see Scheme 4). Approximate chemical shifts (ppm) in CDCl_3 (free bases) or D_6 -DMSO (hydrochlorides).

Primary halides of type 4			Secondary halides of type 6		
Compound	Sequence	δ	Compound	Sequence	δ
14a	$\text{CH}_2\text{CH}-\text{CH}_2$ N	base: 3.4 salt: 3.5	14b	$\text{CH}_2\text{CH}-\text{CH}_2$ Cl	base: 4.1 salt: 4.4
17, 24	$\text{C}_6\text{H}_5\text{CH}-\text{CH}_2$ N	base: 4.0 salt: 4.3	7	$\text{C}_6\text{H}_5\text{CH}-\text{CH}_2$ Cl	salt: 5.4

⁶⁾ Aminohalide **22** is the only one which differs from the general structure **4**. However, rearrangement in this case is irrelevant because of the symmetry of the involved azetidinium ion.

Scheme 9



6. Refunctionalization and transformation of the tricyclic compounds. - Due to their functionality the described tricyclic compounds are suitable for a wide range of refunctionalization and transformation reactions. Thus, ketone **11** was transformed in two steps, involving a *Beckmann*-rearrangement or a *Baeyer-Villiger* oxidation, to the *pyrro*[3,4-*c*]isoquinoline and *benzopyrano*[3,4-*c*]pyrrole skeletons **28** and **31**, respectively (Scheme 9), thereby providing an entry into novel functionalized or substituted derivatives of these ring systems.

I thank Mr. X. Borer, A. Casazza and U. Gisi for assistance with the experimental work, and Mrs. Therese Zardin-Tartaglia and Mr. H.-R. Loosli for their contributions to solving the NMR.-problems.

Experimental Part

General remarks. - Melting points (m.p.) are not corrected. Optical rotations: *Perkin-Elmer* 141 polarimeter. IR.-spectra: *Perkin-Elmer* 21, max. in cm⁻¹. ¹H-NMR.-spectra: *Varian* A60, *Varian* HA-100, *Bruker* HX 90 E and *Bruker* WH 360 (internal standard: $\delta(\text{TMS})=0$ ppm); abbreviations: s=singlet, d=doublet, t=triplet, qa=quartet, m=multiplet, mc=multiplet center, br.=broad, J=spin-spin coupling constant (Hz), DR.=double resonance. Other abbreviations: RT.=room temperature.

1. Preparation of starting materials. - 1.1. *N-Alkylation of 3-(benzylamino)propionitrile with phenacyl bromides (Scheme 3, Method A).* - *General procedure.* To a solution of 3-(benzylamino)propionitrile (1.0 mol) and *N*-ethyl-diisopropylamine (1.0 mol) in acetone (525 ml) a solution of the appropriate phenacyl bromide (1.0 mol) in acetone (525 ml) was added at 22-30° with stirring and cooling (ice-bath). After an additional stirring for 4-14 h at RT. ether (ca. 1 l) was added to precipitate the *N*-ethyl-diisopropylamine hydrobromide completely, which was eliminated by filtration. Evaporation of the filtrate yielded almost quantitatively the practically pure (at RT. unstable) aminoketonitriles (cf. Scheme 5): 3-(*N*-benzyl-*N*-phenacylamino)propionitrile (oil). - IR. (film): 2250, 1690. - ¹H-NMR. (60 MHz, CDCl₃): 2.45 (t, J=7, 2 H); 3.1 (t, J=7, 2 H); 3.9 (s, 2 H); 4.05 (s, 2 H); 7.2-8.0 (10 H). - Hydrogenmaleinate salt, m.p. 119-120°.

C ₂₂ H ₂₂ N ₂ O ₅	Calc.	C 67.0	H 5.6	N 7.1	O 20.3%
(394.4)	Found	66.3	5.6	7.3	20.2%

The *p*-substituted analogues (R=Cl, F, CH₃) were immediately used in the next step.

1.2. *Reduction of aminoketonitriles to aminohydroxynitriles with NaBH₄ (Scheme 5).* - *General procedure.* The above aminoketonitriles are reduced with an excess of NaBH₄ in methanol at RT. After dilution with water and evaporation most of the methanol the aminohydroxynitriles are extracted with ethylacetate or CH₂Cl₂.

1.2.1. 3-[N-Benzyl-N-(2-hydroxyphenethyl)amino]propionitrile (pure oil, 97%)⁷⁾. – IR. (film): 2250, no carbonyl.

1.2.2. 3-[N-Benzyl-N-(p-chloro-2-hydroxyphenethyl)amino]propionitrile (oil), purified as hydrochloride salt (81%); m.p. 173–175° (ethyl acetate). – IR. (nujol): 2250, no carbonyl. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.7–3.9 (7 H, including OH); 4.5 (s, 2 H); 5.1 (d × d × d, J₁ = 12, J₂ = 10, J₃ = 4, 1 H); 7.3–7.8 (9 H); ca. 10 (very br., 1 H).

C ₁₈ H ₂₀ Cl ₂ N ₂ O	Calc.	C 61.5	H 5.7	Cl 20.2	N 8.0%
(351.3)	Found	„ 61.7	„ 5.6	„ 19.6	„ 8.0%

1.2.3. 3-[N-Benzyl-N-(p-fluoro-2-hydroxyphenethyl)amino]propionitrile (oil), purified by alumina filtration (20 parts, CH₂Cl₂) (87%). – IR. (film): 2250, no carbonyl.

1.2.4. 3-[N-Benzyl-N-(2-hydroxy-p-methylphenethyl)amino]propionitrile (oil, purified via hydrochloride and liberation of the free base) (80%). – IR. (film): 2250, no carbonyl. – ¹H-NMR. (100 MHz, CDCl₃): 2.3–3.05 (9 H); 3.25 (br., 1 H, OH); 3.6 and 3.9 (AB-system, J_{gem} = 14, 2 H); 4.65 (d × d, J₁ = 8, J₂ = 4, 1 H); 7.0–7.5 (9 H). – Hydrochloride salt: m.p. 175–177° (acetone/petroleum ether).

C ₁₉ H ₂₃ ClN ₂ O	Calc.	C 69.0	H 7.0	Cl 10.7	N 8.5%
(330.9)	Found	„ 68.8	„ 6.8	„ 10.7	„ 8.4%

1.3. Preparation of N-benzylaminoalcohols by reduction of amino acid derivatives with LiAlH₄. The procedure described for (–)-L-2-benzylamino-3-phenyl-1-propanol ([11], Scheme 6) was followed for the preparation of DL-2-benzylamino-3-phenyl-1-propanol ([12], Scheme 6) and 2-benzylamino-2-phenylethanol ([13], Scheme 5). Analogously prepared were: 3-Benzylamino-3-phenyl-1-propanol (from 3-benzoylamino-3-phenylpropionic acid (Scheme 7)), pure oil (100%). – IR. (CH₂Cl₂): no carbonyl. – Hydrogenoxalate salt, m.p. 171–172° (methanol/ether).

C ₁₈ H ₂₁ NO ₅ (331.4)	Calc.	C 65.2	H 6.4	N 4.2%	Found	C 64.9	H 6.6	N 4.2%
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1.3.1. 3-Benzylamino-2-phenyl-1-propanol (from ethyl 2-phenyl-3-(N-benzylamino)propionate [14] with 2 mol-equiv. of LiAlH₄ (Scheme 8)), pure oil (96%). – IR. (CH₂Cl₂): no carbonyl. – Hydrogenoxalate salt, m.p. 191–192° (methanol/ether).

C ₁₈ H ₂₁ NO ₅ (331.4)	Calc.	C 65.2	H 6.4	N 4.2%	Found	C 65.1	H 6.5	N 4.3%
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1.4. N-Alkylation of aminoalcohols with acrylonitrile (Scheme 3, method B). – General procedure. A solution of the aminoalcohol (0.265 mol), acrylonitrile (1.28 l) and acetic acid (20 ml) in dioxane or methanol (0.6–1.2 l) was refluxed for 14–72 h. The mixture was evaporated and the residue dissolved in ethyl acetate. Unchanged starting aminoalcohol was recovered by extraction with 10% aq. tartaric acid-solution. The organic phase gave, after drying (MgSO₄) and evaporation, the amino-hydroxynitriles:

1.4.1. 3-[N-Benzyl-N-(2-hydroxy-1-phenylethyl)amino]propionitrile (13) (from 2-benzylamino-2-phenylethanol) (pure oil, 72%). – IR. (CH₂Cl₂): 3500, 2250. – ¹H-NMR. (100 MHz, CDCl₃): 2.35 (d × t, J₁ = 14, J₂ = 6, 2 H); 2.3–2.9 (1 exchangeable H); 2.9 (d × t, J₁ = 14, J₂ = 6, 2 H); 3.4 and 3.9 (AB-system, J_{gem} = 14, 2 H); 3.6–4.2 (3 H); 7.4 (10 H).

1.4.2. DL-3-[N-Benzyl-N-(1-hydroxy-3-phenyl-2-propyl)amino]propionitrile (from DL-2-benzylamino-3-phenyl-1-propanol, Scheme 6), m.p. 88–89° (ether/petroleum ether) (64%; 75% related to transformed starting material). – IR. (film): 3450, 2250. – ¹H-NMR. (100 MHz, CDCl₃): 2.25 (t, J = 7, 2 H); 2.9 (t, J = 7, 2 H); 2.2–3.2 (4 additional H, including OH); 3.4 (d, J = 7, 2 H); 3.55 and 3.85 (AB-system, J_{gem} = 14, 2 H); 7–7.6 (10 H).

C ₁₉ H ₂₂ N ₂ O (294.4)	Calc.	C 77.5	H 7.5	N 9.5%	Found	C 77.4	H 7.8	N 9.5%
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1.4.3. L-3-[N-Benzyl-N-(1-hydroxy-3-phenyl-2-propyl)amino]propionitrile (from L-2-benzylamino-3-phenyl-1-propanol, Scheme 6), m.p. 106–107° (CH₂Cl₂/ether) (74%; 86% related to transformed starting material) [α]_D²⁰ = –11.0° (c = 1.0, CH₃OH).

C ₁₉ H ₂₂ N ₂ O (294.4)	Calc.	C 77.5	H 7.5	N 9.5%	Found	C 77.0	H 7.5	N 9.3%
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⁷⁾ This two-step preparation gave a better yield of product than the direct alkylation of 3-(benzylamino)propionitrile with styrene oxide.

1.4.4. 3-[N-Benzyl-N-(3-hydroxy-1-phenyl-1-propyl)amino]propionitrile (from 3-benzylamino-3-phenyl-1-propanol, Scheme 7), m.p. 60–62° (ether/petroleum ether) (70%). – IR. (film): 3350, 2250. – ¹H-NMR. (100 MHz, CDCl₃): 1.7–3.2 (7 H, including OH); 3.3 and 3.8 (AB-system, *J*_{gem} = 14, 2 H); 3.6–4.1 (3 H); 7.3 (10 H).

C₁₉H₂₂N₂O (294.4) Calc. C 77.5 H 7.5 N 9.5% Found C 77.7 H 7.5 N 9.6%

1.5. N-Alkylation of aminoalcohols with chloroacetoneitrile (Scheme 3, method C). – General procedure. A stirred mixture of the aminoalcohol (0.75 mol), K₂CO₃ (249 g), KI (300 g), chloroacetoneitrile (113 ml) and dimethylformamide (2.5 l) was heated for 10 h at 90°. Dilution with water, extraction with ethylacetate, evaporation of the organic phase and filtration of the residue through alumina (10 parts, CH₂Cl₂) yielded the pure aminohydroxynitriles.

1.5.1. N-Benzyl-N-(3-hydroxy-2-phenyl-1-propyl)aminoacetoneitrile (from 3-benzylamino-2-phenyl-1-propanol) (cf. Scheme 8), m.p. 74–75° (ether/petroleum ether) (40%). – IR. (CH₂Cl₂): 3600, 3350, 2240 (very weak). – ¹H-NMR. (100 MHz, CDCl₃): 2.85–3.35 (3 H + OH at 3.15); 3.5 (*d*, *J* = 4, 2 H); 3.7 (center of AB-system, *J*_{gem} = 14, 2 H); 3.8 (center of AB-system, *J*_{gem} = 12, 2 H); 7.1–7.5 (10 H).

C₁₈H₂₀N₂O (280.4) Calc. C 77.1 H 7.2 N 10.0% Found C 77.5 H 7.4 N 10.0%

¹H-NMR. of its acetyl derivative (100 MHz, CDCl₃): 1.95 (*s*, 3 H); 2.8–3.0 (*Y*₂-part of ABXY₂-system, 2 H); 3.0–3.3 (*m*, *X*-part of ABXY₂-system, 1 H); 3.4 (*s*, 2 H); 3.65 (*s*, 2 H); 4.3 (AB-part of ABXY₂-system, *J*_{AB} = 12, *J*_{AX} = *J*_{BX} = 6, 2 H); 7.0–7.5 (10 H).

1.5.2. N-Benzyl-N-(3-hydroxy-1-phenyl-1-propyl)aminoacetoneitrile (from 3-benzylamino-3-phenyl-1-propanol) (cf. Scheme 8), m.p. 75–76° (ether/petroleum ether) (79%). – IR. (CH₂Cl₂): 3600, 2240 (very weak). – ¹H-NMR. (100 MHz, CDCl₃): 1.8–2.5 (2 H + OH at 2.1); 3.25 and 3.5 (AB-system, *J*_{gem} = 16, 2 H); 3.45–3.65 (2 H); 3.6 and 3.75 (AB-system, *J*_{gem} = 14, 2 H); 3.9 (*d* × *d*, *J*₁ = 9, *J*₂ = 6, 1 H); 7.1–7.5 (10 H).

C₁₈H₂₀N₂O (280.4) Calc. C 77.1 H 7.2 N 10.0% Found C 77.4 H 7.3 N 10.2%

1.6. Reaction of aminohydroxynitriles with SOCl₂. – General procedure. Thionyl chloride (60 ml) was added dropwise (exothermic reaction) to a stirred solution of the aminohydroxynitrile (free base or hydrogen chloride, 60 g) in CHCl₃ (600 ml). This solution was refluxed for 15–30 min in the case of **14a**, **17**, **24**, for 2.5 h in the case of **7a–d**, and for 24 h in the case of **22**. In many cases the hydrochloride of the products crystallized in the hot or cooled reaction mixtures, eventually after addition of ether or hexane, and were isolated by filtration. Samples of the stable chlorides **7a–d** were recrystallized for characterization. In the cases where the free bases were isolated, the reaction mixture was shaken with an excess of aq. NaHCO₃-solution. After evaporation of the organic phase at 25°/12 Torr the crude product was purified by filtration through alumina (20 parts, CH₂Cl₂, evaporation at 25°/12 Torr).

1.6.1. 3-[N-Benzyl-N-(2-chlorophenethyl)ammonio]propionitrile chloride (**7a**) (from 3-[N-benzyl-N-(2-hydroxyphenethyl)amino]propionitrile), m.p. 152–154° (CHCl₃/ether) (87%). – IR. (nujol): 2700–2300 (several bands), 2250. – ¹H-NMR. (90 MHz, D₆-DMSO): 2.65–3.45 (6 H); 4.0 (*s*, 2 H); 5.4 (*t*, *J* = 7, 1 H); 7.2–7.6 (10 H); 9.9 (*s*, br., 1 H).

C₁₈H₂₀Cl₂N₂ Calc. C 64.5 H 6.0 Cl 21.1 N 8.4%
(335.3) Found „ 64.2 „ 6.0 „ 21.6 „ 8.4%

The same product was obtained from **13**.

1.6.2. 3-[N-Benzyl-N-(2-chloro-2-(*p*-chlorophenethyl)ethyl)ammonio]propionitrile chloride (**7b**) (from 3-[N-benzyl-N-(*p*-chloro-2-hydroxyphenethyl)ammonio]propionitrile chloride), m.p. 182–184° (methanol/ether) (90%). – IR. (film): 2500 (br.), 2250. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.85–3.65 (6 H); 4.2 (*s*, 2 H); 5.5 (*t*, *J* = 7, 1 H); 7.3–7.6 (9 H); *ca.* 8.1 (br., 1 H).

C₁₈H₁₉Cl₃N₂ (369.7) Calc. C 58.5 H 5.2 N 7.6% Found C 58.7 H 5.4 N 7.5%

1.6.3. 3-[N-Benzyl-N-(2-chloro-2-(*p*-fluorophenethyl)ammonio]propionitrile chloride (**7c**) (from 3-[N-benzyl-N-(*p*-fluoro-2-hydroxyphenethyl)ammonio]propionitrile), m.p. 168–170° (methanol/ether) (86%). – IR. (nujol): 2500 (br.), 2250. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.8–3.7 (6 H); 4.1 (*s*, 2 H); 5.45 (*t*, *J* = 7, 1 H); 7.0–7.6 (9 H); *ca.* 9 (very br., 1 H).

C₁₈H₁₉Cl₂FN₂ (353.3) Calc. C 61.2 H 5.4 N 7.9% Found C 61.8 H 5.6 N 8.3%

1.6.4. 3-[N-Benzyl-N-(2-chloro-p-methylphenethyl)ammonio]propionitrile chloride (**7d**) (from 3-[N-benzyl-N-(2-hydroxy-p-methylphenethyl)ammonio]propionitrile chloride), m.p. 162–164° (CHCl₃) (95%). – IR. (nujol): 2500 (br.), 2250. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.25 (s, 3 H); 2.8–3.7 (6 H); 4.1 (s, 2 H); 5.35 (t, *J* = 7, 1 H); 7.1–7.6 (9 H); *ca.* 9 (very br., 1 H).

C ₁₉ H ₂₂ Cl ₂ N ₂	Calc.	C 65.3	H 6.3	Cl 20.3	N 8.0%
(349.3)	Found	„ 65.9	„ 6.2	„ 19.7	„ 8.0%

1.6.5. DL- and L-3-[N-Benzyl-N-(1-chloro-3-phenyl-2-propyl)ammonio]propionitrile chloride (**14a**) (from DL- and L-3-[N-Benzyl-N-(1-hydroxy-3-phenyl-2-propyl)amino]propionitrile, resp.). To minimize rearrangement the crude product was isolated by evaporation of the reaction mixture at 50°/12 Torr. The mixture was twice dissolved in and evaporated from benzene at 50° to give the crude product (oil, 100%, mixture with *ca.* 20–25% of **14b**), which could be used directly in the next step. When the product was isolated by diluting the cooled reaction mixture with ether, a fairly pure crystalline hydrochloride, (±)-**14a**, m.p. 135–136° (methanol/ether), and (–)-**14a**, m.p. 136–137° (methanol/ether), [*α*]_D²⁰ = –9.7° (*c* = 1.0, CH₃OH), resp., was obtained in 50% yield in which no **14b** could be detected by ¹H-NMR. (100 MHz, D₆-DMSO) [2.5–3.6 (7 H); 3.85 (*d*, *J* = 7, 2 H); 4.2 (center of *AB*-system, *J*_{gem} = 14, 2 H); 7.1–7.7 (10 H); *ca.* 10 (very br., 1 H)]; after addition of D₂O the signal at 10 ppm disappeared and a sharp multiplet was revealed at 3.5 ppm (1 H). – IR. (nujol): 2750–2300 (several bands), 2250. – ¹H-NMR. (100 MHz, CDCl₃) of the free base (oil, prepared by shaking the hydrochloride with aq. NaHCO₃-solution/CH₂Cl₂): 2.1–3.2 (6 H); 3.45 (*m*, *X*-part of *ABX*-system, 1 H); 3.8 (*s*, 2 H); 3.9 (*d* × *d*, *A*-part of *ABX*-system, *J*_{AB} = 14, *J*_{AX} = 4, 1 H); 4.25 (*d* × *d*, *B*-part of *ABX*-system, *J*_{AB} = 14, *J*_{BX} = 9, 1 H); 7.0–7.4 (10 H).

1.6.6. 3-[N-Benzyl-N-(3-chloro-1-phenyl-1-propyl)ammonio]propionitrile chloride (**17**) (from 3-[N-benzyl-N-(3-hydroxy-1-phenyl-1-propyl)amino]propionitrile), isolated by evaporation as described for **14a**. In the crude product (oil, 100%), which could be used directly in the next step, no rearranged product could be detected by ¹H-NMR. The free base could be crystallized from ether/petroleum ether: m.p. 60–61°. – IR. (CH₂Cl₂): 2250. – ¹H-NMR. (100 MHz, CDCl₃): 2.0–3.1 (6 H); 3.35 and 3.75 (*AB*-system, *J*_{gem} = 14, 2 H); 3.65 (*mc*, 2 H); 4.0 (*t*, *J* = 7, 1 H); 7.1–7.5 (10 H).

C ₁₉ H ₂₁ ClN ₂ (312.8)	Calc.	C 72.9	H 6.8	N 9.0%	Found	C 72.9	H 6.7	N 8.9%
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From this crystalline base a pure hydrochloride (amorphous) was obtained. – ¹H-NMR. (90 MHz, D₆-DMSO): 2.5–3.05 (5 H); 3.15–3.9 (3 H); 3.8 and 4.15 (*AB*-system, *J*_{gem} = 14, 2 H); 4.35 (*d* × *d*, *J*₁ = 10, *J*₂ = 6, 1 H); 7.3–7.7 (11 H).

1.6.7. N-Benzyl-N-(3-chloro-2-phenyl-1-propyl)aminoacetoneitrile (**22**) (from N-benzyl-N-(3-hydroxy-2-phenyl-1-propyl)aminoacetoneitrile) (pure oil, 100%). – IR. (CH₂Cl₂): 2250 (very weak). – ¹H-NMR. (100 MHz, CDCl₃): 2.85–3.3 (3 H); 3.35 (*s*, 2 H); 3.7 (*s*, 2 H); 3.8 (*d*, *J* = 6, 2 H); 7.1–7.5 (10 H).

1.6.8. N-Benzyl-N-(3-chloro-1-phenyl-1-propyl)aminoacetoneitrile (**24**) (from N-benzyl-N-(3-hydroxy-1-phenyl-1-propyl)aminoacetoneitrile), m.p. 67–68° (ether/petroleum ether) (72%). – IR. (CH₂Cl₂): 2250 (very weak). – ¹H-NMR. (100 MHz, CDCl₃): 2.0–2.8 (2 H); 3.1–3.6 (4 H); 3.75 (*s*, 2 H); 3.95 (*d* × *d*, *J*₁ = 9, *J*₂ = 5, 1 H); 7.0–7.7 (10 H).

C ₁₈ H ₁₉ ClN ₂	Calc.	C 72.3	H 6.4	Cl 11.9	N 9.4%
(298.8)	Found	„ 72.2	„ 6.4	„ 12.1	„ 9.3%

The mother liquid seemed to contain some rearranged product as indicated by a small triplet (*J* = 7) at 5.0 ppm (CDCl₃) resp. 5.1 ppm (D₆-DMSO) in the ¹H-NMR. (100 MHz). On the other hand **24** was stable when refluxed in toluene for 1 h.

1.7. Thermal rearrangement of (±)-3-[N-benzyl-N-(1-chloro-3-phenyl-2-propyl)ammonio]propionitrile chloride (**14a**) to 3-[N-benzyl-N-(2-chloro-3-phenyl-1-propyl)amino]propionitrile (**14b**). Heating crystalline **14a** for 15 min at 140° gave almost quantitatively **14b**·HCl (resinous oil). – IR. (CH₂Cl₂): 2500 (weak, br.), 2250. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.6–3.6 (8 H); 4.1 (2 H); 4.4 (*m*, 1 H); 7.0–7.8 (10 H); *ca.* 10 (very br., 1 H). – ¹H-NMR. (360 MHz, CDCl₃) of the free base (oil, prepared by shaking the hydrochloride with aq. NaHCO₃-solution/CH₂Cl₂): 2.45 (*t*, *J* = 8, 2 H); 2.8 (*d* × *d*, *A*-part of *ABC*₂*X*-system, *J*_{AB} = 14, *J*_{AX} = 9, 1 H); 2.89 (*d*, *C*₂-part of *ABC*₂*X*-system, *J*_{CX} = 8, 2 H); 2.92 (*t*, *J* = 8, 2 H); 3.27 (*d* × *d*, *B*-part of *ABC*₂*X*-system, *J*_{AB} = 14, *J*_{BX} = 6, 1 H); 3.75 (center of *AB*-system, *J*_{gem} = 14, 2 H); 4.05 (*m*, *X*-part of *ABC*₂*X*-system, 1 H); 7.0–7.6 (10 H).

2. Preparation and refunctionalization of pyrrolidines **8**, **15a**, **15b**, **23**, **25** and piperidine **18**. –

2.1. *Carbanionic ring closure of aminochloronitriles*. – *General procedure*. An excess of 20% or more of sodium hexamethyldisilazane (ca. 0.9 molar in benzene) [15] was used for all cyclizations, but in some cases similar results were obtained with potassium amide in liquid ammonia. When the ammoniochloronitrile chlorides were used for cyclization, an additional mol-equiv. of reagent was added to liberate the free base *in situ*. A solution of sodium hexamethyldisilazane in benzene was added dropwise to a stirred 5% solution or suspension of the aminochloronitrile (free base or hydrochloride) in tetrahydrofuran under N₂ at –60° (for **7a–d**), 0° (for **24**), or 20° (for **14a,b**, **17**, **22**), resp. After stirring at 20° for 30–60 min an excess of satd. aq. NH₄Cl-solution was added. Extraction with ethyl acetate gave the pyrrolidines and piperidines.

2.1.1. *trans-1-Benzyl-4-phenylpyrrolidino-3-carbonitrile oxalate (8a)* (from **7a**·HCl), m.p. 198–199° (methanol/ether) (80%). – ¹H-NMR. (60 MHz, D₆-DMSO): 2.7–3.8 (6 H); 3.95 (s, 2 H); 7.2–7.5 (s, 10 H); 7.8–8.2 (2 H).

C₂₀H₂₀N₂O₄ (352.4) Calc. C 68.2 H 5.7 N 7.9% Found C 68.1 H 5.8 N 8.0%

IR. of the free base (film): 2240.

(In one experiment, probably the *cis*-isomer was detected as by-product, which could be isomerized to the *trans*-compound by treatment with potassium ethylate.)

2.1.2. *trans-1-Benzyl-4-(p-chlorophenyl)pyrrolidine-3-carbonitrile (8b)* (from **7b**·HCl), unstable oil, was used directly in the next step.

2.1.3. *trans-1-Benzyl-4-(p-fluorophenyl)pyrrolidino-3-carbonitrile oxalate (8c)* (from **7c**·HCl), m.p. 201–202° (ethanol) (78%).

C₂₀H₁₉FN₂O₄ Calc. C 64.9 H 5.2 F 5.1 N 7.6%
(370.4) Found „ 65.2 „ 5.1 „ 5.1 „ 7.7%

IR. of the free base (CH₂Cl₂): 2250. – ¹H-NMR. of the free base (60 MHz, CDCl₃): 2.65–3.6 (6 H); 3.65 (s, 2 H); 6.7–7.4 (9 H).

2.1.4. *trans-1-Benzyl-4-(p-tolyl)pyrrolidino-3-carbonitrile fumarate (8d)* (from **7d**·HCl), m.p. 150–151° (ethanol/ether) (70%). – IR. (nujol): 2240. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.3 (s, 3 H); 2.7–3.6 (6 H); 3.7 (s, 2 H); 3.8–5.5 (2 exchangeable H); 6.6 (s, 2 H); 7.0–7.4 (9 H).

C₂₃H₂₄N₂O₄ (392.5) Calc. C 70.4 H 6.2 N 7.1% Found C 70.3 H 6.1 N 7.2%

2.1.5. *DL- and L-1,5-Dibenzylpyrrolidine-3-carbonitrile (15a)* (from DL- and L-**14a**·HCl, resp.), oil, (4:1)-mixture of epimers (97% yield starting from crystalline **14a**·HCl, 99% pure; 100% yield starting from crude oily **14a**·HCl, containing 23% of isomer **15b**). – IR. (CH₂Cl₂): 2250. – Samples of pure racemic epimers were obtained by chromatography of the racemic mixture on 200 parts of silica gel (CH₂Cl₂/methanol (100:0)→(99.5:0.5)).

Main epimer, m.p. 90–91° (ether/petroleum ether). – ¹H-NMR. (90 MHz, CDCl₃): 1.8–2.15 (2 H); 2.25–3.3 (6 H); 3.3 and 4.05 (AB-system, J_{gem} = 13, 2 H); 7.0–7.4 (10 H).

C₁₉H₂₀N₂ (276.4) Calc. C 82.6 H 7.3 N 10.1% Found C 82.2 H 7.4 N 10.1%

Minor epimer (oil) [¹H-NMR. (90 MHz, CDCl₃): 1.8–2.4 (2 H); 2.5–3.4 (6 H); 3.55 and 4.15 (AB-system, J_{gem} = 13, 2 H); 7.0–7.6 (10 H)].

2.1.6. *1,4-Dibenzylpyrrolidine-3-carbonitrile (15b)* (from **14b**·HCl), (65:35)-mixture of epimers (oil, 75%). – IR. (CH₂Cl₂): 2250. – ¹H-NMR. (90 MHz, CDCl₃): 2.3–3.2 (8 H); 3.6 (center of AB-system, J_{gem} = 14, 1.3 H) and 3.65 (center of AB-system, J_{gem} = 14, 0.7 H); 7.1–7.5 (10 H). – TLC., IR. and ¹H-NMR. spectral comparison confirmed the identity of **15b** with authentic material [6].

2.1.7. *1-Benzyl-6-phenylpiperidine-3-carbonitrile (18)* (from **17**, free base), mixture of epimers, from which 52% of pure *trans*-epimer and 30% of pure *cis*-epimer were isolated by chromatography on 200 parts of silica gel (CH₂Cl₂), but the crude mixture of epimers was used for the next step.

trans-Epimer, m.p. 94–95° (ether/petroleum ether). – IR. (CH₂Cl₂): 2250. – ¹H-NMR. (100 MHz, CDCl₃): 1.4–2.4 (4 H); 2.15 (t, J = 12, 1 H); 2.7 (m, 1 H); 2.85 and 3.75 (AB-system, J_{gem} = 14, 2 H); 3.15 (d×d, J₁ = 12, J₂ = 3, 1 H); 3.2 (m, 1 H); 7.0–7.6 (10 H); complete interpretation by addition of D₇-Eu(fod)₃ and by DR. experiments: 2.25 (m, 2 H, 2 H–C(5)); 2.7 (qa×d, J₁ = 12, J₂ = 4, 1 H, H_{ax}–C(4)); 3.2 (1 H, H_{eq}–C(4)); 3.15 and 4.05 (AB-system, J_{gem} = 14, 2 benzylic H); 3.2 (t, J = 12,

1H, H_{ax} -C(2)); 3.6 ($d \times d$, $J_1 = 10$, $J_2 = 5$, 1H, H_{ax} -C(6)); 4.25 ($d \times d$, $J_1 = 12$, $J_2 = 3$, 1H, H_{eq} -C(2)); 4.5 ($t \times t$, $J_1 = 12$, $J_2 = 3$, 1H, H_{ax} -C(3)); 7.1–7.8 (10 H).

$C_{19}H_{20}N_2$ (276.4) Calc. C 82.6 H 7.3 N 10.1% Found C 82.9 H 7.4 N 10.0%

cis-Epimer, m.p. 122–123° (ether/petroleum ether). – IR. (CH_2Cl_2): 2250. – 1H -NMR. (100 MHz, $CDCl_3$, complete interpretation by DR. experiments): 1.6–2.4 (4 H, H–C(4) and H–C(5)); 2.15 ($d \times d$, $J_1 = 12$, $J_2 = 3$, 1H, H_{ax} -C(2)); 2.9 and 3.8 (*AB*-system, $J_{gem} = 14$, 2 H); 2.85 (*m*, 1H, H_{eq} -C(3)); 3.16 ($d \times d$, $J_1 = 12$, $J_2 = 2$, 1H, H_{eq} -C(2)); 3.18 ($d \times d$, $J_1 = 10$, $J_2 = 5$, 1H, H_{ax} -C(6)); 7.1–7.6 (10 H).

$C_{19}H_{20}N_2$ (276.4) Calc. C 82.6 H 7.3 N 10.1% Found C 82.9 H 7.1 N 10.2%

2.1.8. *1-Benzyl-4-phenylpyrrolidine-2-carbonitrile* (**23**) (from **22**, free base), *ca.* (1:1)-mixture of isomers (oil, 100%). – IR. (CH_2Cl_2): 2240 (weak). – 1H -NMR. (360 MHz, $CDCl_3$): 2.25–2.85 (3 H); 2.98 ($d \times d$, $J_1 = 5$, $J_2 = 10$, 0.5 H); 3.07 (*t*, $J = 10$, 0.5 H); 3.27 ($d \times d$, $J_1 = 8$, $J_2 = 10$, 0.5 H); 3.4–3.65 (1 H); 3.74/3.96 and 3.75/3.99 (2 *AB*-systems of equal intensity, $J_{gem} = J_{gem'} = 13$, total of 2 H); 3.9 (*m*, 0.5 H); 7.2–7.5 (10 H).

2.1.9. *1-Benzyl-5-phenylpyrrolidine-2-carbonitrile* (**25**) (from **24**, free base), mixture of epimers (oil, 80% after filtration through 20 parts of aluminum oxide with CH_2Cl_2). – IR. (CH_2Cl_2): 2250 (weak). – 1H -NMR. (100 MHz, $CDCl_3$): 1.5–2.6 (4 H); 3.4 and 3.8 (*AB*-system, $J_{gem} = 13$, 2 H); 3.4–4.0 (2 H); 7.1–7.6 (10 H).

Samples of enriched single isomers were obtained by careful chromatography on silica gel (petroleum ether/ethyl acetate (99:1)→(96:4)). These samples could be isomerized to the original mixture of epimers by treatment with potassium ethoxide in ethanol.

2.2. *Ethanolysis of pyrrolidine- and piperinecarbonitriles to ethyl carboxylates. – General procedure.* A 10% solution of the carbonitrile (0.27 mol) in ethanol was saturated at 0° with HCl. After 15 h of reflux 16 ml of water were added and reflux was continued for 3 h. The mixture was evaporated to dryness and taken up in an excess of aq. $NaHCO_3$ -solution. Extraction with CH_2Cl_2 gave the ethyl carboxylates.

2.2.1. *Ethyl trans-1-benzyl-4-phenylpyrrolidine-3-carboxylate* (**9a**) (from **8a**), TLC.-pure oil (100%), which was used directly in the next step. Hydrogen oxalate: m.p. 144–145° (ethanol/ether).

$C_{22}H_{25}NO_6$ (399.4) Calc. C 66.2 H 6.3 N 3.5% Found C 65.9 H 6.3 N 3.5%

2.2.2. *Ethyl trans-1-benzyl-4-(p-chlorophenyl)pyrrolidine-3-carboxylate* (**9b**) (from crude **8b**), TLC.-pure oil (60% from **7b** after chromatography on 25 parts of silica gel with CH_2Cl_2/C_2H_5OH (100:0)→(98:2)). Hydrogen oxalate; m.p. 156–158° (methanol/ether).

$C_{22}H_{24}ClNO_6$ (433.9) Calc. C 60.9 H 5.6 Cl 8.2 N 3.2%
Found „ 61.2 „ 5.4 „ 8.5 „ 3.4%

2.2.3. *Ethyl trans-1-benzyl-4-(p-fluorophenyl)pyrrolidine-3-carboxylate* (**9c**) (from **8c**), TLC.-pure oil (64%) after filtration through 20 parts of aluminum oxide with ethyl acetate, which was used directly in the next step. Hydrogen fumarate: m.p. 122–124° (ethanol/ether).

$C_{24}H_{26}FNO_6$ (443.5) Calc. C 65.0 H 5.9 F 4.3 N 3.2%
Found „ 65.0 „ 5.9 „ 4.4 „ 3.1%

2.2.4. *Ethyl trans-1-benzyl-4-(p-tolyl)pyrrolidine-3-carboxylate* (**9d**) (from **8d**), hydrogen oxalate (90%), m.p. 120–124° (methanol/ether).

$C_{23}H_{27}NO_6$ (413.5) Calc. C 66.8 H 6.6 N 3.4 O 23.2%
Found „ 66.4 „ 6.5 „ 3.6 „ 23.0%

2.2.5. *Ethyl 1-benzyl-6-phenylpiperidine-3-carboxylate* (**19a**) (from mixture of epimers **18**), epimeric mixture (oil, 100%), directly used in the next step.

2.3. *Hydrogenolysis of 19a to ethyl 6-phenylpiperidine-3-carboxylate* (**19b**). A solution of **19a** (epimeric mixture, 15.7 g) in ethanol (200 ml) was hydrogenolyzed in the presence of oxalic acid (4.36 g) and (10%) Pd/C (1.5 g) at 25° over night. The title compound was isolated as an epimeric mixture of the free bases (oil, 100%) by shaking with an excess of aq. Na_2CO_3 -solution and CH_2Cl_2 , and used directly in the next step.

2.4. *Hydrolysis of ethyl pyrrolidine- and piperidinecarboxylates to carboxylic acids.* – *General procedure.* A 10% solution of the ethyl carboxylate (1.0 mol) in ethanol was refluxed for 15 h together with a saturated aq. Ba(OH)₂-solution (1.1 mol). After neutralisation with aq. 10% H₂SO₄-solution to pH 7 the BaSO₄ was removed by filtration through hyflo and the filtrate evaporated to dryness. The residue was taken up in and evaporated from benzene several times to eliminate water completely. The aminoacid was extracted from the dry residue with ethanol.

2.4.1. *trans-1-Benzyl-4-phenylpyrrolidine-3-carboxylic acid (10a)* (from **9a**), practically pure oil (96%), used directly in the next step. A monohydrate crystallized from methanol/acetone, m.p. 146–148°.

C₁₈H₂₁NO₃ (299.4) Calc. C 72.2 H 7.1 N 4.7% Found C 72.3 H 6.9 N 4.5%

2.4.2. *trans-1-Benzyl-4-(p-chlorophenyl)pyrrolidine-3-carboxylic acid (10b)* (from **9b**), crude oil, directly used in the next step, crystals from ethanol, m.p. 152–154°. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.5–2.75 (1H); 2.75–3.1 (4H); 3.3–3.7 (1H); 3.65 (s, 2H); 7.15–7.4 (9H); ca. 7.5 (br., 1 exchangeable H).

C₁₈H₁₈ClNO₂ Calc. C 68.5 H 5.7 Cl 11.2 N 4.4%
(315.8) Found „ 68.2 „ 6.0 „ 11.0 „ 4.1%

2.4.3. *trans-1-Benzyl-4-(p-fluorophenyl)pyrrolidine-3-carboxylic acid (10c)* (from **9c**), m.p. 145–147° (acetone/ether) (72%).

C₁₈H₁₈FNO₂ Calc. C 72.2 H 6.1 F 6.3 N 4.7%
(299.3) Found „ 72.5 „ 6.1 „ 6.4 „ 4.7%

2.4.4. *trans-1-Benzyl-4-(p-tolyl)pyrrolidine-3-carboxylic acid (10d)* (from **9d**), TLC.-pure oil (100%), used directly in the next step. – ¹H-NMR. (100 MHz, D₆-DMSO): 2.3 (s, 3H); 2.7–3.1 (5H); 3.4–3.75 (1H); 3.65 (s, 2H); 6.6–7.6 (10H).

2.4.5. *6-Phenylpiperidine-3-carboxylic acid (20)* (from epimeric mixture of **19b**), epimeric mixture (oil, 70%), used directly in the next step. The *trans*-isomer crystallized from methanol/ether in 55% yield, m.p. 246–248°. – ¹H-NMR. (100 MHz, D₆-DMSO): 1.3–2.3 (4H); 2.5 (*m*, 1H); 2.8 (*t*, *J* = 11, 1H); 3.4 (*d* × *d*, *J*₁ = 11, *J*₂ = 3, 1H); 3.75 (*d* × *d*, *J*₁ = 10, *J*₂ = 3, 1H); 6.6–7.6 (7H).

C₁₂H₁₅NO₂ (205.3) Calc. C 70.2 H 7.4 N 6.8% Found C 70.5 H 7.5 N 7.1%

2.5. *Hydrolysis of 1-benzyl-5-phenylpyrrolidine-2-carbonitrile (25) to 1-benzyl-5-phenylpyrrolidine-2-carboxamide (26).* An epimeric mixture of the nitrile **25** (9.3 g) was heated in conc. H₂SO₄-solution (100 ml) for 20 min at 100°. The cold mixture was poured on ice (300 g) and made alkaline with aq. conc. NaOH-solution. Extraction with CH₂Cl₂ gave an epimeric mixture of carboxamide **26** (oil, 100%) from which one single epimer crystallized in 50% yield: m.p. 121–122° (ether/petroleum ether). – IR. (CH₂Cl₂): 3500, 1680. – ¹H-NMR. of single isomer (100 MHz, CDCl₃): 1.65–2.7 (4H); 3.4–3.9 (3H); 4.35 (*d* × *d*, *J*₁ = 8, *J*₂ = 4, 1H); 6.3–6.6 (s, 2H); 7.0–7.4 (10H). In the epimeric mixture the benzylic methine proton of the second epimer appears together with 3 other protons as a complex signal between 3.4 and 3.9.

C₁₈H₂₀N₂O (280.4) Calc. C 77.1 H 7.2 N 10.0% Found C 77.3 H 7.5 N 10.0%

3. *Cyclization of pyrrolidines 10, 15a, 15b, and piperidine 20 to tricyclic compounds.* – 3.1. *General procedure.* A mixture of 1 part of the pyrrolidine or piperidine derivative and 10 parts of cyclization reagent (A) P₂O₅/CH₃SO₃H [16]; B) 5 parts of polyphosphoric acid + 1 part of P₂O₅; C) 20 parts of polyphosphoric acid + 1 part of water, homogenized for 1 h at 100°) was heated (details see below). The mixture was poured on ice and made alkaline with aq. NaOH-solution and immediately extracted with ethyl acetate to give the tricyclic compounds.

3.1.1. *cis-2-Benzyl-1,2,3,3a-tetrahydro-8aH-indeno[1,2-c]pyrrole-8-one (11a)* (from crude **10a** with reagent A, 1 h, 100°), pure oil (85%) after filtration through 10 parts of basic aluminum oxide with CH₂Cl₂. – IR. (CH₂Cl₂): 1710. – ¹H-NMR. (100 MHz, CDCl₃, complete interpretation by DR. experiments): 2.4 (*t*, *J* = 9, 1H, H_{ax}–C(1)); 2.55 (*d* × *d*, *J*₁ = 9, *J*₂ = 8, 1H, H_{ax}–C(3)); 2.9 (*d* × *d*, *J*₁ = 9, *J*₂ = 2, 1H, H_{eq}–C(1)); 3.0 (*d* × *d* × *d*, *J*₁ = 9, *J*₂ = 8, *J*₃ = 2, 1H, H–C(8a)); 3.15 (*d* × *d*, *J*₁ = 9, *J*₂ = 2, 1H, H_{eq}–C(3)); 3.45 (s, 2 benzylic H); 3.7 (*r* × *d*, *J*₁ = 8, *J*₂ = 2, 1H, H–C(3a)); 6.9–7.6 (8H); 7.7 (*d* × *d*, *J*_{ortho} = 9, *J*_{meta} = 2, 1H, H–C(7)).

Hydrogen oxalate of 11a, m.p. 175–178° (ethanol). – $^1\text{H-NMR}$. (100 MHz, $\text{D}_6\text{-DMSO}$): 2.8–3.5 (5 H); 3.9 (s, 2 H); 3.9–4.2 (1 H); 7.1–7.8 (9 H); 11.75 (s, 2 exchangeable H).

$\text{C}_{20}\text{H}_{19}\text{NO}_5$ (353.4) Calc. C 68.0 H 5.4 N 4.0% Found C 67.9 H 5.4 N 3.9%

3.1.2. *cis-2-Benzyl-6-chloro-1,2,3,3a-tetrahydro-8aH-indeno[1,2-c]pyrrole-8-one (11b)* (from crude **10b** with reagent B, 5 h, 130°), m.p. 69–70° (ether/petroleum ether) (70% from **9b** over two steps). – IR. (CH_2Cl_2): 1710. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.5 (t, $J=8$, 1 H); 2.6 (t, $J=8$, 1 H); 2.9 (d, $J=8$, 1 H); 3.1 (t, $J=8$, 1 H); 3.25 (d, $J=8$, 1 H); 3.5 (s, 2 H); 3.75 (t, $J=8$, 1 H); 7.0–7.6 (7 H); 7.65 (d, $J_{\text{meta}}=2$, 1 H).

$\text{C}_{18}\text{H}_{16}\text{ClNO}$ Calc. C 72.6 H 5.4 Cl 11.9 N 4.7%
(297.8) Found „ 72.5 „ 5.2 „ 11.9 „ 4.6%

Hydrogen oxalate of 11b, m.p. 193–194° (methanol). – $^1\text{H-NMR}$.: no H above 2.7.

$\text{C}_{20}\text{H}_{18}\text{ClNO}_5$ Calc. C 61.9 H 4.7 Cl 9.1 N 3.6%
(387.8) Found „ 62.1 „ 4.7 „ 9.3 „ 3.3%

3.1.3. *cis-2-Benzyl-6-fluoro-1,2,3,3a-tetrahydro-8aH-indeno[1,2-c]pyrrole-8-one (11c)* (from **10c** with reagent A, 2 h, 150°), pure oil (84%). – IR. (CH_2Cl_2): 1710. – $^1\text{H-NMR}$. (60 MHz, CDCl_3): 2.3–3.4 (5 H); 3.5 (s, 2 H); 3.75 (t, $J=8$, 1 H); 6.9–7.6 (8 H).

Hydrogen fumarate of 11c, crystallizes with 1 mol-equiv. of CH_3OH , m.p. 194–196° (methanol/ether).

$\text{C}_{22}\text{H}_{20}\text{FNO}_5 \cdot \text{CH}_3\text{OH}$ Calc. C 64.3 H 5.6 F 4.4 N 3.3%
(429.4) Found „ 64.4 „ 5.3 „ 4.4 „ 3.2%

3.1.4. *cis-2-Benzyl-1,2,3,3a-tetrahydro-8aH-6-methylindeno[1,2-c]pyrrole-8-one (11d)* (from **10d** with reagent A, 3 h, 100°), isolated as hydrogen oxalate, m.p. 165–167° (methanol/ether) (85%). – $^1\text{H-NMR}$. (100 MHz, $\text{D}_6\text{-DMSO}$): no H above 2.7 except CH_3 -signal at 2.4 (s).

$\text{C}_{21}\text{H}_{21}\text{NO}_5$ (367.4) Calc. C 68.7 H 5.8 N 3.8% Found C 68.4 H 5.8 N 3.8%

Free base (oil). – IR. (CH_2Cl_2): 1700. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.35 (s, 3 H); 2.4 (t, $J=8$, 1 H); 2.55 (t, $J=8$, 1 H); 2.85 (d, $J=8$, 1 H); 3.05 (t, $J=8$, 1 H); 3.2 (d, $J=8$, 1 H); 3.5 (s, 2 H); 3.75 (t, $J=8$, 1 H); 7.0–7.5 (8 H).

3.1.5. *DL-3-Benzyl-2,5-methano-1,2,3,4-tetrahydro-5H-3-benzazocine-6-one (16a)* (from epimeric mixture of **DL-15a** with reagent C, 2 h, 160°), isolated as hydrogen oxalate, m.p. 238–239° (methanol/ether) (67%). – $^1\text{H-NMR}$. (100 MHz, $\text{D}_6\text{-DMSO}$): 1.8–2.7 (2 H); 3.0–3.7 (5 H); 3.8–4.6 (3 H); 7.1–7.7 (9 H); 8.3 (s, 2 exchangeable H).

$\text{C}_{21}\text{H}_{21}\text{NO}_5$ (367.4) Calc. C 68.7 H 5.8 N 3.8% Found C 69.0 H 5.9 N 4.0%

Free base (oil). – IR. (film): 1680. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.1 (d, A-part of $ABXY$ -system, $J_{AB}=14$, $J_{AX}=J_{AY}=0$, 1 H); 2.45 (d $\times$ t, B-part of $ABXY$ -system, $J_{AB}=14$, $J_{BX}=J_{BY}=8$, 1 H); 2.8–3.65 (6 H); 3.8 (center of AB -system, $J_{\text{gem}}=12$, 2 H); 6.9–7.6 (8 H); 7.7 (d $\times$ d, $J_{\text{ortho}}=9$, $J_{\text{meta}}=3$, 1 H). – The $^{13}\text{C-NMR}$. was in excellent accord with structure **16a**.

3.1.6. *L-3-Benzyl-2,5-methano-1,2,3,4-tetrahydro-5H-3-benzazocine-6-one (16a)* (from an epimeric mixture of **L-15a**), oil, $[\alpha]_{\text{D}}^{20} = -34.1^\circ$ ($c=1.0$, CHCl_3), $\geq 99\%$ e.e. according to FT- $^1\text{H-NMR}$. analysis (90 MHz, CDCl_3 , 600 accumulations) of a 15 mg sample using tris[3-(heptafluoropropyl)hydroxy-methylene]-d-camphoratoeuropium(III), 99+%, GOLDLABEL (Aldrich). (This reagent split the aromatic proton of the racemate at 7.7 ppm into two signals of equal intensity).

3.1.7. *2-Benzyl-1,2,3,3a,9,9a-hexahydro-4H-benz[*f*]isoindole-4-one (16b)*. A small sample of an epimeric mixture of **15b** was cyclized (reagent C, 2 h, 160°) to give an epimeric mixture of **16b**, from which a hydrogen oxalate ((3:1)-mixture of epimers), m.p. 181–183° (methanol/ether), crystallized. – $^1\text{H-NMR}$. (100 MHz, $\text{D}_6\text{-DMSO}$): 2.7–3.7 (8 H); 4.15 (main epimer) and 4.4 (minor epimer) (2 s, totally 2 H); 7.1–7.65 (8 H); 7.8 (d, $J=9$, 1 H); 10.85 (s, 2 exchangeable H).

$\text{C}_{21}\text{H}_{21}\text{NO}_5$ (367.4) Calc. C 68.7 H 5.8 N 3.8% Found C 68.5 H 5.7 N 3.7%

Free base (oil). – IR. (CH_2Cl_2): 1675. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.3–3.3 (8 H); 3.6 (main epimer) and 3.8 (minor epimer) (2 s, totally 2 H); 7.0–7.6 (8 H); 7.85 (main epimer) and 8.0 (minor epimer) ($d \times d$, $J_{ortho} = 9$, $J_{meta} = 2$, totally 1 H).

Hydrogen oxalate, mixed m.p., TLC., IR. and $^1\text{H-NMR}$. spectral comparison confirmed the identity of **16b** with authentic material [6].

3.1.8. *1,4-Ethano-1,2,3,4-tetrahydro-5H-2-benzazepine-5-one* (**21**) (from an epimeric mixture of **20** with reagent B, 1 h, 200°), isolated as oxalate, m.p. 249–250° (methanol/water) (75%). – $^1\text{H-NMR}$. (100 MHz, $\text{D}_6\text{-DMSO}$, at 140°): 1.5–2.6 (4 H); 2.8–3.4 (3 H); 4.4 ($d \times d$, $J_1 = 5$, $J_2 = 2$, 1 H); 6.5 (s, 2 H); 7.2–7.6 (3 H); 7.9 ($d \times d$, $J_{ortho} = 9$, $J_{meta} = 2$, 1 H).

$\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_6$ (464.5) Calc. C 67.2 H 6.1 N 6.0% Found C 67.2 H 6.2 N 5.9%

Free base (oil). – IR. (film): 1675. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 1.5–2.5 (5 H, including NH as s at 2.1); 2.8–3.4 (3 H); 4.3 ($d \times d$, $J_1 = 6$, $J_2 = 3$, 1 H); 7.15–7.55 (3 H); 8.05 ($d \times d$, $J_{ortho} = 9$, $J_{meta} = 2$, 1 H).

4. Refunctionalization and ring transformation reactions of **11**. – 4.1. Preparation of oximes **27**. –

General procedure. A mixture of **11** (free base, 0.93 mol), hydroxylamine hydrochloride (194 g), and potassium carbonate (193 g) in methanol (3 l) and water (60 ml) was refluxed for 3 h. After filtration and evaporation to dryness the residue was shaken with water/ CH_2Cl_2 to give the *cis*-2-benzyl-1,2,3,3a-tetrahydro-8aH-indeno[1,2-c]pyrrole-8-one oximes (**27**).

4.1.1. *cis*-2-Benzyl-1,2,3,3a-tetrahydro-8aH-indeno[1,2-c]pyrrole-8-one oxime (**27a**), m.p. 147–151° (CHCl_3 /ether) (81%). – IR. (CH_2Cl_2): 3575, 1650 (weak). – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.5–3.2 (4 H); 3.6 (s, 2 H); 3.7–4.0 (2 H); 7.2–7.4 (8 H); 7.6 ($d \times d$, $J_1 = 9$, $J_2 = 2$, 1 H); ca. 8.6 (br., 1 H).

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}$ (278.4) Calc. C 77.7 H 6.5 N 10.1% Found C 77.4 H 6.7 N 9.9%

4.1.2. *cis*-2-Benzyl-6-chloro-1,2,3,3a-tetrahydro-8aH-indeno[1,2-c]pyrrole-8-one oxime (**27b**), m.p. 166–167° (methanol/ether) (81%). – IR. (nujol): 3150–3050, 1650.

$\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}$ Calc. C 69.1 H 5.5 Cl 11.3 N 9.0%
(312.8) Found .. 69.0 .. 5.5 .. 11.7 .. 8.8%

4.1.3. *cis*-2-Benzyl-1,2,3,3a-tetrahydro-8aH-6-methylindeno[1,2-c]pyrrole-8-one oxime (**27c**), m.p. 134–135° (ethylacetate/ether) (80%). – IR. (nujol): 3150–3050, 1650.

$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$ (292.4) Calc. C 78.1 H 6.9 N 9.6% Found C 78.1 H 7.0 N 9.5%

4.2. Beckmann rearrangement of oximes **27**. – *General procedure*. The oxime **27** (1 part) is added to polyphosphoric acid (10 parts, preheated to 100°) under stirring. The mixture is heated for 1 h at 200°, cooled to RT., poured on ice/water, made alkaline with aq. NaOH-solution and extracted with ethyl acetate to give, after crystallization, *cis*-2-benzyl-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[3,4-c]-isoquinoline-5-ones (**28**) as the main products. In the case of **27c** the isomeric compound **29c** was isolated as a by-product.

4.2.1. *cis*-2-Benzyl-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[3,4-c]isoquinoline-5-one (**28a**), m.p. 159–161° (acetone/ether) (50%). – IR. (CH_2Cl_2): 3400, 1665. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.5–2.8 (2 H); 3.1–3.65 (3 H); 3.7 (s, 2 H); 4.35 (m, 1 H); 6.9 (s, NH); 7.1–7.5 (8 H); 8.1 ($d \times d$, $J_{ortho} = 9$, $J_{meta} = 2$, 1 H).

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}$ (278.4) Calc. C 77.7 H 6.5 N 10.1% Found C 77.5 H 6.5 N 9.9%

4.2.2. *cis*-2-Benzyl-7-chloro-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[3,4-c]isoquinoline-5-one (**28b**), m.p. 167–169° (acetone) (63%). – IR. (CH_2Cl_2): 3400, 1670. – $^1\text{H-NMR}$. (100 MHz, CDCl_3): 2.55–2.8 (2 H); 3.1–3.65 (3 H); 3.7 (s, 2 H); 4.35 (m, 1 H); 6.9–7.5 (8 H, including NH); 8.1 (d , $J_{meta} = 2$, 1 H).

$\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}$ Calc. C 69.1 H 5.5 Cl 11.3 N 9.0%
(312.8) Found .. 69.0 .. 5.6 .. 11.2 .. 9.2%

4.2.3. *cis*-2-Benzyl-7-methyl-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[3,4-c]isoquinoline-5-one (**28c**), m.p. 133–134° (acetone/ether) (45%). – IR. (CH_2Cl_2): 3400, 1665. – $^1\text{H-NMR}$. (60 MHz, CDCl_3):

2.4 (s, 3 H); 2.5–2.8 (2 H); 3.05–3.65 (3 H); 3.7 (s, 2 H); 4.3 (m, 1 H); 6.75 (NH); 6.9–7.4 (7 H); 7.95 (d, $J_{meta}=2$, 1 H).

$C_{19}H_{20}N_2O$ (292.4) Calc. C 78.1 H 6.9 N 9.6% Found C 77.7 H 6.9 N 9.4%

Chromatography of the mother liquid on 50 parts of silica gel (petroleum ether/ethyl acetate 1:1) gave the isomeric *cis*-2-benzyl-7-methyl-1,2,3,3a,5,9b-hexahydro-4H-pyrrolo[3,4-c]quinoline-4-one (**29c**), m.p. 173–175° (acetone/ether) (7%). – IR. (nujol): 3200, 3100, 1660. – 1H -NMR. (100 MHz, D_6 -DMSO): 2.0–2.6 (4 H, including CH_3 as s at 2.2); 2.7–3.25 (4 H); 3.3–3.7 (1 H); 3.55 (s, 2 H); 6.65 (2 H); 6.95 (d, $J_{ortho}=8$, 1 H); 7.25 (5 H); 10.05 (s, NH).

$C_{19}H_{20}N_2O$ (292.4) Calc. C 78.1 H 6.9 N 9.6% Found C 77.9 H 7.1 N 9.6%

5. Direct transformation of compounds 11 into phenyl *cis*-8-oxo-1,2,3,3a,8,8a-hexahydroindeno-[1,2-c]pyrrole-2-carboxylates (30). – 5.1. *General procedure.* To a solution of **11** (2.0 mol) in CH_2Cl_2 (4 l) phenyl chloroformate (313 g) was added dropwise at 20° (exothermic reaction). The solution was kept at 20° for 24 h, washed with 10% aq. tartaric acid-solution, dried ($MgSO_4$) and evaporated to constant weight to give almost quantitatively the title compounds. – IR. (CH_2Cl_2): 1720.

5.1.1. *Phenyl cis-8-oxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-2-carboxylate (30a)* (oil). – 1H -NMR. (360 MHz, $CDCl_3$): 3.4 ($t \times d$, $J_1=9$, $J_2=3$, 1 H); 3.7–4.2 (5 H); 6.9–7.4 (5 H); 7.48 ($t \times d$, $J_{ortho}=8$, $J_{meta}=2$, 1 H); 7.55 ($d \times d$, $J_{ortho}=8$, $J_{meta}=2$, 1 H); 7.7 ($t \times d$, $J_{ortho}=8$, $J_{meta}=2$, 1 H); 7.78 ($d \times d$, $J_{ortho}=8$, $J_{meta}=2$, 1 H).

5.1.2. *Phenyl cis-6-chloro-8-oxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-2-carboxylate (30b)* (oil). – 1H -NMR. (100 MHz, $CDCl_3$): 3.25–3.55 (1 H); 3.65–4.2 (5 H); 6.9–7.1 (2 H); 7.1–7.4 (3 H); 7.45 (d, $J=8$, 1 H); 7.65 ($d \times d$, $J_{ortho}=10$, $J_{meta}=2$, 1 H); 7.7 (d, $J_{meta}=2$, 1 H).

5.1.3. *Phenyl cis-6-fluoro-8-oxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-2-carboxylate (30c)* (oil). – 1H -NMR. (60 MHz, $CDCl_3$): 3.2–3.65 (1 H); 3.7–4.2 (5 H); 6.9–7.6 (8 H).

6. Baeyer-Villiger oxidation of ketones 30 to phenyl *cis*-1,2,3,3a,4,9b-hexahydro-4-oxo-[1]benzopyrano[3,4-c]pyrrole-2-carboxylates (31). – 6.1. *General procedure.* To a solution of **30** (0.10 mol) in acetic acid (300 ml) and conc. H_2SO_4 -solution (150 ml), peracetic acid (30%-solution, 70 ml) was added dropwise at 10° under stirring. After stirring for 16 h at 20° the mixture was poured on ice/water and extracted with CH_2Cl_2 . The organic phase was washed with an excess of aq. $FeSO_4$ -solution, dried ($MgSO_4$) and evaporated to give, after filtration through 15 parts of silica gel (CH_2Cl_2), the pure lactones **31**.

6.1.1. *Phenyl cis-1,2,3,3a,4,9b-hexahydro-4-oxo[1]benzopyrano[3,4-c]pyrrole-2-carboxylate (31a)*, m.p. 137–139° (CH_2Cl_2 /ether) (76%). – IR. (CH_2Cl_2): 1765, 1720. – 1H -NMR. (100 MHz, $CDCl_3$): 3.1–3.5 (2 H); 3.5–4.1 (3 H); 4.3 ($t \times d$, $J_1=11$, $J_2=2$, 1 H); 6.9–7.4 (9 H).

$C_{18}H_{15}NO_4$ (309.3) Calc. C 69.9 H 4.9 N 4.5% Found C 69.9 H 5.1 N 4.7%

6.1.2. *Phenyl cis-7-chloro-1,2,3,3a,4,9b-hexahydro-4-oxo-[1]benzopyrano[3,4-c]pyrrole-2-carboxylate (31b)*, m.p. 105–106° (CH_2Cl_2 /ether) (89%). – IR. (CH_2Cl_2): 1775, 1725. – 1H -NMR. (100 MHz, $CDCl_3$): 3.2–3.55 (2 H); 3.55–4.2 (3 H); 4.35 ($t \times d$, $J_1=11$, $J_2=2$, 1 H); 7.0–7.45 (8 H).

$C_{18}H_{14}ClNO_4$ (343.8) Calc. C 62.9 H 4.1 Cl 10.3 N 4.1%
Found .. 63.2 .. 4.2 .. 10.4 .. 4.2%

6.1.3. *Phenyl cis-7-fluoro-1,2,3,3a,4,9b-hexahydro-4-oxo-[1]benzopyrano[3,4-c]pyrrole-2-carboxylate (31c)*, m.p. 104–105° (acetone/ether) (61%). – IR. (CH_2Cl_2): 1770, 1720. – 1H -NMR. (100 MHz, $CDCl_3$): 3.2–3.55 (2 H); 3.55–4.2 (3 H); 4.4 ($t \times d$, $J_1=10$, $J_2=2$, 1 H); 6.75–7.5 (8 H).

$C_{18}H_{14}FNO_4$ (327.3) Calc. C 66.1 H 4.3 F 5.8 N 4.3%
Found .. 66.2 .. 4.3 .. 5.9 .. 4.4%

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