156. Total Synthesis of Racemic Ajmalicine and 19-*epi*-Ajmalicine

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Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

(3.11.81)

Summary

rac.-Ajmalicine (**31**) and 19-*epi*-ajmalicine (**30**) have been synthesized by a convergent route from the preformed D,E-ring moieties **25** and **27** and tryptophyl bromide. Two syntheses of the *trans*-1-benzoyl-3-vinyl-4-piperidineacetic acid (**13**), used in the preparation of **25** and **27**, are also described.

The alkaloids of heteroyohimbine family with normal configuration [1] are known to exhibit cardiovascular activities, and therefore, they have been subject of a continuous investigation by isolation from natural sources and synthesis. Ajmalicine (**31**), isolated originally from *Rauwolfia serpentina* in 1931 [2], is used in medicine for treatment of angina, *Raynaud*'s disease and *arteritis obliterans* [3]. Its C(19) epimer, 19-*epi*-ajmalicine (**30**) is not yet found in nature, although its substituted analogs [4] and oxindole relatives [5] are well known. Both compounds in racemic forms have been previously obtained by total syntheses [6]. Optically active ajmalicine has been synthesized from naturally occurring elenolic acid [7]. In this report we describe the synthesis of racemic ajmalicine (**31**) and 19-*epi*-ajmalicine (**30**) by assembling their molecules from the fully preformed D,E-ring moieties and tryptophyl bromide [8]. This synthetic approach is convenient for the preparation of differently substituted derivatives by using the appropriate tryptophyl bromides. The C(19) epimeric *trans*-D,E-ring moieties **25** and **27** were synthesized from the *trans*-1-benzoyl-3-vinyl-4-piperidine-acetic acid methyl ester (**14**).

The ester **14** was obtained by two different methods, both leading to the intermediate chlorinated ester **8** *(Scheme 1)*. In the first case [9], we started from the known *trans*-piperidoneacetic acid ester **1** [10], which was transformed in high yield to piperidineacetic acid ester **3**. This was accomplished by *O*-alkylation with triethyloxonium fluoroborate and reduction of the imino ether **2** with sodium borohydride. The functionalization of the ethyl side chain was effected by *Löffler-Freitag* rearrangement: Chlorination of **3** or **4** with *N*-chlorosuccinimide (NCS) in ether gave in high yields the chloroamines **5** or **6**, which on irradiation in trifluoro-

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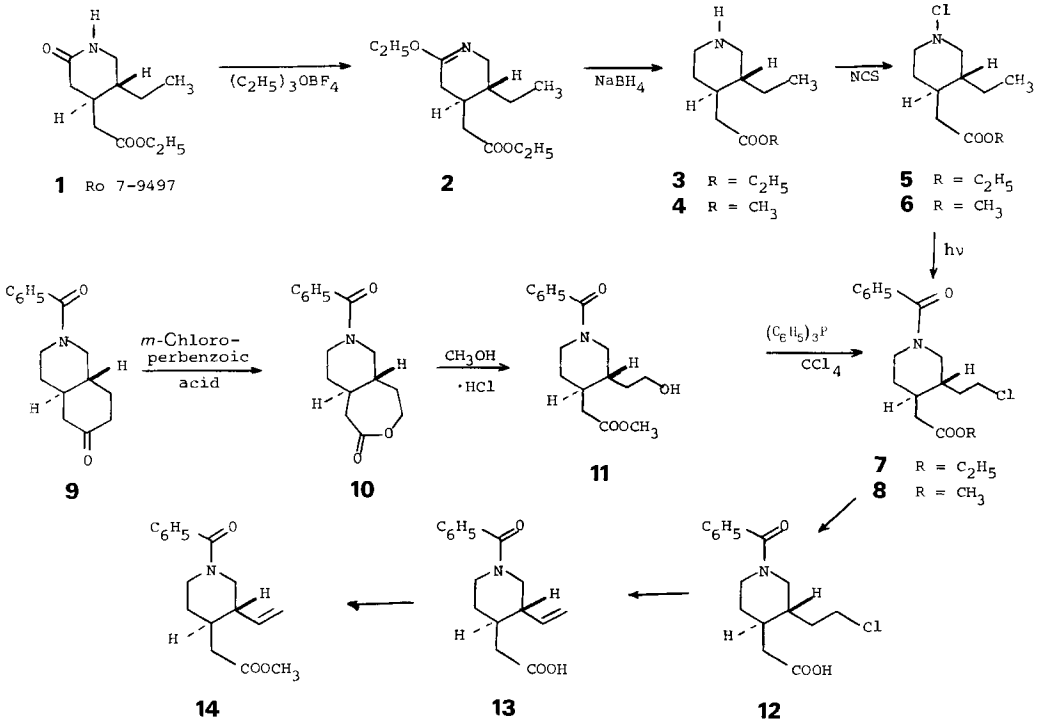
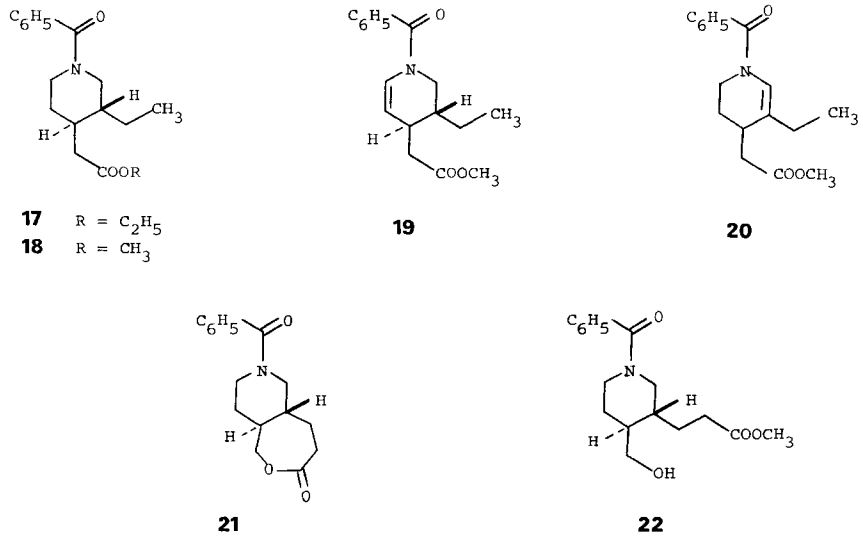
Scheme 1



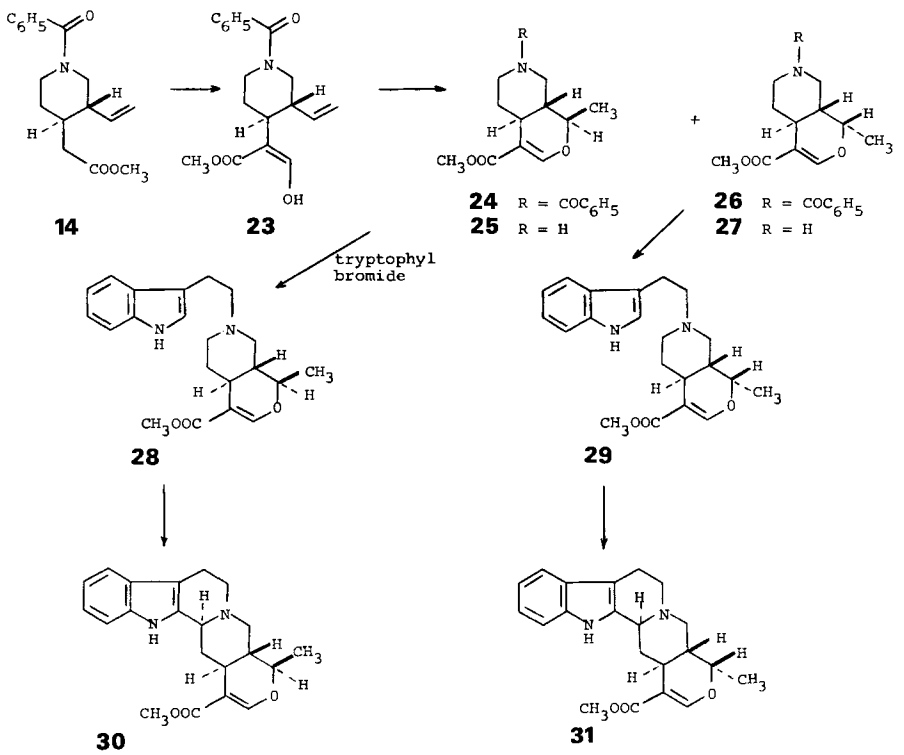
1 Ro 7-9497 **2** **3** R = C_2H_5 **4** R = CH_3 **5** R = C_2H_5 **6** R = CH_3 **7** R = C_2H_5 **8** R = CH_3 **9** **10** **11** **12** **13** **14**

Scheme 2



17 R = C_2H_5 **18** R = CH_3 **19** **20** **21** **22**

Scheme 3



acetic acid followed by benzoylation, gave desired chlorinated piperidine acetic acid esters **7** or **8**. This rearrangement was more efficient in the case of the methyl (50%) than the ethyl ester (31%). The methyl case was studied in more detail. Besides **8**, the dechlorinated product **18** and two dehydro-products **19** and **20** were also isolated *(Scheme2)*. A mechanism for the formation of these by-products has been previously proposed [9].

As a second source of the chlorinated ester **8**, we have used the *trans-N*-benzoylisoquinolone **9** [11]. *Baeyer-Villiger* oxidation with *m*-chloroperbenzoic acid in the presence of sodium hydrogen carbonate resulted in an unseparable mixture of the desired lactone **10** and its isomer **21** *(Scheme 2)*. However, after treatment of this mixture with methanolic HCl-solution, the hydroxy ester **11** could be separated by chromatography from its isomer **22** *(Scheme 2)*. The overall yield of **11** from **9** was 57%. The replacement of the hydroxyl group with chlorine was effected by treatment with triphenylphosphine and carbon tetrachloride to give the ester **8** in 93% yield.

Hydrolysis of the ester **7** or **8** gave *trans*-1-benzoyl-3-(2-chloroethyl)-4-piperidine-acetic acid (**12**) in high yield. A smooth elimination of hydrogen chloride to give the vinyl side chain was achieved almost quantitatively by treatment of **12** with potassium *t*-butoxide in benzene/dimethylsulfoxide 1:1 at 70°. The acid **13** is a

nicely crystalline compound, the structure of which was fully supported by ^{1}H-NMR. and IR. spectra and analysis.

The formation of the E-ring enolether-ester grouping was envisaged by cyclization of the formyl ester **23** *(Scheme 3)*. Examining different methods for the preparation of **23**, we have discovered that a high yield formylation of ester **14** in the *a*-position could be effected by treatment with an excess of bis(dimethylamino)-*t*-butoxymethane [12], followed by acid hydrolysis of the intermediate vinologous carbamate. The formylated ester **23** was obtained by this method in 95% yield. Cyclization of **23** with mercuric acetate was investigated in various solvents and at different temperatures. The best results were obtained by carrying out this reaction in dimethylformamide at 50°. A mixture of epimeric enol ethers **24** and **26** was formed in 70% yield. The removal of their protecting *N*-benzoyl groups turned out to be treacherous. Many attempts to achieve this hydrolytically were unsuccessful. This deblocking was finally effected in a rather low yield reductively with diisopropylaluminium hydride in toluene/tetrahydrofuran solution at −78°. After separation by preparative layer chromatography, the amine **25**, corresponding to 19-*epi*-ajmalicine (**30**) was obtained in 31% yield, and the one corresponding to ajmalicine (**31**), amine **27**, in 15% yield.

Alkylation of the bicyclic precursors **25** and **27** with tryptophylbromide in dimethylformamide in the presence of potassium carbonate as base led in high yield to the respective *seco*-alkaloids **28** and **29**. The structures of these products were fully secured by ^{1}H-NMR. and mass spectra. Oxidative cyclization to the pentacyclic alkaloids was achieved by using excess mercuric acetate/ethylenediaminetetraacetic acid disodium salt 1:1 followed by reduction of the iminium intermediates with sodium borohydride. The resulting crude products were purified by chromatography. Racemic 19-*epi*-ajmalicine (**30**) was obtained from **28** in 20% yield and racemic ajmalicine (**31**) from **29** in 28% yield. No C(3) epimers of **30** and **31** could be detected as products of cyclization. The ^{1}H-NMR. spectra of the crude reaction mixtures indicated also that major by-products in each case resulted from further hydration of the enol double bond. These byproducts could not be isolated in pure form.

Experimental Part

Melting points were taken on a *Kofler* hot stage apparatus and are not corrected. IR. spectra were determined either on a *Beckmann* IR-9 or IR-12 spectrophotometer. The UV. spectra were recorded on a *Cary* 14M spectrophotometer, the ^{1}H-NMR. spectra on a *Varian* A-60 or HA-100 spectrophotometer using TMS as internal standard. The mass spectra (MS.) were taken with a *CEC* 21-110 mass spectrometer at 70 cV using a direct insertion probe. *Merck* silica gel GF_{254} was used as sorbent for preparative layer (2 mm) chromatography. Usual work-up means washing the organic phase with water or sat. NaCl-solution, drying over anhydrous Na_2SO_4 for $CHCl_3$ or CH_2Cl_2, or over anhydrous $MgSO_4$ for ethereal solutions, and evaporation to dryness *in vacuo* (i.V.).

Racemic trans-*3-ethyl-4-piperidineacetic acid ethyl ester* (**3**). A solution of 0.640 g (3.0 mmol) of racemic trans-*5-ethyl-2-oxo-4-piperidineacetic acid ethyl ester* (**1**) and 0.684 g (0.0036 mol) of triethyloxonium fluoroborate in 20 ml of anhydrous CH_2Cl_2 was stirred at RT. for 65 h, and then evaporated i.V. The crude enol-ether **2** was dissolved in 20 ml of abs. ethanol, the solution was cooled to 0° and 0.25 g (6.6 mmol) of $NaBH_4$ was added in portions. The reaction mixture was stirred for 23 h at RT., then diluted with 50 ml of water and extracted with 1 l of CH_2Cl_2. The extract was washed with water (3 times 50 ml), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved

in 7 ml of ice-cold 1N HCl, the resulting solution diluted with 100 ml of water and washed 5 times by shaking with 50 ml of ether. It was then made alkaline with 8 ml of 1N NaOH and extracted with 1 l of CH_2Cl_2. The extract was washed 3 times with 50 ml of water, dried over anhydrous Na_2SO_4 and evaporated to dryness, to give 0.591 g (99%) of the piperidine ethyl ester **3**, b.p. 91–92° (bath) at 0.5 Torr. – IR. ($CHCl_3$): 1740 (ester carbonyl). – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 3 H, CH_3CH_2–C(3)); 1.26 (*t*, J=7, 3 H, O–CH_2CH_3); 1.71 (*s*, 1, N*H*); 4.13 (*qa*, J=7, 2 H, O–CH_2CH_3). – MS.: 199 (M^+).

$C_{11}H_{21}NO_2$ (199.29) Calc. C 66.29 H 10.62 N 7.03% Found C 66.19 H 10.79 N 7.08%

Racemic trans-*3-ethyl-4-piperidineacetic acid methyl ester* (**4**) *from* **3**. A solution of 9.2 g (46.2 mmol) of the ethyl ester **3** in 500 ml of 6% HCl-solution in abs. CH_3OH was refluxed for 16 h and then evaporated to dryness. This operation was repeated once more for 5 h. The thusly obtained residue was dissolved in 1 l of $CHCl_3$ and extracted three times with 50 ml of 1N aq. NaOH and then combined. Aqueous layers were re-extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4 and evaporated to give 5.7 g of oily methyl ester **4**. The aqueous extract was neutralized to pH 6 and evaporated to dryness and the residue triturated with abs. ethanol. The resulting ethanolic solution was evaporated and the residue was dissolved in 250 ml of 6% methanolic HCl-solution and refluxed overnight. It was worked up as above, to give 2.05 g of **4**. Total yield: 7.75 g or 90.6%.

Racemic trans-*1-chloro-3-ethyl-4-piperidineacetic acid ethyl ester* (**5**) *from* **3**. To a stirred suspension of 2.803 g (21.0 mmol) of *N*-chlorosuccinimide (NCS) in 75 ml of anhydrous ether under N_2 was added 3.5 g (17.5 mmol) of the piperidine ethyl ester **3**, and the mixture was stirred for 1 h. After dilution with 2 l of ether, the reaction mixture was washed in sequence 3 times with 50 ml of water, 2 times with 50 ml of 5N K_2CO_3, 2 times with 50 ml of water, 2 times with 50 ml of 2.5N H_2SO_4 and 2 times with 50 ml of water. The ethereal solution was then dried over anhydrous $MgSO_4$, filtered, and evaporated, to give 3.9 g (95%) of TLC.-pure oily *N*-chloropiperidineacetic acid ethyl ester **5**, which was immediately used in the next step.

Racemic trans-*1-chloro-3-ethyl-4-piperidineacetic acid methyl ester* (**6**). Conversion of 6.94 g (37.4 mmol) of **4** into 7.5 g (92%) of the crude *N*-chloropiperidineacetic acid methyl ester **6** was effected by the method described in the preceeding experiment. The crude product **6** was used immediately in the next experiment.

Racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid ethyl ester* (**7**) *from* **5**. A solution of 3.9 g (16.7 mmol) of **5** in 150 ml of trifluoroacetic acid in a quartz flask was flushed with N_2 and cooled to 10° for 30 min. Under a continuous stream of N_2 and cooling, it was irradiated with a 200W *Hanovia* lamp for 3⅓ h, when TLC. and a negative starch iodide test indicated the absence of starting material **5**. Evaporation i.V. gave the crude product containing racemic trans-*3-ethyl-4-piperidinioacetic acid ethyl ester trifluoroacetate* admixed with rac. trans-*3-(2-chloroethyl)-4-piperidinioacetic acid ethyl ester trifluoroacetate*. To the stirred solution of these salts in 300 ml of benzene 5.6 g (39.8 mmol) of benzoyl chloride and then, dropwise, 5N K_2CO_3 were added until pH *ca.* 9 was reached. Stirring was then continued for 1 h. The reaction mixture was diluted with 3 l of benzene and extracted in sequence with 3 times 100 ml of 6N NaOH, 3 times 100 ml of water, 3 times 100 ml of 1N HCl and 100 ml of water. The benzene solution was then dried over anhydrous Na_2SO_4 and evaporated. The crude product was chromatographed on *Brinkmann* silica gel preparative plates with ether/petroleum ether 1:1 and the separated components were eluted with a 3:1 chloroform/methanol mixture. Each product was dissolved in ether, the ethereal solution was washed with 1N NaOH and water, dried over anhydrous $MgSO_4$ and evaporated. Less polar product: 1.476 g (as oil) (29.2%) of racemic trans-*1-benzoyl-3-ethyl-4-piperidineacetic acid ethyl ester* (**17**). – IR. ($CHCl_3$): 1730 and 1245 (–$COOC_2H_5$); 1625 (amide). – ^{1}H-NMR. ($CDCl_3$): 0.86 (distorted *t*, 3 H, CH_3CH_2–C(3)); 1.24 (*t*, J=7.5, 3 H, O–CH_2CH_3); 2.57 and 2.11 (*AB* of *ABX*.., J_{gem}=14, J_{AX}=3.5, J_{BX}=8, 2 H, $CH_2COOC_2H_5$); 4.14 (*qa*, J=7.5, 2 H, O–CH_2CH_3); 7.37 (*s*, 5 H, C_6H_5). – MS.: 303 (M^+).

More polar product: 1.767 g (31.3%) of racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid ethyl ester* (**7**), an oil. – ^{1}H-NMR. ($CDCl_3$): 1.24 (*t*, J=7.5, 3 H, O–CH_2CH_3); 2.57, 2.17 (*AB* of *ABX*.., J_{gem}=15, J_{AX}=4, J_{BX}=8, 2 H, $CH_2COOC_2H_5$); 4.17 (*qa*, J=7.5, 2 H, O–CH_2CH_3); 7.41 (*s*, 5 H, C_6H_5). – MS.: 337 (M^+).

$C_{18}H_{24}ClNO_3$ (337.85) Calc. C 64.02 H 7.16 N 4.15% Found C 64.21 H 6.93 N 4.20%

Racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid methyl ester* (**8**) *from* **6**. A solution of 7.5 g (34.7 mmol) of **6** in 150 ml of trifluoroacetic acid in a quartz flask was flushed with N_2 for 30 min. Under a continuous stream of N_2 at 15–20° it was irradiated with 200W *Hanovia* lamp for 3 h and 25 min, when TLC. and a negative starch iodide test indicated the absence of starting material **6**. Evaporation i.V. gave the crude irradiation product. To the stirred solution of this product in 500 ml of benzene was added first 11.24 g of benzoyl chloride and then dropwise 5N K_2CO_3 until pH *ca.* 9 was reached. Stirring was then continued for 1 h. The reaction mixture was diluted with 4 l of benzene and extracted in sequence with 3 times 100 ml of 6N NaOH, 2 times 100 ml of water, 2 times 100 ml of 3N HCl, and with 100 ml portions of water to neutrality. The benzene solution was then dried over anhydrous Na_2SO_4 and evaporated, to give 15.96 g of benzoylation product which was taken up in 1200 ml of ether and washed with 5 times 50 ml of 1N NaOH. The aqueous layer was rewashed with ether, and the combined ether solutions were dried over anhydrous $MgSO_4$ and evaporated. The 13.4 g of the crude product was chromatographed on a 1 kg column made of 3:1 mixture of silica gel 0.05–0.2 mm and silica gel PF_{254} with ether/petroleum ether 1:1. The following products were eluted in sequence: racemic trans-*1-benzoyl-3-ethyl-1,2,3,4-tetrahydro-4-pyridineacetic acid methyl ester* (**19**), an unstable oil [IR. ($CHCl_3$): 1730 ($COOCH_3$), 1630 (amide); ^{1}H-NMR. ($CDCl_3$): 0.98 (*t*, J = 6.5, 3 H, CH_2CH_3); 3.67 (*s*, 3 H, OCH_3); 4.79 (br., 1 H, =C*H*–CH); 6.44 (br. *s*, 1 H, N–C*H*=); 7.42 (*s*, 5, C_6H_5); MS.: 287 (M^+)]; racemic *1-benzoyl-3-ethyl-1,4,5,6-tetrahydro-4-pyridineacetic acid methyl ester* (**20**), also an unstable oil [IR. ($CDCl_3$): 1730 ($COOCH_3$), 1630 (amide); ^{1}H-NMR. ($CDCl_3$): 0.92 (*t*, J = 6.5, 3 H, CH_2CH_3); 3.77 (*s*, 3 H, OCH_3); 6.33 (br. *s*, 1 H, N–C*H*=); 7.44 (*s*, 5 H, C_6H_5); MS.: 287 (M^+)]. racemic trans-*1-benzoyl-3-ethyl-4-piperidineacetic acid methyl ester* (**18**), an oil [IR. ($CHCl_3$): 1728 ($COOCH_3$), 1628 (amide); ^{1}H-NMR. ($CDCl_3$): 0.87 (distorted *t*, 3 H, CH_2CH_3); 3.67 (*s*, 3 H, OCH_3); 7.38 (*s*, 5 H, C_6H_5); MS.: 289 (M^+)]; racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid methyl ester* (**8**), 4.341 g (50.4%), an oil [IR. ($CHCl_3$): 1735 ($COOCH_3$), 1630 (amide); ^{1}H-NMR. ($CDCl_3$): 3.68 (*s*, 3 H, $COOCH_3$); 7.38 (*s*, 5 H, C_6H_5); MS.: 323 (M^+)].

$C_{17}H_{22}ClNO_3$	Calc.	C 63.05	H 6.85	Cl 10.95	N 4.33%
(323.8)	Found	„ 62.84	„ 6.99	„ 11.10	„ 4.20%

Racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid* (**12**) *from* **7**. To a solution of 2.72 g (8.05 mmol) of **7** in 37.5 ml of CH_3OH was added 37.5 ml of 1N NaOH solution and the mixture was stirred at RT. for 36 h. CH_3OH was removed by distillation. The residue was acidified with 3N HCl, extracted well with CH_2Cl_2, and the extract was dried over anhydrous Na_2SO_4, filtered and evaporated. It gave 2.409 g (96.5%) of the crystalline acid **12**, m.p. 122–124° (from CH_2Cl_2/ether). – IR. ($CHCl_3$): 3520 and 1716 (–COOH); 1630 (amide). – MS.: 309 (M^+).

$C_{16}H_{20}ClNO_3$	Calc.	C 62.03	H 6.50	Cl 11.44	N 4.52%
(309.79)	Found	„ 62.30	„ 6.68	„ 11.71	„ 4.26%

Racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid* (**12**) *from* **8**. Hydrolysis of 6.55 g (20.2 mmol) of the methyl ester **8** under the same conditions as described in the preceeding experiment gave 5.435 g (87% yield) of **12**, m.p. 122–125° (from ether).

Racemic trans-*1-benzoyl-3-vinyl-4-piperidineacetic acid* (**13**) *from* **12**. To a solution of 5.71 g (18.43 mmol) of **12** in 90 ml of anhydrous benzene was added 4.5 g (40.1 mmol) of potassium *t*-butoxide in 90 ml of dimethylsulfoxide, and the mixture was stirred and heated at 70° under N_2 overnight. The benzene was removed by distillation, and after addition of 75 ml of 1N NaOH, the residue was extracted with 2 times 50 ml of CH_2Cl_2. The aqueous phase was acidified with conc. HCl-solution and extracted with 3 times 500 ml of 1:1 benzene/ether mixture. This extract was dried over anhydrous Na_2SO_4, filtered and evaporated, to give 4.9 g (97.2%) of **13**, which crystallized from ether on cooling. – ^{1}H-NMR. ($CDCl_3$): 4.9–5.8 (*m*, 3 H, C*H*=CH_2); 7.36 (*s*, 5 H, C_6H_5). – MS.: 273 (M^+).

$C_{16}H_{19}NO_3$ (273.336) Calc. C 70.31 H 7.01 N 5.13% Found C 70.33 H 7.00 N 4.94%

Racemic trans-*1-benzoyl-3-vinyl-4-piperidineacetic acid methyl ester* (**14**) *from* **13**. To a stirred, ice-cold solution of 2.94 g (10.8 mmol) of **13** in 45 ml of CH_3OH was added, in two portions, a total of 68 ml of diazomethane solution (*ca.* 3 g/100 ml in ethanol/ether), and stirring was continued for 1 h. This was followed by addition of several drops of glacial acetic acid and by evaporation to dryness. It gave 3.37 g of crude product, which was chromatographed on preparative silica gel plates with ethyl

acetate and eluted with ethyl acetate. This gave 2.737 g (88.7%) of the methyl ester **14**. – ^{1}H-NMR. ($CDCl_3$): 3.64 (*s*, 3 H, OCH_3); 4.9–5.8 (*m*, 3 H, $-CH{=}CH_2$); 7.37 (*s*, 5 H, C_6H_5). – MS.: 287 (M^+).

$C_{17}H_{21}NO_3$ (287.36) Calc. C 71.05 H 7.37 N 4.87% Found C 70.92 H 7.59 N 4.62%

Racemic trans-*1-benzoyl-3-(2-hydroxyethyl)-4-piperidineacetic acid methyl ester* (**11**) *from racemic* trans-*2-benzoyl-decahydro-6-isoquinolone* (**9**). To a solution of 5.0 g (19.4 mmol) of **9** in 80 ml of CH_2Cl_2 was added 6.67 g (33 mmol) of 85% *m*-chloroperbenzoic acid and 10 g of $NaHCO_3$. The reaction mixture was stirred overnight which was followed by addition of 30 ml of 10% aq. $NaHSO_3$-solution. After the starch-iodide paper test became negative, the reaction mixture was diluted with 200 ml of CH_2Cl_2 and extracted sequentially with 100 ml each of 7.5% aq. $NaHCO_3$-solution, water, and sat. aq. NaCl-solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was chromatographed on a 750 g silica gel column with 1:1 benzene/ethyl acetate mixture to give 4.94 g (93%) of a mixture of racemic trans-*1-benzoyl-3-(2-hydroxyethyl)-4-piperidineacetolactone* (**10**) and *1-benzoyl-4-hydroxymethyl-3-piperidine-β-propionolactone* (**21**). A solution of this mixture in 200 ml of 0.05% methanolic HCl-solution was stirred overnight and then evaporated to dryness. The residue was separated by repeated chromatography on silica gel column with hexane/chloroform/*t*-butylalcohol 6:2:2 eluent into 3.103 g (53%) of the methyl ester **11** and 1.99 g (37%) of isomeric racemic trans-*1-benzoyl-4-hydroxymethyl-3-piperidine-β-propionic acid methyl ester* (**22**). An analytical sample of **11** was obtained as an oil on further purification by prep. TLC. – IR. ($CHCl_3$): 3630 (OH), 1735 ($COOCH_3$), 1625 (amide). – ^{1}H-NMR. ($CDCl_3$): 3.75 (*s*, 3 H, $COOCH_3$); 7.42 (*s*, 5 H, C_6H_5). – MS.: 305 (M^+).

$C_{17}H_{23}NO_4$ (305.36) Calc. C 66.87 H 7.59 N 4.59% Found C 66.92 H 7.68 N 4.54%

Racemic trans-*1-benzoyl-3-(2-hydroxyethyl)-4-piperidineacetolactone* (**10**) *from* **11**. A solution of 0.610 g (2.0 mmol) of **11** and 20 mg of *p*-toluenesulfonic acid in 150 ml of benzene was heated at reflux overnight. After cooling to RT., the reaction mixture was extracted twice with 50 ml of 7.5% aqueous $NaHCO_3$-solution and once with 50 ml of sat. aq. NaCl-solution. The organic phase was dried over Na_2SO_4, filtered, and evaporated to give 0.32 g (59%) of the lactone **10**. An analytical sample was obtained by recrystallization from benzene, m.p. 183.5–184°. – IR. ($CHCl_3$): 1735 (ester), 1625 cm^{-1} (amide). – ^{1}H-NMR. ($CDCl_3$): 2.50 (*m*, 2 H, CH_2COO); 4.28 (unresolved *m*, 2 H, $COOCH_2$); 7.41 (*s*, 5 H, C_6H_5). – MS.: 273 (M^+).

$C_{16}H_{19}NO_3$ (273.337) Calc. C 70.31 H 7.01 N 5.12% Found C 70.49 H 7.08 N 5.00%

Racemic trans-*1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid methyl ester* (**8**) *from* **11**. To a solution of 1.525 g (5 mmol) of **11** in 48 ml of dimethylformamide was added 1.53 g (5.86 mmol) of triphenylphosphine and 0.949 g (6.2 mmol) of CCl_4. The reaction mixture was stirred in the dark at RT. for 22 h, and then evaporated to dryness. The residue was chromatographed on a silica gel column with benzene/ethyl acetate 1:1 to give 1.497 g (93%) of amorphous ester **8**. Analytical sample was prepared by distillation. – IR. ($CHCl_3$): 1735 ($COOCH_3$), 1630 cm^{-1} (amide). – ^{1}H-NMR. ($CDCl_3$): 3.67 (*s*, 3 H, $COOCH_3$); 7.42 (*s*, 5 H, C_6H_5). – MS.: 323 (M^+).

$C_{17}H_{22}ClNO_3$	Calc.	C 63.06	H 6.85	Cl 10.95	N 4.33%
(323.81)	Found	„ 62.92	„ 6.99	„ 10.97	„ 4.23%

Racemic trans-*1-benzoyl-3-vinyl-4-piperidinemalonaldehydic acid methyl ester* (**23**) *from* **14**. A solution of 0.85 g (2.96 mmol) of **14** in 4 ml of bis(dimethylamino)-*t*-butoxymethane was kept under N_2 at 120° for 43 h. Ether (80 ml) and 30 ml of 1N aq. HCl were added, and the mixture was stirred vigorously at 20° for 4 h. The aqueous layer was basified to give a *ca.* 1N NaOH, and partition between ether and 1N aq. NaOH was effected. The combined aqueous phases were acidified with ice cooling by addition of 6N HCl to *ca.* pH 2, saturated with NaCl and extracted thoroughly with $CHCl_3$. Usual work-up afforded 0.9 g (*ca.* 95%) of **23** as a viscous oil. – UV. (0.1N KOH): 273 (19,700). – IR. ($CHCl_3$): 1700, 1670, 1620, 1600 (carbonyl region), 1000 and 930 (vinyl). – MS.: 315 (M^+), 105 (100).

Mixture of racemic trans-transoid- *and* trans-cisoid-*7-benzoyl-4a,5,6,7,8,8a-hexahydro-1-methyl-1H-pyrano[3,4-c]pyridine-4-carboxylic acid methyl esters* (**24** *and* **26**) *from* **23**. A solution of 2.1 g (6.7 mmol) of the ester **23** and 4 g of mercuric acetate in 20 ml of dry dimethylformamide was kept at 50° for 60 h. The solvent was removed i.V. (bath temp. *ca.* 50°), the residue suspended in 100 ml of CH_3OH,

cooled to 0°, and 2 g of solid $NaBH_4$ was added batchwise (30 min) to the stirred mixture. The reaction was quenched by addition of 1N aq. HCl, the pH adjusted to 8 with Na_2CO_3, and CH_3OH stripped. The residue was partitioned between water and ether and worked up as usual to give, after filtration through *Celite*, 1.47 g (70%) of a mixture of amorphous epimeric enol ethers **24** and **26**. – UV. (Ethanol): 236 (15,900). – IR. ($CHCl_3$): 1690 (ester), 1610 (enol), 1170 and 1090 (C–O). – NMR. ($CDCl_3$): indicates epimeric mixture. – MS.: 315 (M^+), 105 (100).

Racemic trans-transoid-*4a,5,6,7,8,8a-hexahydro-1-methyl-1*H-*pyrano[3,4-c]pyridine-4-carboxylic acid methyl ester* (**25**) *and racemic* trans-cisoid-*4a,5,6,7,8,8a-hexahydro-1-methyl-1*H-*pyrano[3,4-c]-pyridine-4-carboxylic acid methyl ester* (**27**) *from mixture of* **24** *and* **26**. To a solution of 0.96 g (3.05 mmol) of crude, dry *trans-N*-benzoyl enol ethers **24** and **26** in 50 ml of dry toluene/tetrahydrofuran 9:1, stirred under N_2 at −78°, was added dropwise (90 min) a total of 5.5 ml (*ca.* 1.5 mol-equiv.) of *ca.* 1.5M DIBAH in toluene while the reaction was monitored by TLC. Methanol/water 1:1 (3 ml) was added at −78°, stirring was continued at ambient temp. for 18 h, and the mixture was partitioned between 1N aq. HCl and ether. The aqueous phase was basified with conc. NH_4OH-solution (pH *ca.* 9), and extracted thoroughly with $CHCl_3$ to give, after usual work-up, 0.43 g of crude bases. Separation by preparative layer chromatography (silica gel GF_{254}; chloroform/triethylamine 9:1, 2 times developed) gave 0.199 g (31%) of the semi-crystalline (m.p. 86–105°), unstable amine **25** which resisted all attempts of recrystallization and 0.096 (15%) of the more polar, semi-crystalline (m.p. 75–86°) amine **27**.

Physical data for amine **25**. – UV. (Ethanol): 239 (10,780). – IR. ($CHCl_3$): 1710 ($COOCH_3$), 1630 (C=C), 1200 and 1110 (C–O). – ^{1}H-NMR. ($CDCl_3$): 1.28 (*d*, J = 6.5 Hz, 3 H, CCH_3); 3.65 (*s*, 3 H, OCH_3); 3.74 (*m*, J = 10 and 6.5 Hz, 1 H, H–C(1)); 7.51 (*d*, J = 1 Hz, 1 H, H–C(3)). – MS.: 211 (M^+, $C_{11}H_{17}NO_3$).

Physical data for amine **27**. – UV. (Ethanol): 239 (11,080). – IR. ($CHCl_3$): 1705 ($COOCH_3$), 1620 (C=C), 1190 and 1100 (C–O). – ^{1}H-NMR. ($CDCl_3$): 1.1 (*d*, J = 6.5 Hz, 3 H, CCH_3); 3.65 (*s*, 3 H, OCH_3); 4.28 (*d*×*qa*, J = 6.5 and 3.5 Hz, 1 H, H–C(1)); 7.44 (*d*, J = 1 Hz, 1 H, H–C(3)). – MS.: 211 (M^+, $C_{11}H_{17}NO_3$).

*Racemic 2,3-*seco-*19-*epi-*ajmalicine* (**28**) *from tryptophyl bromide and* **25**. To a solution of 0.22 g (1.04 mmol) of amine **25** and 0.43 g (1.9 mmol) of tryptophyl bromide in 20 ml of dry dimethylformamide was added 0.2 g of anhydrous K_2CO_3, and the mixture was kept under N_2 for 2½ days. The solvent was stripped i.V., the residue partitioned between 0.5N 43% methanolic aq. HCl and *Skelly* solve B/ether 1:1, and the aq. phase was worked up as above. The crude bases were purified by preparative layer chromatography (silica gel GF_{254}; $CHCl_3/CH_3OH$ 19:1) to give 0.33 g (*ca.* 90%) of amorphous **28**. – UV. (ethanol): 221/2 (41,600), 240 *S*. (11,100), 273/4 (5800), 281/2 (6280), 289/90 (5500). – IR. ($CHCl_3$): 3480 (NH), 2760–2810 *(Bohlmann)*, 1700 ($COOCH_3$) and 1620 cm^{-1} (C=C). – ^{1}H-NMR. ($CDCl_3$): 1.28 (*d*, J = 6.5 Hz, 3 H, CCH_3); 3.66 (*s*, 3 H, OCH_3); 3.83 (*m*, J = 10 and 6.5 Hz, 1 H, H–C(1)); 6.98 (br. *d*, 1 H, H–C(2)); *ca.* 7.05–7.65 (4 aromatic protons); 7.51 (*d*, J = 1 Hz, 1 H, H–C(3)); 8.19 (br., 1 H, NH). – MS.: 354 (M^+, $C_{21}H_{26}N_2O_3$), 130 (100).

*Racemic 2,3-*seco-*ajmalicine* (**29**) *from tryptophyl bromide and* **27**. To a solution of 0.2 g (0.95 mmol) of amine **27** and 0.35 g (1.56 mmol) of tryptophyl bromide in 20 ml of dimethylformamide was added 0.2 g of anhydrous K_2CO_3 and the resulting mixture was kept at 50° for 2½ days. The solvent was stripped i.V., the residue partitioned between *Skelly* solve B/ether 1:1 and 0.5N 50% methanolic aq. HCl-solution and the aqueous phase was neutralized with conc. NH_4OH-solution and extracted thoroughly with $CHCl_3$. Usual work-up gave 0.27 g (81%) of amorphous *seco*-compound **29** which was further purified by preparative layer chromatography. – UV. (ethanol): 222 (48,300), 240 (sh, 11,700), 274/5 (6320), 282 (6830), 290 (6000). – IR. ($CHCl_3$): 3480 (NH), 2770–2820 *(Bohlmann)*, 1700 ($COOCH_3$), 1610 (C=C). – ^{1}H-NMR. ($CDCl_3$): 1.11 (*d*, J = 6.5 Hz, 3 H, CCH_3); 3.66 (*s*, 3 H, OCH_3); 4.30 (*m*, largest J = 6.5 Hz, 1 H, H–C(1)); 6.95 (*m*, 1 H, H–C(2)); *ca.* 7.0–7.65 (4 aromatic H); 7.47 (*s*, $J \leqq 1$ Hz, 1 H, H–C(3)); 8.24 (br., 1 H, NH). – MS.: 354 (M^+, $C_{21}H_{26}N_2O_3$), 130 (100).

*Racemic 19-*epi-*ajmalicine* (**30**) *from* **28**. To a solution of 0.25 g (0.71 mmol) of *seco*-compound **28** in 10 ml of ethanol was added 20 ml of 0.2M aq. mercuric acetate/disodium ethylenediamine tetraacetate 1:1 and the degassed homogeneous solution was kept under N_2 at 80° for 80 min. After 30 min. at ambient temp., the brown mixture was cooled in an ice bath, 10 ml of *ca.* 3% aq. NH_4OH-solution and excess solid $NaBH_4$ were added to the stirred mixture. After 10 min., the excess $NaBH_4$ was destroyed

by addition of 1N aq. HCl the pH was adjusted to *ca.* 10 by addition of NaOH-solution, and the aqueous phase was extracted thoroughly with CH_2Cl_2. Usual work-up afforded 0.25 g of mixture which was separated by prep. layer chromatography to give 50 mg (20%) of crystalline **30**, which was obtained as a monohydrate after recrystallization from ether; m.p. 111–115°. – UV. (ethanol): 226/7 (38,000), 250 *S* (10,500), 275 (6820), 283 (7080), 290 (6000). – IR. ($CHCl_3$): 3470 (NH), 2750–2850 (*Bohlmann*), 1700 ($COOCH_3$), 1620 (C=C). – ^{1}H-NMR. ($CDCl_3$): 1.33 (*d*, J = 6.5 Hz, 3 H, CCH_3); 3.69 (*s*, 3 H, OCH_3); *ca.* 3.81 (*m*, largest J = 10 Hz, 1 H, H–C(1)); *ca.* 7–7.5 (4 aromatic H); 7.53 (*d*, J = 1 Hz, 1 H, H–C(3)); 8.1 (br., NH). – MS.: 352 (100, M^+), 351, 184, 170, 169, 156.

$C_{21}H_{24}N_2O_3 \cdot H_2O$ (370.43) Calc. C 68.09 H 7.07 N 7.56% Found C 68.05 H 7.36 N 7.80%

Racemic ajmalicine (**31**) *from* **29**. To a solution of 0.16 g (0.45 mmol) of *seco*-compound **29** in 10 ml of 5% aq. acetic acid solution was added 10 ml of 0.2M aq. mercuric acetate/disodium ethylenediamine tetraacetate 1:1, and the resulting homogeneous solution was kept under N_2 at 50° for 16 h, then at 80° for 4 h. CH_3OH (10 ml) was added to the cold reaction mixture, the pH was adjusted to *ca.* 9 by addition of 1N aq. NaOH, and to the ice-cold mixture was added excess solid $NaBH_4$. After destroying the excess $NaBH_4$ by addition of acetic acid, the mixture was basified again and extracted thoroughly with CH_2Cl_2 to give, after the usual work-up, 0.15 g of crude product. Separation by preparative layer chromatography (ethyl acetate) afforded, 44 mg (29%) of unreacted starting material and 45 mg (30%) of the crystalline **31**, which was isolated as a semihydrate after recrystallization from CH_3OH, m.p. 216–219° (dec.), loss of water with darkening at 110–120°. – UV. (ethanol): 224/5 (44,200), 272/3 (7850), 279/81 (8250), 287/9 (7000). – IR. ($CHCl_3$): 3470 (NH), 2750–2850 (*Bohlmann*), 1700 ($COOCH_3$) and 1620 cm^{-1} (C=C). – ^{1}H-NMR. ($CDCl_3$): 1.12 (*d*, J = 6.5 Hz, 3 H, CCH_3); 3.66 (*s*, 3 H, OCH_3); 4.33 (*m*, largest J = 6.5 Hz, 1 H, H–C(1)); *ca.* 7–7.6 (4 aromatic H); 7.48 (*d*, J = 1 Hz, 1 H, H–C(3)); 8.21 (br., 1 H, NH). – MS.: 352 (M^+), 351, 184, 169, 156 (100).

$C_{21}H_{24}N_2O_3 \cdot 0.5\ H_2O$ (361.43) Calc. C 69.77 H 6.97 N 7.75% Found C 69.51 H 6.95 N 7.50%

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