

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

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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.

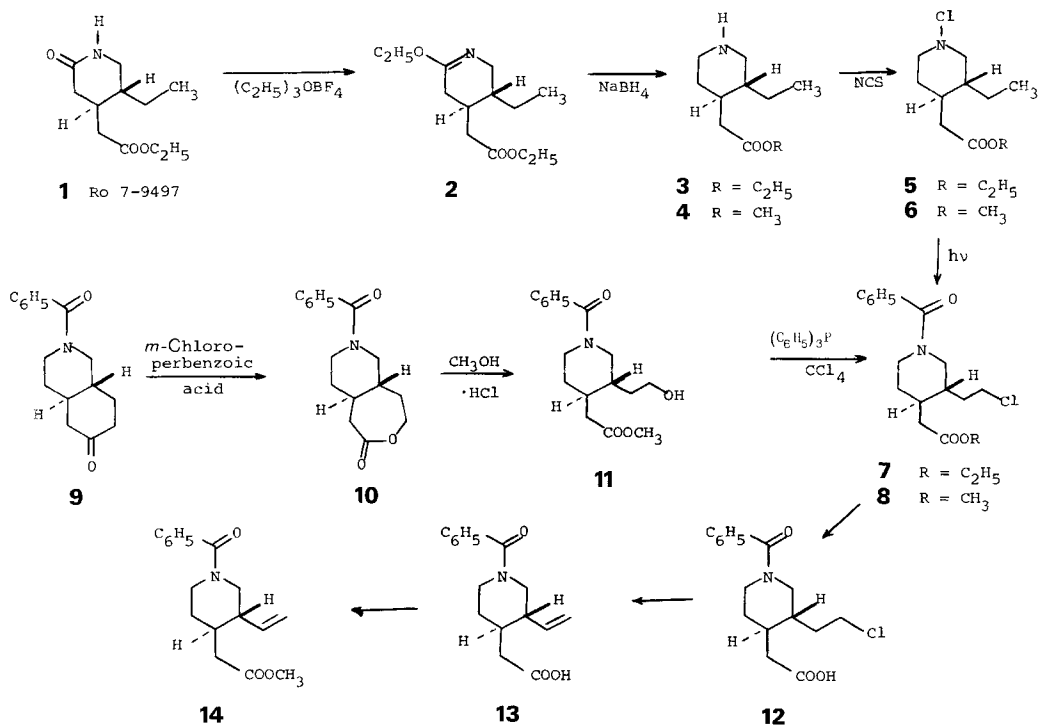
The alkaloids of heteroyohimbine family with normal configuration [1] are known to exhibit cardiovascular activities, and therefore, they have been subject of a continuous investigation by isolation from natural sources and synthesis. Ajmalicine (**31**), isolated originally from *Rauwolfia serpentina* 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-

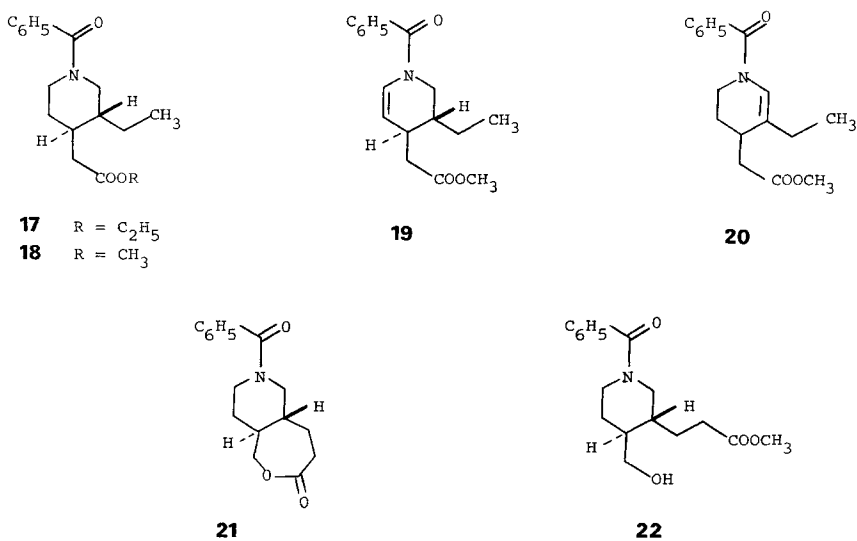
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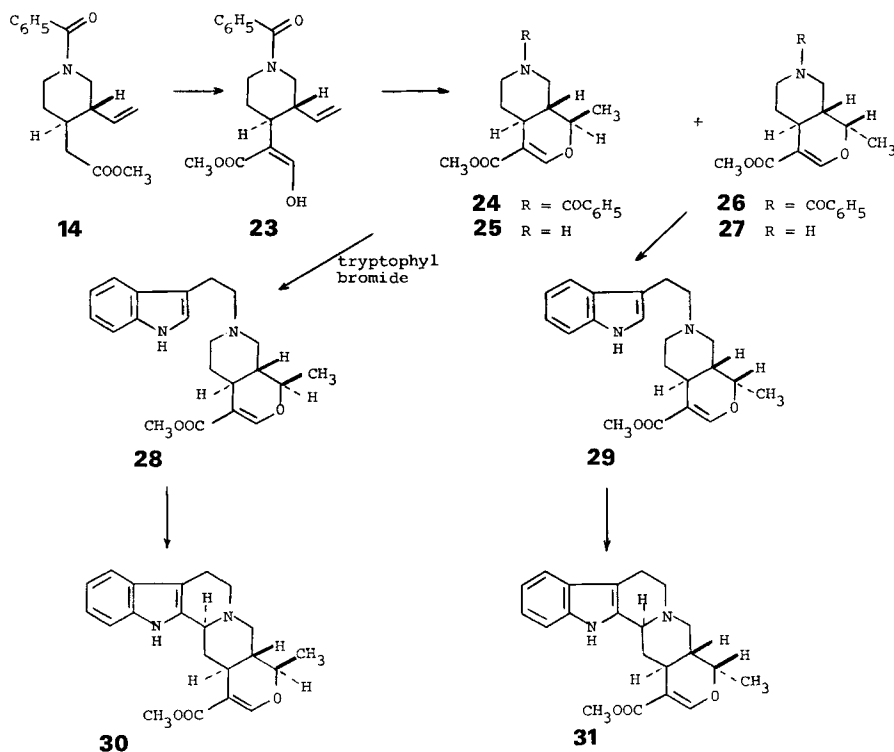
Scheme 1



Scheme 2



Scheme 3



acetic acid followed by benzylation, 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 (Scheme 2). 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 $^1\text{H-NMR}$. and IR. spectra and analysis.

The formation of the E-ring enoether-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 α -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 $^1\text{H-NMR}$. and mass spectra. Oxidative cyclization to the pentacyclic alkaloids was achieved by using excess mercuric acetate/ethylene-diaminetetraacetic 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 $^1\text{H-NMR}$. 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 $^1\text{H-NMR}$. 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 eV 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 Na₂SO₄ for CHCl₃ or CH₂Cl₂, or over anhydrous MgSO₄ 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 triethyl-oxonium fluoroborate in 20 ml of anhydrous CH₂Cl₂ 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 NaBH₄ 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 CH₂Cl₂. The extract was washed with water (3 times 50 ml), dried over anhydrous Na₂SO₄ 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). - $^1\text{H-NMR}$. (CDCl_3): 0.85 (*t*, 3 H, $\text{CH}_3\text{CH}_2\text{-C}(3)$); 1.26 (*t*, *J* = 7, 3 H, $\text{O-CH}_2\text{CH}_3$); 1.71 (*s*, 1, *NH*); 4.13 (*qa*, *J* = 7, 2 H, $\text{O-CH}_2\text{CH}_3$). - MS.: 199 (M^+).

$\text{C}_{11}\text{H}_{21}\text{NO}_2$ (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 3½ 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 ($-\text{COOC}_2\text{H}_5$); 1625 (amide). - $^1\text{H-NMR}$. (CDCl_3): 0.86 (distorted *t*, 3 H, $\text{CH}_3\text{CH}_2\text{-C}(3)$); 1.24 (*t*, *J* = 7.5, 3 H, $\text{O-CH}_2\text{CH}_3$); 2.57 and 2.11 (*AB* of *ABX*..., $J_{\text{gem}} = 14$, $J_{\text{AX}} = 3.5$, $J_{\text{BX}} = 8$, 2 H, $\text{CH}_2\text{COOC}_2\text{H}_5$); 4.14 (*qa*, *J* = 7.5, 2 H, $\text{O-CH}_2\text{CH}_3$); 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. - $^1\text{H-NMR}$. (CDCl_3): 1.24 (*t*, *J* = 7.5, 3 H, $\text{O-CH}_2\text{CH}_3$); 2.57, 2.17 (*AB* of *ABX*..., $J_{\text{gem}} = 15$, $J_{\text{AX}} = 4$, $J_{\text{BX}} = 8$, 2 H, $\text{CH}_2\text{COOC}_2\text{H}_5$); 4.17 (*qa*, *J* = 7.5, 2 H, $\text{O-CH}_2\text{CH}_3$); 7.41 (*s*, 5 H, C_6H_5). - MS.: 337 (M^+).

$\text{C}_{18}\text{H}_{24}\text{ClNO}_3$ (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 N₂ for 30 min. Under a continuous stream of N₂ 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 K₂CO₃ 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 Na₂SO₄ 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 rewash with ether, and the combined ether solutions were dried over anhydrous MgSO₄ 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 PF₂₅₄ 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. (CHCl₃): 1730 (COOCH₃), 1630 (amide); ¹H-NMR. (CDCl₃): 0.98 (t, J=6.5, 3 H, CH₂CH₃); 3.67 (s, 3 H, OCH₃); 4.79 (br. s, 1 H, =CH–CH); 6.44 (br. s, 1 H, N–CH=); 7.42 (s, 5, C₆H₅); MS.: 287 (M⁺)]; racemic *1-benzoyl-3-ethyl-1,4,5,6-tetrahydro-4-pyridineacetic acid methyl ester (20)*, also an unstable oil [IR. (CDCl₃): 1730 (COOCH₃), 1630 (amide); ¹H-NMR. (CDCl₃): 0.92 (t, J=6.5, 3 H, CH₂CH₃); 3.77 (s, 3 H, OCH₃); 6.33 (br. s, 1 H, N–CH=); 7.44 (s, 5 H, C₆H₅); MS.: 287 (M⁺)]; racemic *trans-1-benzoyl-3-ethyl-4-piperidineacetic acid methyl ester (18)*, an oil [IR. (CHCl₃): 1728 (COOCH₃), 1628 (amide); ¹H-NMR. (CDCl₃): 0.87 (distorted t, 3 H, CH₂CH₃); 3.67 (s, 3 H, OCH₃); 7.38 (s, 5 H, C₆H₅); MS.: 289 (M⁺)]; racemic *trans-1-benzoyl-3-(2-chloroethyl)-4-piperidineacetic acid methyl ester (8)*, 4.341 g (50.4%), an oil [IR. (CHCl₃): 1735 (COOCH₃), 1630 (amide); ¹H-NMR. (CDCl₃): 3.68 (s, 3 H, COOCH₃); 7.38 (s, 5 H, C₆H₅); 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 CH₃OH was added 37.5 ml of 1N NaOH solution and the mixture was stirred at RT. for 36 h. CH₃OH was removed by distillation. The residue was acidified with 3N HCl, extracted well with CH₂Cl₂, and the extract was dried over anhydrous Na₂SO₄, filtered and evaporated. It gave 2.409 g (96.5%) of the crystalline acid **12**, m.p. 122–124° (from CH₂Cl₂/ether). – IR. (CHCl₃): 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 preceding 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 N₂ 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 CH₂Cl₂. 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 Na₂SO₄, filtered and evaporated, to give 4.9 g (97.2%) of **13**, which crystallized from ether on cooling. – ¹H-NMR. (CDCl₃): 4.9–5.8 (m, 3 H, CH=CH₂); 7.36 (s, 5 H, C₆H₅). – 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%
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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 CH₃OH 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**. - $^1\text{H-NMR}$. (CDCl_3): 3.64 (s, 3 H, OCH_3); 4.9-5.8 (m, 3 H, $-\text{CH}=\text{CH}_2$); 7.37 (s, 5 H, C_6H_5). - MS.: 287 (M^+).

$\text{C}_{17}\text{H}_{21}\text{NO}_3$ (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). - $^1\text{H-NMR}$. (CDCl_3): 3.75 (s, 3 H, COOCH_3); 7.42 (s, 5 H, C_6H_5). - MS.: 305 (M^+).

$\text{C}_{17}\text{H}_{23}\text{NO}_4$ (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). - $^1\text{H-NMR}$. (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^+).

$\text{C}_{16}\text{H}_{19}\text{NO}_3$ (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). - $^1\text{H-NMR}$. (CDCl_3): 3.67 (s, 3 H, COOCH_3); 7.42 (s, 5 H, C_6H_5). - MS.: 323 (M^+).

$\text{C}_{17}\text{H}_{22}\text{ClNO}_3$ 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-piperidinemalonaldehdic 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 NaBH₄ 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 Na₂CO₃, and CH₃OH 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. (CHCl₃): 1690 (ester), 1610 (enol), 1170 and 1090 (C–O). – NMR. (CDCl₃): indicates epimeric mixture. – MS.: 315 (*M*⁺), 105 (100).

Racemic trans-transoid-4a, 5, 6, 7, 8, 8a-hexahydro-1-methyl-1H-pyrano[3,4-c]pyridine-4-carboxylic acid methyl ester (25) and racemic trans-cisoid-4a, 5, 6, 7, 8, 8a-hexahydro-1-methyl-1H-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 N₂ 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. NH₄OH-solution (pH *ca.* 9), and extracted thoroughly with CHCl₃ to give, after usual work-up, 0.43 g of crude bases. Separation by preparative layer chromatography (silica gel GF₂₅₄; 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. (CHCl₃): 1710 (COOCH₃), 1630 (C=C), 1200 and 1110 (C–O). – ¹H-NMR. (CDCl₃): 1.28 (*d*, *J* = 6.5 Hz, 3 H, CCH₃); 3.65 (*s*, 3 H, OCH₃); 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*⁺, C₁₁H₁₇NO₃).

Physical data for amine 27. – UV. (Ethanol): 239 (11,080). – IR. (CHCl₃): 1705 (COOCH₃), 1620 (C=C), 1190 and 1100 (C–O). – ¹H-NMR. (CDCl₃): 1.1 (*d*, *J* = 6.5 Hz, 3 H, CCH₃); 3.65 (*s*, 3 H, OCH₃); 4.28 (*d* *ex* *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*⁺, C₁₁H₁₇NO₃).

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 K₂CO₃, and the mixture was kept under N₂ 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 GF₂₅₄; CHCl₃/CH₃OH 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. (CHCl₃): 3480 (NH), 2760–2810 (*Bohlmann*), 1700 (COOCH₃) and 1620 cm^{–1} (C=C). – ¹H-NMR. (CDCl₃): 1.28 (*d*, *J* = 6.5 Hz, 3 H, CCH₃); 3.66 (*s*, 3 H, OCH₃); 3.83 (*m*, *J* = 10 and 6.5 Hz, 1 H, H–C(1)); 6.98 (*br.*, 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*⁺, C₂₁H₂₆N₂O₃), 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 K₂CO₃ 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. NH₄OH-solution and extracted thoroughly with CHCl₃. 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. (CHCl₃): 3480 (NH), 2770–2820 (*Bohlmann*), 1700 (COOCH₃), 1610 (C=C). – ¹H-NMR. (CDCl₃): 1.11 (*d*, *J* = 6.5 Hz, 3 H, CCH₃); 3.66 (*s*, 3 H, OCH₃); 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* ≤ 1 Hz, 1 H, H–C(3)); 8.24 (*br.*, 1 H, NH). – MS.: 354 (*M*⁺, C₂₁H₂₆N₂O₃), 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 N₂ 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. NH₄OH-solution and excess solid NaBH₄ were added to the stirred mixture. After 10 min., the excess NaBH₄ 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 ($\text{C}=\text{C}$). – $^1\text{H-NMR}$. (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, $\text{H}-\text{C}(1)$); *ca.* 7–7.5 (4 aromatic H); 7.53 (*d*, $J=1$ Hz, 1 H, $\text{H}-\text{C}(3)$); 8.1 (*br.*, NH). – MS.: 352 (100, M^+), 351, 184, 170, 169, 156.

$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O}$ (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} ($\text{C}=\text{C}$). – $^1\text{H-NMR}$. (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, $\text{H}-\text{C}(1)$); *ca.* 7–7.6 (4 aromatic H); 7.48 (*d*, $J=1$ Hz, 1 H, $\text{H}-\text{C}(3)$); 8.21 (*br.*, 1 H, NH). – MS.: 352 (M^+), 351, 184, 169, 156 (100).

$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3 \cdot 0.5 \text{H}_2\text{O}$ (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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