

165. Structural Analogues of Aporphines

Part II: Synthesis of Some Isomers of Lysergic Acid Derivatives

by Daniel Berney

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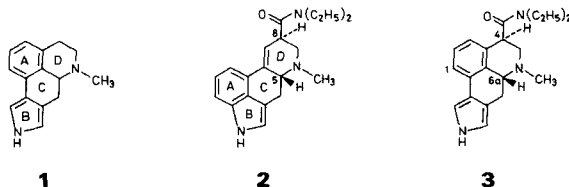
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Summary

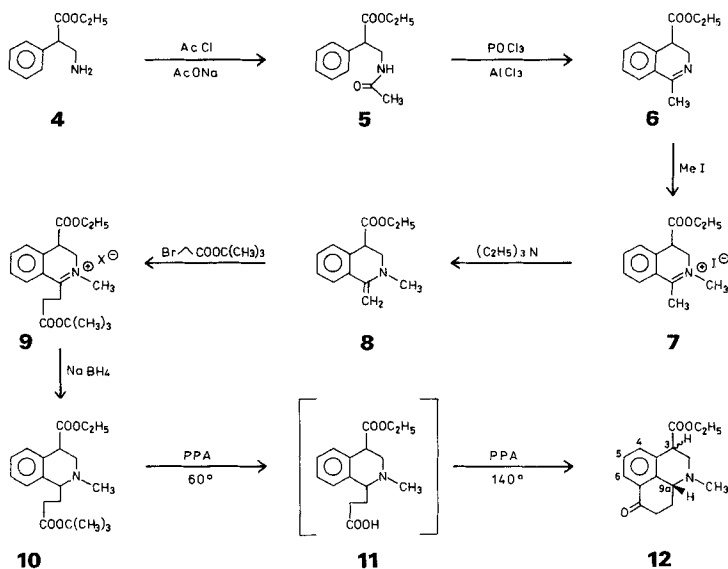
Isomers of lysergic acid derivatives (**3**, **22**, **23** and **24**), analogous to aporphine, have been synthesized from the key intermediate ketone **12**.

Introduction. – We have previously reported the synthesis of aporphine analogues in which the catechol moiety of aporphine was replaced by 5-membered heterocycles [1]. One of those compounds, **1**, contained the pyrrolo-[3,4-*g*]quinoline ring system (B, C, D) present in the ergolines, but it differed from these by the position of ring A. It was thought of interest to apply this new 'isomeric ergoline' system to lysergic acid derivatives, such as LSD (**2**). The syntheses of compound **3**, having a *N,N*-diethylcarboxamide side chain with the same configuration as LSD, and of a number of related structures are reported in the present publication.

Scheme 1

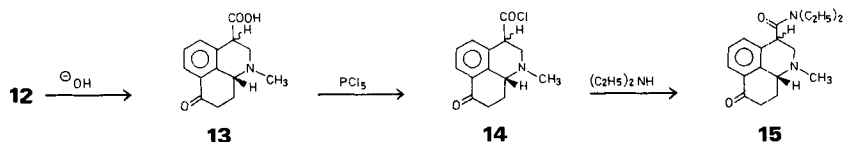


Scheme 2



triethylammonium iodide formed during the transformation of 7 to 8. Compound 9 was next reduced with NaBH_4 to the tetrahydroisoquinoline 10. No effort was made to elucidate the configuration of 10; this product gave one spot on TLC. in all systems used and the melting point of the hydrochloride was sharp and constant. On these grounds, it was concluded that the compound represents one stereoisomer. Heating compound 10 in polyphosphoric acid (PPA) at 140° resulted in cleavage of the *t*-butyl ester, with formation of the carboxylic acid 11¹⁾ which spontaneously cyclized to the ketone 12. As shown by TLC., product 12 consisted of a (1:1)-mixture of stereoisomers which were separated for analytical purposes. However, as isomerization of the asymmetric centre C(3) was found to occur to some extent during subsequent stages, it was decided to proceed with the mixture of stereoisomers and to effect the separation in the final stage. Consequently, the mixture of stereoisomers 12 was hydrolyzed to the carboxylic acids 13, and these were converted *via* their acid chlorides 14 to the diethylamides 15²⁾. The dimethylamino-

Scheme 3

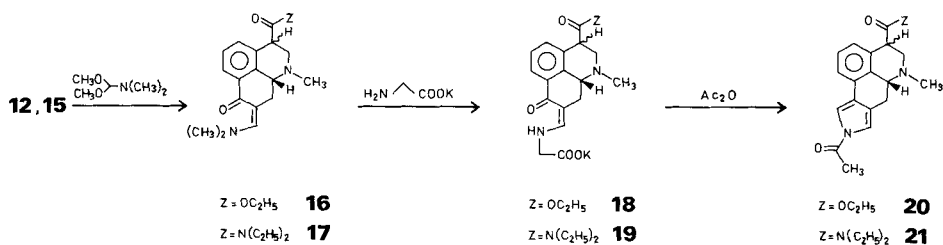


¹⁾ Heating 10 in PPA at 60° for 30 min gave compound 11 exclusively. At this temperature, there was no evidence of compound 12 being formed.

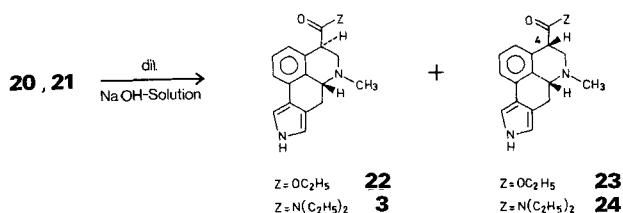
²⁾ Attempts to transform 12 to 15 directly were unsuccessful.

methylidene derivatives **16** and **17** were prepared by reaction of DMF acetal with the esters **12** and the amides **15**, respectively; subsequent treatment with glycine potassium salt gave **18** and **19**, which were cyclized in acetic anhydride to yield the acetylated compounds **20** and **21**. After hydrolysis, the two pairs of stereoisomers **22**, **23** and **3**, **24** respectively, were isolated by fractional crystallization.

Scheme 4



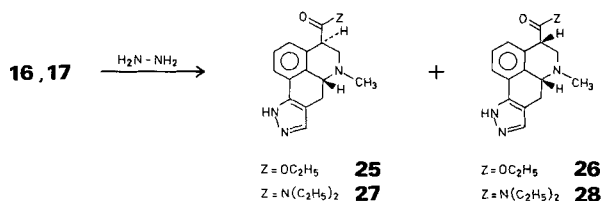
Scheme 5



The procedure employed here for building up the pyrrole ring system has been described [2]. In some of the stages, it permits the use of milder conditions than those we described previously [1].

The configuration of the pairs of stereoisomers was elucidated by ¹H-NMR spectroscopy. The very characteristic signal of H-C(4) appears in compound **3** as a double doublet at δ 4.25 ppm (in DMSO) $J=4$ and 14 Hz, which is in good agreement with an axial configuration. In the stereoisomer **24**, the signal for H-C(4) appears under similar conditions in lower field (4.0 ppm) as a narrow absorption compared to that of **3**, with $J=2$ and 4 Hz, in accord with the equatorial configuration. Similar differences were observed in the spectra of compounds **22** and **23**.

Scheme 6



Compounds **16** and **17** were also convenient intermediates for the synthesis of the corresponding pyrazolo-analogues. Reaction with hydrazine hydrochloride readily yielded stereoisomers **25**, **26** and **27**, **28**, respectively. The configurations of the stereoisomers were again established on the basis of their $^1\text{H-NMR}$. spectra.

I thank *H.R. Helbling* for his excellent experimental assistance. I am also indebted to Mrs. *Th. Zardin* from *Sandoz AG*, Basle, for the analysis of some of the $^1\text{H-NMR}$. spectra.

Experimental Part

General. $^1\text{H-NMR}$. spectra were taken at 60, 90 or 360 MHz in CDCl_3 with TMS as internal standard, using the NMR. spectrometers *Varian T-60*, *Bruker HX-90* and *WH-360*. 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, *qa* quadruplet, *qi* quintuplet, *m* multiplet, *br.* broad; chemical shifts in δ -values (ppm).

Ethyl β -(Acetylamino)- α -phenylpropionate (5). Compound **4** $\cdot$ HCl (97.4 g, 0.425 mol) was suspended in THF (1300 ml) and AcONa (348 g, 4.25 mol) was added in small portions. The stirred mixture was cooled to about 5° and acetyl chloride (36.3 g, 0.462 mol) in THF (200 ml) was added dropwise, the temp. being kept below 10° . The temperature was then allowed to rise to r.t. and the mixture was stirred at r.t. overnight. Water (1000 ml) was added and the mixture was extracted with toluene (1500 ml). The extract was dried and evaporated to give 105 g of crude **5** as a light brown oil. – $^1\text{H-NMR}$.: 7.3 (*s*, 5 H, arom. H); 6.1 (*br.* signal, HN); 4.15 (*qa*, $\text{COOCH}_2\text{CH}_3$); 1.9 (*s*, CH_3CO); 1.2 (*t*, $\text{COOCH}_2\text{CH}_3$).

Ethyl 1-methyl-3,4-dihydroisoquinoline-4-carboxylate (6). Crude compound **5** (82.5 g, ~ 0.35 mol) was dissolved in POCl_3 (960 ml), and AlCl_3 (74 g, 0.555 mol) was added in small portions. The stirred mixture was then heated to 120° for 8.5 h and then evaporated under vacuum nearly to dryness. The residue was dissolved in CHCl_3 (200 ml) and the solution was poured onto ice (1 kg). After the addition of water (1500 ml) and ether (1000 ml), the mixture was thoroughly shaken and the organic phase, which contained some impurities and starting material, was discarded. After the addition of ice (about 1 kg), the aqueous phase was adjusted to pH 8 with 30% NaOH-solution, filtered through *Kieselguhr* and extracted with CHCl_3 . The extract was dried and evaporated. Crude yield: 47 g of **6** as an oil. – $^1\text{H-NMR}$.: 7.4 (*m*, 4 H, arom. H); 4.2 (*qa*, $\text{COOCH}_2\text{CH}_3$); 3.65 (*m*, 2 H–C(3)); 2.4 (narrow *t*, $\text{H}_3\text{C}–\text{C}(1)$, homoallylic coupling with $\text{H}_2\text{C}(3)$); 1.25 (*t*, $\text{COOCH}_2\text{CH}_3$).

4-(Ethoxycarbonyl)-1,2-dimethyl-3,4-dihydroisoquinolinium iodide (7). To a solution of crude compound **6** (50 g, 0.23 mol) in acetone (1700 ml) methyl iodide (66.1 g, 0.47 mol) was added and the mixture was refluxed for 3.5 h. The mixture was then concentrated to about 600 ml and the product allowed to crystallize at -20° , to give 62 g (48% from **4**) as yellow crystals, m.p. $140–143^\circ$. – $^1\text{H-NMR}$. (this quaternary salt was soluble in CDCl_3): 4.1 (*qa*, $\text{COOCH}_2\text{CH}_3$); 3.8 (*s*, $\text{H}_3\text{C}–\text{N}$); 3.0 (*s*, $\text{H}_3\text{C}–\text{C}(1)$); 1.5 (*t*, $\text{COOCH}_2\text{CH}_3$).

$\text{C}_{14}\text{H}_{18}\text{INO}_2$ (359.2) Calc. C 46.8 H 5.1 N 3.9% Found C 46.8 H 5.3 N 3.9%

1-[2-(*t*-Butoxycarbonyl)ethyl]-4-(ethoxycarbonyl)-2-methyl-3,4-dihydroisoquinolinium chloride (9, X=Cl). Compound **7** (50 g, 0.139 mol) was suspended in acetone (750 ml), and triethylamine (15.5 g, 0.153 mol) was added with stirring to give the enamine **8**. *t*-Butyl bromoacetate (33.9 g, 0.174 mol) was then added dropwise with stirring, and the precipitate of triethylamine bromide and iodide was filtered off. The clear filtrate was kept for 5 h at r.t., ether was added to slight turbidity and the mixture of bromide and iodide **9** was then allowed to crystallize in the cold, giving 57 g of greenish crystals, m.p. $115–125^\circ$. The iodide/bromide mixture **9** (56 g, ~ 0.1 mol) was reduced in abs. ethanol (600 ml) at $0–5^\circ$ with NaBH_4 (5.9 g, 0.156 mol), to give 35 g of crude **10** as an oil which was converted to the hydrochloride, m.p. $160–163^\circ$. – $^1\text{H-NMR}$.: 7.1 (*s*, 4 H, arom. H); 4.2 (*qa*, $\text{COOCH}_2\text{CH}_3$); 2.4 (*s*, $\text{H}_3\text{C}–\text{N}$); 1.4 (*s*, $(\text{H}_3\text{C})_3\text{C}$); 1.25 (*t*, $\text{COOCH}_2\text{CH}_3$).

$\text{C}_{20}\text{H}_{30}\text{ClNO}_4$ (383.9) Calc. C 62.6 H 7.9 N 3.6% Found C 63.3 H 7.5 N 3.6%

Ethyl 1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-3-carboxylate (12). Compound **10** $\cdot$ HCl (50 g) in PPA (500 g) was heated at $135–140^\circ$ for 1.5 h, with stirring. The reaction mixture was poured onto ice (about 5 kg) and made alkaline to pH 10 with 30% NaOH-solution, the temp. being kept below 5° . The solution was then extracted with CHCl_3 . Evaporation of the dried extract gave

27 g of an oil which on treatment with HCl/ethanol/ether yielded 16.5 g (41%) of a (1:1)-mixture the isomers **12**·HCl, m.p. 202–220°.

$C_{16}H_{20}ClNO_3$ (309.8) Calc. C 62.0 H 6.5 N 4.5% Found C 61.7 H 6.3 N 4.6%

For analysis they were separated by fractional crystallization in methanol, the less soluble isomer being the (3*R*,9*aS*)-isomer, m.p. 218–221°. – 1H -NMR.: 7.9–7.3 (*m*, 3 H, arom. H); 4.15 (*m*, $COOCH_2CH_3$ and H–C(3)); 2.35 (*s*, H_3C-N); 1.2 (*t*, $COOCH_2CH_3$). The mother liquors were evaporated to dryness and the residue was treated with ethanol/ether, from which the (3*R*,9*aR*)-isomer crystallized in the cold, m.p. 212–218°. – 1H -NMR.: 7.9–7.2 (*m*, 3 H, arom. H); 4.1 (*qa*, $COOCH_2CH_3$); 3.85 (narrow *m*, H–C(3)); 2.35 (*s*, H_3C-N); 1.15 (*t*, $COOCH_2CH_3$).

1-Methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-3-carboxylic acid (13). The mixture of isomers **12**·HCl (20 g, 0.646 mol) was heated under reflux in methanolic 1*N* KOH (200 ml) and H_2O (80 ml) for 35 min. The solution was acidified with conc. HCl-solution and evaporated. To the residue H_2O (240 ml) and NaCl (40 g) were added, and the solution was adjusted to pH 5.0 with 2*N* NaOH, and extracted with $CHCl_3$ in a continuous extractor for 2 weeks, yielding 11.7 g (~74%) of the mixture of the isomers **13** as an amorphous powder. A portion was crystallized from methanol/ether/hexane, m.p. 209–212°. – 1H -NMR.: 10.4 (br. *s*, COOH); 7.95 (*m*, H–C(6)); 7.6 (*m*, H–C(4)); 7.3 (*m*, H–C(5)); 2.75 (*s*, H_3C-N).

$C_{14}H_{15}NO_3$ (245.3) Calc. C 68.6 H 6.2 N 5.7% Found C 68.4 H 6.3 N 5.9%

N,N-Diethyl-1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-3-carboxamide (15). Compound **13** (18.8 g, 0.0767 mol) was dissolved in dry CH_2Cl_2 (900 ml) and cooled to 0–5°. PCl_5 (18.8 g, 0.0903 mol) was added in small portions and the mixture was then stirred for a further 35 min at r.t. The solution was again cooled to 0–5° and diethylamine (35.1 g, 0.48 mol) was added dropwise. After being allowed to stand at r.t. for 45 min, the mixture was poured into dilute HCl-solution and the aqueous phase was separated, made alkaline with K_2CO_3 , and extracted with CH_2Cl_2 . The organic phase was dried and evaporated, giving 23 g of the crude mixture of stereoisomers **15** as an oil. – 1H -NMR.: 7.9 (*m*, H–C(6)); 7.2 (*m*, H–C(4) and H–C(5)); 3.45 (*m*, $CON(CH_2CH_3)_2$); 2.50 and 2.45 (2 *s*, H_3C-N , mixture of stereoisomers); 1.25 (*m*, $CON(CH_2CH_3)_2$).

Ethyl 8-(dimethylamino)methylidene-1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-3-carboxylate (16). The mixture of stereoisomers **12** (8.6 g, 0.0315 mol) was dissolved in *N,N*-dimethylformamide dimethylacetal (14.3 g, 0.12 mol) and the solution was heated under reflux for 1.5 h. The solution was evaporated under high vacuum, yielding 10.8 g of crude **16**.

8-(Dimethylamino)methylidene-N,N-diethyl-1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-3-carboxamide (17). The amide **15** was converted to crude **17**, using conditions similar to those described above for the preparation of compound **16**.

Potassium N-[(3-ethoxycarbonyl-1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-8-ylidene)methyl]aminoacetate (18). The crude mixture of stereoisomers **16** (20.1 g, ~0.06 mol) was dissolved in absolute ethanol (160 ml), potassium glycinate (6.8 g, 0.06 mol) was added and the mixture was refluxed for 1.5 h. After concentration to about 30 ml, the product was precipitated by the addition of ether (200 ml) and by cooling overnight at –20°. After decantation, about 27 g of crude **18** were obtained.

*Potassium N-[(3-(*N,N*-diethylcarboxamido)-1-methyl-7-oxo-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-8-ylidene)methyl]aminoacetate (19)*. The amide **17** was converted to crude compound **19**, using conditions similar to those described above for the preparation of compound **18**. The crude mixture **19** was not purified but used directly for the next stage.

*Ethyl (4*R*,6*aR*)- and (4*R*,6*aS*)-6-methyl-4,5,6,6*a*,7,9-hexahydropyrrolo[3,4-*g*][6]benzoquinoline-4-carboxylate (22 and 23)*. A solution of the crude mixture of stereoisomers **18** (27 g) in acetic anhydride (200 ml) was heated under reflux for 1 h. The mixture was then evaporated to dryness under vacuum. The residue, containing **20**, was dissolved in ethanol (300 ml), H_2O (300 ml) and 2*N* NaOH (100 ml) were added and the mixture was stirred at r.t. for 45 min and then extracted with $CHCl_3$. The organic extract was dried and evaporated to dryness. The isomers **22** and **23** were separated by flash chromatography on *Merck* silica gel 60 (0.040–0.063 mm), using heptane/ $CHCl_3$ /ethanol 6:4:2. The first fraction afforded compound **23** which was crystallized from MeOH/AcOEt, giving 1.64 g (9.4% from **12**, 4 steps); m.p. 163–164°. – 1H -NMR.: 10.75 (br. signal, HN); 7.4–6.55 (*m*, 5 H, arom. H and H–C(8,10)); 4.2 (*qa*, $COOCH_2CH_3$); 4.05 (*d* × *d*, *J* = 4 and 14, H–C(4)); 2.45 (*s*, H_3C-N); 1.25 (*t*, $COOCH_2CH_3$). The

second fraction gave the isomer **22**, crystallized from MeOH/AcOEt, yielding 1.24 g (7.1% from **12**); m.p. 176–180°. – ¹H-NMR.: 10.7 (br. signal, HN); 7.4–6.5 (*m*, 5 H, 3 arom. H and H–C(8,10)); 4.05 (*qa*, COOCH₂CH₃); 3.7 (narrow signal, H–C(4)); 2.35 (*s*, H₃C–N); 1.1 (*t*, COOCH₂CH₃).

(*4R*, *6aR*)- and (*4R*, *6aS*)-*N,N*-Diethyl-6-methyl-4, 5, 6, 6a, 7, 9-hexahydropyrrolo[3, 4-*g*][6]benzoquinoline-4-carboxamide (**3** and **24**). Compound **19** reacted under conditions similar to those used to prepare **22** and **23** from **18**. The resulting crude mixture of isomers **3** and **24** was dissolved in heptane/CHCl₃/ethanol 65:40:20 and isomer **24**, which crystallized out on standing, was recrystallized from methanol, yielding 0.78 g (2.3% from **12**, in 6 stages); m.p. 250–253°. – ¹H-NMR.: 10.65 (br. signal, HN); 7.35–6.5 (*m*, 5 H, 3 arom. H and H–C(8,10)); 4.0 (*d* × *d*, *J* = 2 and 4, H–C(4)); 2.4 (*s*, H₃C–N); 1.1 (*t*, N(CH₂CH₃)₂).

C₁₈H₂₀N₂O₂ (296.4) Calc. C 72.9 H 6.8 N 9.5% Found C 73.1 H 7.1 N 9.8%

The isomer **3** was purified by flash chromatography on Merck silica gel 60 (0.015–0.040 mm), using heptane/CHCl₃/ethanol 65:40:20. Recrystallization from MeOH/AcOEt yielded 2.3 g (6.8% from **12**, in 6 stages), m.p. 211–213°. – ¹H-NMR.: 10.7 (br. signal, HN); 7.4–6.4 (*m*, 5 H, 3 arom. H and H–C(8,10)); 4.25 (*d* × *d*, *J* = 4 and 14, H–C(4)); 2.45 (*s*, H₃C–N); 1.15 (double *t*, N(CH₂CH₃)₂).

C₁₈H₂₀N₂O₂ (296.4) Calc. C 72.9 H 6.8 N 9.5% Found C 72.8 H 6.8 N 9.5%

Ethyl (*4R*, *6aR*)- and (*4R*, *6aS*)-6-methyl-4, 5, 6, 6a, 7, 10-hexahydropyrrolo[3, 4-*g*][6]benzoquinoline-4-carboxylate (**25** and **26**). Hydrazine hydrochloride (2 g, 0.029 mol) was added to a solution of crude compound **16** (9.7 g, ~0.03 mol) in methanol (30 ml), and the solution was heated under reflux for 40 min. After cooling, the mixture was poured into CH₂Cl₂ and extracted with 2N K₂CO₃. The organic phase was dried and evaporated to dryness. Isomers **25** and **26** were separated by flash chromatography on Merck silica gel 60 (0.015–0.040 mm), using heptane/CHCl₃/ethanol 1:1:1. The first fraction after recrystallization from CH₂Cl₂/ether gave 1.55 g (18.2% from **12**, 2 stages) of **26**, m.p. 171–174°. – ¹H-NMR.: 7.8–7.0 (*m*, 5 H, 3 H arom. and H–C(8,9)); 4.2 (*qa*, COOCH₂CH₃); 3.7 (narrow *m*, H–C(4)); 2.5 (*s*, H₃C–N); 1.25 (*t*, COOCH₂CH₃).

C₁₇H₁₈N₃O₂ (295.3) Calc. C 69.1 H 5.8 N 14.2% Found C 68.6 H 6.3 N 14.0%

The second fraction was treated with HCl/ethanol to give 1.11 g (10.6% from **12**) of **25** dihydrochloride, m.p. 220–223°. – ¹H-NMR.: 12.35 (br. signal, HN); 7.7–6.9 (*m*, 3 H arom. and H–C(8,9)); 4.15 (*qa*, COOCH₂CH₃); 4.05 (*d* × *d*, *J* = 4 and 14); 2.4 (*s*, H₃C–N); 1.2 (*t*, COOCH₂CH₃).

C₁₇H₂₀Cl₂N₃O₂ (369.4) Calc. 55.2 H 5.5 N 11.4% Found C 55.6 H 5.9 N 11.5%

(*4R*, *6aR*)- and (*4R*, *6aS*)-*N,N*-Diethyl-6-methyl-4, 5, 6, 6a, 7, 10-hexahydropyrrolo[3, 4-*g*][6]benzoquinoline-4-carboxamide (**27** and **28**). Crude compound **17** (22 g) reacted under conditions similar to those used to prepare **25** and **26** from **16**. Compound **28** was allowed to crystallize from the mixture of **27** and **28** in heptane/CHCl₃/ethanol 65:40:20 then recrystallized from methanol, to give 2.46 g (6.5% from **12**, 4 stages), m.p. 230–235°. – ¹H-NMR.: 7.7–6.8 (*m*, 3 H arom. and H–C(8,9)); 4.1 (narrow *m*, H–C(4)); 2.4 (*s*, H₃C–N); 1.1 (br. signal, N(CH₂CH₃)₂).

C₁₉H₂₄N₄O (324.4) Calc. C 70.3 H 7.5 N 17.3% Found C 70.3 H 7.7 N 17.3%

The mother liquor was passed through Woelm neutral aluminium oxide. Finally, the isomer **27** was purified by flash chromatography on Merck silica gel 60 (0.015–0.040 mm), using heptane/CHCl₃/ethanol, and recrystallized from AcOEt, giving 1.06 g (3.4% from **12**), m.p. 178–180°. – ¹H-NMR.: 7.7–6.7 (*m*, 3 H arom. and H–C(8,9)); 4.35 (*d* × *d*, *J* = 4 and 14, H–C(4)); 2.45 (*s*, H₃C–N); 1.15 (double *t*, N(CH₂CH₃)₂).

C₁₉H₂₄N₄O (324.4) Calc. C 70.3 H 7.5 N 17.3% Found C 70.6 H 7.8 N 17.1%

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