CONSTRUCTION OF 12-AZAEBURNANE SKELETON: SYNTHESIS OF ETHYL 12-AZAAPOVINCAMINATE

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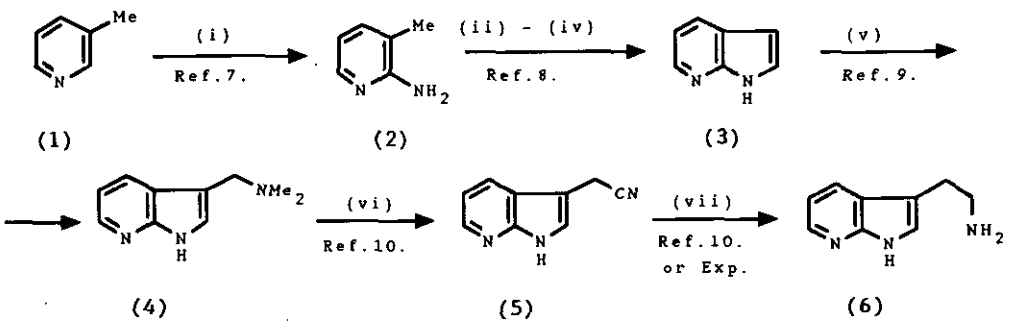
Abstract - A synthesis of 12-azaeburnane skeleton is described. The synthetic sequence has been successfully applied to the preparation of 12-aza analogue of the cerebral vasodilator, ethyl apovincaminate (Cavinton®) and some related derivatives.

The eburnamine-vincamine alkaloids represent an important and therapeutically potent group of natural products.[1] A non-natural semi-synthetic derivative, ethyl apovincaminate (Vinpocetine, Cavinton®) has been in medical use in several countries as a cerebral vasodilator.[2] Although aza analogues of bioactive cyclic compounds are often favorite target of analogue research, of the possible azaeburnane skeletons only the 15-aza[3], the 17-aza[4] and 18-aza[5] structures have been synthesised and published until now. As part of our researeh activities towards potentially active analogues of vinpocetine, we have synthesised the first examples of 12-azaeburnane derivatives.[6]

7-Azatryptamine was prepared according to the literature[7-10] (Scheme 1). The reduction of nitrile (5), however, was more conveniently performed - particularly on a larger scale - by using Ni/Al alloy instead of the reported catalytic hydrogenation[10] (see Experimental).

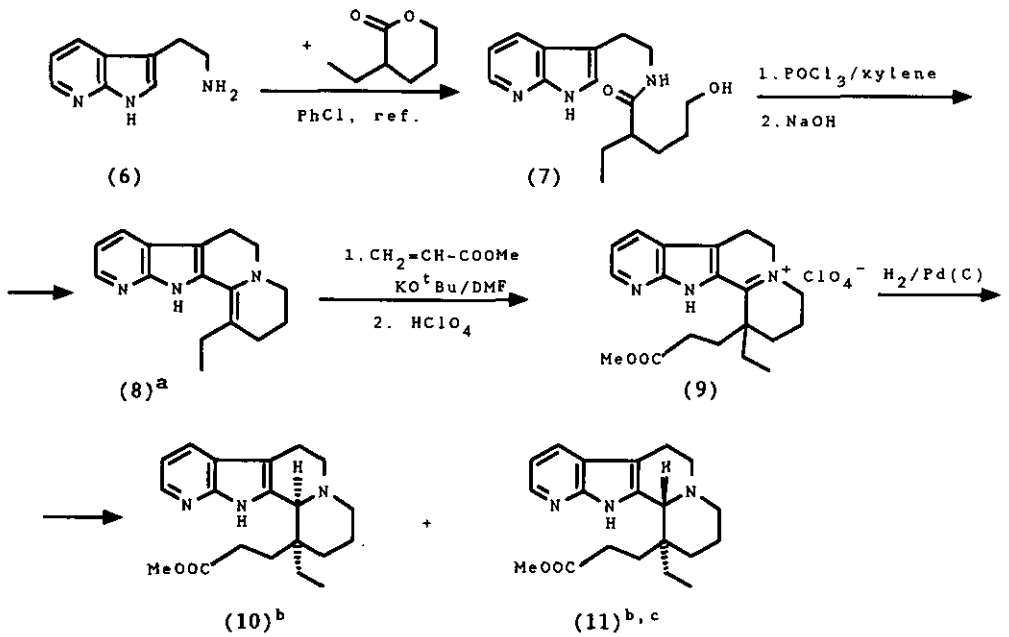
Scheme 1 Preparation of 7-azatryptamine



Reagents: (i) $NaNH_2$; (ii) $CH(OEt)_3$; (iii) PhNHMe; (iv) $NaNH_2$/PhNHMe; (v) $HCHO/HNMe_2$; (vi) Me_2SO_4, KCN; (vii) H_2/Raney Ni (Ref.10.) or Ni-Al/NaOH (see Exp.)

For construction of rings C and D we followed the route elaborated on by Szántay and co-workers for the synthesis of the corresponding carba analogues[11] (Sceheme 2). The reaction of 7-azatryptamine (6) with 3-ethyltetrahydropyran-2-one[11] (α-ethyl-δ-valerolactone) in refluxing chlorobenzene resulted in amide (7) in good yield. Bischler-Napieralski closure of ring C was performed in refluxing $POCl_3$ with simultaneous chlorination of the terminal OH group. Subsequent treatment with NaOH solution resulted in intramolecular *N*-alkylation to give the desired key intermediate (8) - the aza analogue of "Wenkert's enamine"[12] - in good yield.

Scheme 2 Furnishing the 11-azaindolo[2,3-a]quinolizidine skeleton



(6) (7) (8)[a] (9) (10)[b] (11)[b,c]

[a] characterized as fumarate salt (see Exp.). [b] isolated both in perchlorate salt and in base form (see Exp.). [c] The corresponding ethyl ester (11a) has also been prepared (see Exp.).

Of the several available strategies for the construction of the E ring, the acrylate addition - reduction - nitrosation - NO-elimination sequence[13] was chosen (Schemes 2 and 4). In the reaction of methyl acrylate with enamine (8), latter proved to be less reactive than the corresponding C-compound (presumably due to the electron withdrawing effect of the pyridine N atom): No reaction was observed under those conditions which were successfully used in the case of the carba analogue.[13] The desired addition could be realized, however, when a strong base (KO'Bu) was applied. This behaviour can be rationalized by assuming the deprotonation of the NH group: the negatively charged azaindole ring would have no more electron withdrawing effect on the conjugated exocyclic double bond. The resulting adduct was converted for easy isolation into iminium perchlorate (9), which was isolated in 45% yield.

Catalytic hydrogenation of 9 introduces two chiral centre into the molecule simultaneously, and results consequently in the formation of diastereomeric products. From the reaction mixture two diastereomer perchlorate salts (10 x $HClO_4$ and 11 x $HClO_4$) were isolated and separated by kinetic crystallization in nearly quantitative (95.5 %) overall yield, in a ratio

of 2.2:1. The quinolizidine ring exists in both isomers in the trans configuration, which is indicated by the Bohlmann bonds (2800 - 2700 cm^{-1}) in their ir spectra,[14] by the signal of the 12b proton at 3.3 ppm in the ^{1}H-nmr spectra, and by the C-4 (56.9 ppm) and C-7 (21.9 ppm) carbon signals in the ^{13}C-nmr spectra.[15] Further analysis of the ^{1}H-nmr spectra of the corresponding bases (10 and 11) allowed determination of the cis or trans arrangement of the C(12b)H and C(1)Et groups and made it possible to select the isomer which is stereochemically equivalent (cis) with the corresponding vinpocetine intermediate. The assignations were based on the CH_3(Et) proton signals, which showed the same characteristic stereo-dependence as in the case of the analogue carba derivatives.[15]

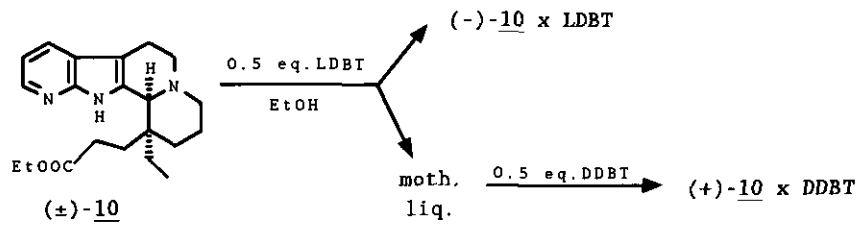
Table 1 Stereo-correlation of the characteristic nmr signals of carba[15]- and azaindolo[2,3-*a*]quinolizine structures

	Me(Et)	12b-H	C-4	C-7
carba cis (12b-H:α; 1-Et:α)	1.16	3.33	56.7	21.9
carba trans (12b-H:α; 1-Et:)	0.67	3.32	56.9	22.1
10 base (cis)	1.12	3.33	56.8	21.7
11 base (trans)	0.68	3.33	56.9	21.9

Interestingly, in the ^{1}H-nmr spectrum of the protonated form of 11 ($HClO_4$ salt) - where the bridgehead nitrogen atom becomes stereogenic - the diastereomeric C/D-cis and C/D-trans forms exhibit separate signals; in our case in a ratio of approx. 9:1, in favour of the C/D-trans species (see Exp.).

The selected cis-isomer (10) was resolved with dibenzoyltartaric acid in practically quantitative yield (Scheme 3). The corresponding enantiomeric acids [(+)- and (-)-10a] and ethyl esters [(+)- and (-)-12] were also prepared in good yields by hydrolysis or trans-esterification of (+)- and (-)-10, respectively. The optical purity of the isolated enantiomeric methyl ester bases [(+)- and (-)-10] were checked by optically active nmr shift reagent [Eu(tfc)$_3$] : no peak duplication was observed (positive control: racemic 10, see Exp.).

Scheme 3 Optical resolution of (±)-10[a]



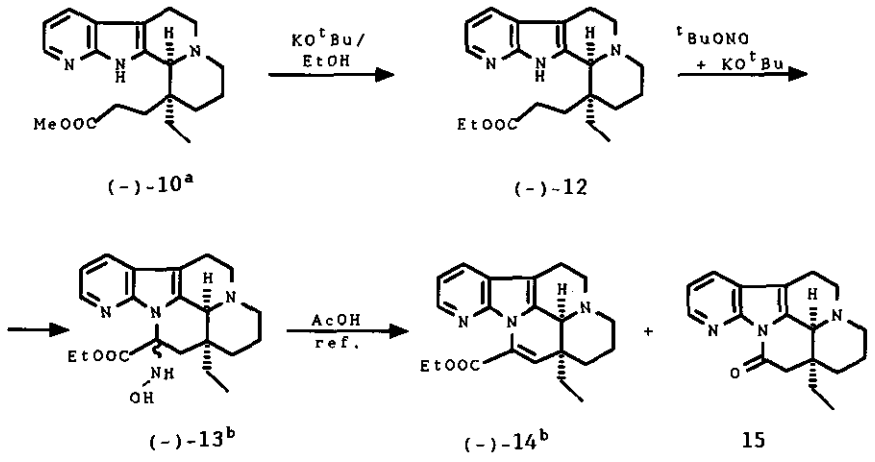
DBT = dibenzoyltartaric acid

[a] The corresponding carboxylic acids [(+)- and (-)-10a] have also been prepared (see Exp.).

The separated enantiomers were compared with the corresponding vinpocetine intermediate[15] by using circular dichroism spectroscopy, to select the enantiomer of identical absolute configuration. Although no unambiguous conclusion could be drawn from the spectra, (-)-10 was suggested as the most likely enantio-equivalent isomer (i.e.1*S*,12b*S*) and was consequently selected for further transformations. This suggestion was proven later by the CD analysis of the final product: (-)-ethyl 12-azaapovincaminate [(-)-14] gave practically identical CD spectrum to that of vinpocetine (Figure1). Methyl ester [(-)-10] was next converted to ethyl ester (12); this trans-esterification was found to be most conveniently performed at this stage of the sequence. The reaction was performed with potassium tert-butoxide in abs. ethanol to give (-)-12 in high yield (Scheme 4).

Nitrosation at the α position of the ester side chain was carried out with tert-butyl nitrite/potassium tert-butoxide in dimethylformamide solution. Contrary to the carba analogues,[16] the hydroxyimino-propionate intermediate ring-closes in situ, and hydroxylamino-ester [(-)-13] was directly obtained from the reaction. The product was isolated and purified in L-dibenzoyltartrate salt form.

Scheme 4 Construction of the E ring



(-)-10[a] (-)-12 (-)-13[b] (-)-14[b] 15

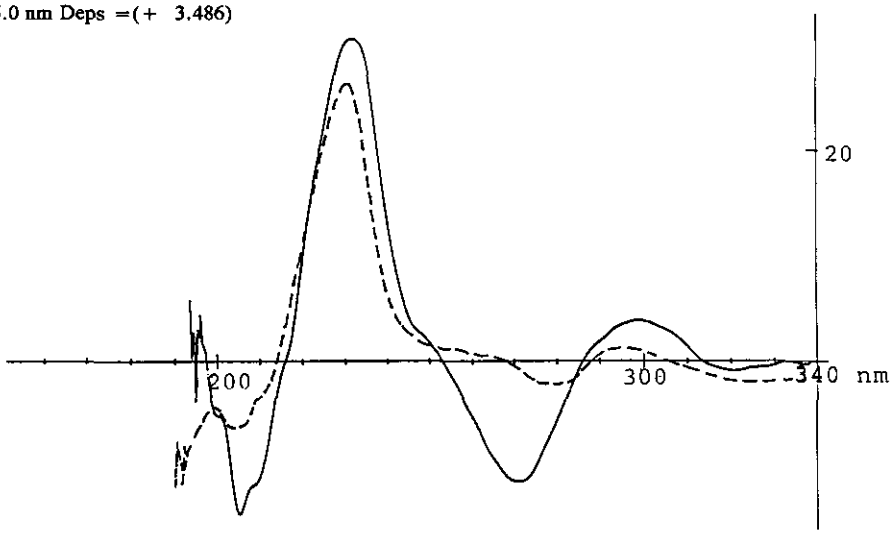
[a] prepared from the corresponding L-DBT salt (Scheme 3.) by extraction (see Exp.).
[b] purified via L-DBT salt (see Exp.)

Elimination of hydroxylamine from the carba analogue of 13 can be easily performed by acidic treatment.[16] However, with compound (13), no reaction was observed under similar conditions. Preventing the protonation of the hydroxylamine group by the neighbouring, positively charged protonated pyridine nitrogen atom seems to be reasonable explanation of this failure. After several unsuccessful attempts, finally the oxidative elimination of the NHOH function led us to the desired azaapovincaminate derivative [(-)-14], which was purified via L-dibenzoyltartrate salt form. As a side product, the corresponding azaeburnamonine (15) was also isolated in comparable yield (mp 183 - 185 °C). Based on their CD spectra [(-)14] was shown to have identical absolute configuration (3*S*,16*S*) to that of vinpocetine (Figure 1). Compound [(-)-14)] was tested for it's cardiovascular activity, and exhibited no considerable effect.

Figure 1 CD spectra of vinpocetine and it's 12-aza analogue [(-)-14]

Name of comp.: CAVINTON (--------)
Mol.w.: 350.42
Solvent: ethanol
Molar conc.: 0.77621 mmol/l
L = 325.6 nm Deps = − 4.673
L = 294.2 nm Deps = + 3.625
L = 278.4 nm Deps = − 5.212
L = 231.2 nm Deps = + 66.998
L = 203.2 nm Deps = − 14.511
L = 255.0 nm Deps =(+ 3.486)

Name of comp.: (-)-14 (————)
Mol.w.: 351.44
Solvent: ethanol
Molar conc.: 0.24684 mmol/l
L = 298.8 nm Deps = + 3.857
L = 271.2 nm Deps = − 11.442
L = 231.8 nm Deps = + 30.543
L = 205.2 nm Deps = − 14.296
L = 248.0 nm Deps =(+ 2.705)



EXPERIMENTAL

Melting points were taken on a Büchi 535 capillary melting point apparatus and are uncorrected. Ir spectra were obtained on a Nicolet 20 DXC FT-IR spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded either on a VARIAN VXR-300 (300(H) and 75(C) MHz) or on a VARIAN EM-360 (60 MHz) spectrometer. Elemental analyses for C,H,N were performed on Heraeus C,H,N Rapid model. Circular dichroism spectra were recorded on a Jobin Yvon Dichrograph III. instrument. Abbreviations LDBT and DDBT are used for L- and D-dibenzoyltartrate.

3-(2-Aminoethyl)pyrrolo[2,3-*b*]pyridine (7-azatryptamine) (6). To a stirred solution of nitrile (5)[10] (48.0 g, 0.3 mol) in a mixture of ethanol (600 ml) and 2.5 N NaOH (600 ml) nickel-aluminum alloy (Fluka No. 72240, 580 g) was added in 1 h, while keeping the temperature below 20°C. After stirring the mixture for another hour at room temperature the catalyst was filtered off and the ethanol was evaporated under reduced pressure. The resulting aqueous solution was extracted with dichloromethane (5 x 100 ml), the dichloromethane solution was dried over anh. Na_2SO_4, then evaporated to dryness to yield 6 (44.6 g, 90.6 %) as a yellow solid, mp 126 - 127°C . For identification a sample was converted into acetate salt, and had identical melting point to the published data[10] (155 - 160 °C).

***N*-(2-Ethyl-5-hydroxypentanoyl)-7-azatryptamine (7).** A solution of amine (6) (116.8 g, 0.725 mol) and 3-ethyltetrahydropyran-2-one[11] (α-ethyl-δ-valerolactone, 105 g, 0.82 mol) in chlorobenzene (700 ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was crystallized with ether to give 7 (161.6 g, 77%), mp 91 - 92 °C. Recrystallization from ethyl acetate gave pure 7 monohydrate, as a white powder, mp 92 - 94 °C; ir: 3600 - 2400 (NH + OH), 1635 (C=O), 1065 (C-OH) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6): 11.40 (1H, b, indole NH), 8.29 (1H, dd, J = 4.8 and 1.4 Hz), 8.05 (1H, dd, J = 7.1 and 1.4 Hz), 7.30 (1H, b), 7.10 (1H, dd, J = 7.1 and 4.8 Hz, arom.), 8.00 (1H, b, CONH), 4.10 - 1.00 (16H, m, 6 x CH_2 + CH + OH + H_2O), 0.80 (3H, t, J = 6.2 Hz, CH_3); Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.68; H, 7.84; N, 13.06.

11-Aza-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (8). A solution of amide (7) (20.0 g, 0.07 mol) in a mixture of phosphorus oxychloride (100 ml, 1.07 mol) and xylene (100 ml) was stirred and refluxed for 1 h. The mixture was evaporated under reduced pressure, and to the residue 4N NaOH solution (300 ml) was added. The solution was stirred at 100 °C for 1 h then diluted with water (700 ml) and extracted with dichloromethane (5 x 100 ml). The organic solution was dried over anh. Na_2SO_4, then evaporated to dryness to give 12.8 g (71%) of solid product which was used for the next step without further purification. For analytical sample the solid residue (1.28 g) was dissolved in hot ethanol (10 ml), treated with charcoal, then a hot solution of fumaric acid (0.58 g, 5 mmol) in ethanol (7.5 ml) was added while stirring. The resulting salt was allowed to crystallize at 5 °C overnight then was filtered off and washed with ether to give 0.39 g yellow solid, mp 208 °C. Recrystallization from methanol (32 ml) resulted in pure fumarate (8 x $C_4H_4O_4$) (0.38 g, 20%), mp 225 - 226 °C; ir: 3200 -2200 (NH^+), 1705 (COOH), 1660, 1628 (C=C) cm^{-1}; Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.27; N, 11.37. Found: C, 65.54; H, 6.29; N, 11.51.

11-Aza-1-ethyl-2,3,4,6,7,12-hexahydro-1-(2-methoxycarbonylethyl)-1H-indolo[2,3-*a*]quinolizin-5-ium perchlorate (9). Crude enamine (8) (25.3 g, 0.1 mol), methyl acrylate (20.8 ml, 0.23 mol) and potassium tert-butoxide (13.4 g, 0.12 mol) were dissolved in dimethylformamide (500 ml) containing 0.5% water. The solution was stirred at room temperature for 20 h, then evaporated to dryness under reduced pressure. The residue was dissolved in methanol (1000 ml) and, while cooling in ice-bath, 60% perchloric acid (approx. 41 ml, 0.25 mol) was added to set the pH to 2. The resulting potassium perchlorate was crystallized at 5°C overnight then filtered off. To the filtrate 1N $NaHCO_3$ solution (approx. 300 ml) was added to set the pH to 7. The methanol was removed under reduced pressure, and to the residue ether (500 ml) was added. the product was allowed to crystallize at 5°C overnight then was filtered off and washed with distilled water and ether successively to give iminium perchlorate (9) (19.7 g, 45 %), mp 180 - 182 °C; ir: 3270 (NH), 1700 (C=O), 1620 (C=N), 1220 (C-O-C), 1070 (b, ClO_4) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6 - $CDCl_3$/TMS): 12.60 (1H, b, NH), 8.68 (1H, dd, J = 4.8 and 1.4 Hz), 8.32 (1H, dd, J = 7.9 and 1.4 Hz), 7.33 (1H, dd, J = 7.9 and 4.8 Hz, arom.), 4.40 - 3.90 (4H, m, 2 x NCH_2), 3.60 (3H, s, OMe), 3.50 - 1.60 (12H, m, 6 x CH_2), 0.78 (3H, t, J = 6.2 Hz, CH_3/Et); Anal. Calcd for $C_{20}H_{26}N_3O_6Cl$: C, 54.61; H, 5.96; N, 9.55. Found: C, 54.60; H, 6.00; N, 9.55.

(1*RS*,12b*RS*)-11-Aza-1-ethyl-1-(2-methoxycarbonylethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (10). Iminium perchlorate (9) (17.6 g, 40 mmol), dissolved in a mixture of dimethylformamide (460 ml) and water (2.4 ml) was hydrogenated in the presence of 10% palladium/charcoal catalyst (1.76 g) by bubbling a hydrogen stream through the stirred solution for approx. 5 h (tlc). After filtration the solution was evaporated under reduced pressure to dryness. The residue was crystallized with ethanol (100 ml) at room temperature to yield cis-perchlorate (10 x $HClO_4$)

(11.6 g, 66%), mp 221 - 223°C; ir: 3680 - 3200 (NH), 1712 (C=O), 1650 (C-N), 1110 (ClO_4), 1607, 1588, 780 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6/TMS): 10.80 (1H, br s, NH), 9.30 (1H, b, NH^+), 8.43 (1H, dd, J = 4.8 and 1.4 Hz), 8.10 (1H, dd, J = 7.9 and 1.4 Hz), 7.23 (1H, dd, J = 7.9 and 4.8 Hz, arom.), 4.80 (1H, b, 12b-H), 3.65 (3H, s, COOMe), 3.80 - 1.10 (16H, m, 8 x CH_2), 1.07 (3H, t, J = 7.1 Hz, CH_3/Et); Anal. Calcd for $C_{20}H_{28}N_3O_6Cl$: C, 54.36; H, 6.39; N, 9.51. Found: C, 54.18; H, 6.73; N, 9.03.

The corresponding base was prepared with chloroform and 1 M $NaHCO_3$ by standard procedures, and was recrystallized from 5x volume of ethyl acetate to give pure 10 (6.6 g, 74%), mp 112-114°C; ir: 2800, 2755, 2690 (N-CH_2), 1738 (C=O), 1283, 1165 (C-O-C),1608, 1586, 768 (arom.) cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$/TMS): 8.32 (1H, s, NH), 8.20 (1H, dd, J = 4.8 and 1.4 Hz), 7.75 (1H, dd, J = 7.9 and 1.4 Hz), 7.04 (1H, dd, J = 7.9 and 4.8 Hz, arom.), 3.55 (3H, s, OMe), 3.35 (1H, s, 12b-H), 3.10 - 1.40 (16H, m, 8 x CH_2), 1.13 (3H, t, J = 7.1 Hz, Me); ^{13}C-nmr (75 MHz, $CDCl_3$): 174.5 (C=O), 148.7, 142.4, 133.6, 125.8, 119.2, 114.8, 110.4 (azaindole), 65.9 (N-CH), 56.8, 53.8 (2 x N-CH_2), 51.4 (OCH_3), 39.3 (C/q/), 32.3, 30.7, 28.5, 28.4, 21.9, 21.7 (6 x CH_2), 7.9 (CH_3/Et); Anal. Calcd for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.46; H, 8.04; N, 11.90.

(1*RS*,12b*SR*)-11-Aza-1-ethyl-1-(2-methoxycarbonylethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (11). The ethanolic mother liquor from preparation of perchlorate (10) was left to crystallize at room temperature for 3 days. The separated crystals were isolated by filtration and the crude product (5.2 g) was recrystallized from methanol (75 ml) to give trans-perchlorate (11 x $HClO_4$) (4.7 g, 26.6%), mp 222 - 223°C; ir: 3426, 3279, 3078 (OH + NH + NH^+), 1727, 1714 (C=O), 1221 (C-O-C), 1112 (ClO_4), 1609, 1587, 774, 756 (arom.) cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6/TMS; minor peaks in parentheses: see Discussion): 11.00 (11.50) (1H, s, NH), 9.00 (10.10) (1H, m, NH^+), 8.30 (1H, dd, J = 3.4 and 1.4 Hz), 7.94 (1H, dd, J = 6.4 and 1.4 Hz), 7.13 (1H, dd, J = 6.4 and 3.4 Hz, arom.), 4.85 (4.55) (1H, d, J = 10.6 Hz, 12b-H), 3.67 (3H, s, COOMe), 3.80 - 1.10 (16H, m, 8 x CH_2), 0.76 (0.55) (3H, t, J = 7.4 Hz, CH_3/Et); ^{13}C-nmr (75 MHz, DMSO-d_6): 173.2 (C=O), 143.7, 142.6, 127.5, 126.5, 117.7, 116.0, 108.1 (azaindole), 66.7 (N-CH), 54.7, 51.4 (2 x N-CH_2), 53.6 (OCH_3), 38.7 (C/q/), 31.3, 28.7, 28.1, 23.4, 18.8, 18.5 (6 x CH_2), 6.8 (CH_3/Et); Anal. Calcd for $C_{20}H_{28}N_3O_6Cl$: C, 54.36; H, 6.39; N, 9.51. Found: C, 54.28; H, 6.40; N, 9.40.

The corresponding base (11) was prepared as above (10) and recrystallized from ethyl acetate to give 11 (3.3 g, 95%), mp 136 - 137°C; ir: 3330 (NH), 2800, 2760 (N-CH_2), 1718 (C=O), 1203, 1037 (C-O-C), 1604, 1579, 772, 761 (arom.) cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$/TMS): 9.21 (1H, s, NH), 8.23 (1H, dd, J = 4.8 and 1.6 Hz), 7.73 (1H, dd, J = 7.7 and 1.6 Hz), 7.00 (1H, dd, J = 7.7 and 4.8 Hz, arom.), 3.80 (3H, s, COOMe), 3.34 (1H, s, 12b-H), 3.02 - 1.26 (14H, m, 7 x CH_2), 2.01 (1H, m), 1.17 (1H, m) (CH_2/Et), 0.68 (3H, t, J = 10.5 Hz, CH_3/Et); ^{13}C-nmr (75 MHz, $CDCl_3$): 175.2 (C=O), 149.1, 142.6, 133.5, 125.5, 119.1, 115.5, 110.3 (azaindole), 66.3 (N-CH), 56.9, 53.8 (2 x N-CH_2), 52.3 (OCH_3), 39.5 (C/q/), 32.9, 32.0, 28.3, 25.4, 22.0, 21.9 (6 x CH_2), 7.3 (CH_3/Et); Anal. Calcd for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.45; H, 7.99; N, 12.56.

(1*RS*,12b*SR*)-11-Aza-1-(2-ethoxycarbonylethyl)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine(11a). Methyl ester (11) was trans-esterified as described for transformation of compound (10) to 12 (see below) to yield trans-ethyl ester (11a) (67.5%), mp 85 - 86°C, ir: 3290 (NH), 2770 (N-CH_2), 1708 (C=O), 1140 (C-O-C), 1606, 1584, 790, 769 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$/TMS): 9.35 (1H, b, NH), 8.25 (1H, dd, J = 4.8 and 1.4 Hz) 7.75 (1H,

dd, J = 7.9 and 1.4 Hz), 6.99 (1H, dd, J = 7.9 and 4.8 Hz, arom.), 4.30 (2H, q, J = 7.1 Hz, CH_2/OEt), 3.31 (1H, br s, 12b-H), 3.30 - 1.30 (16H, m, 8 x CH_2), 1.38 (3H, t, J = 7.1 Hz, CH_3/OEt), 0.70 (3H, t, J = 7.9 Hz, CH_3); Anal. Calcd for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 71.17; H, 8.09; N, 12.33.

Optical resolution of (±)-10. To a well stirred solution of racemic base [(±)-10] (10.25 g, 30 mmol) in ethanol (150 ml) (-)-O,O'-dibenzoyl-L-tartaric acid monohydrate (5.65 g, 15 mmol) was added at 5°C, and the mixture was stirred at the same temperature for 1 h. The precipitated salt was filtered off and washed with cold ethanol to yield (-)-(1*S*,12b*S*)-10 x LDBT salt monohydrate (10.2 g, 95%), mp 142 - 144°C; $[\alpha]_D$ = -122.9° (c = 0.8, ethanol - DMF 2:1); ir: 3470 (NH), 1720 (C=O), 1265, 1112 (C-O-C), 1625, 1600, 726 (arom.) cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$ + DMSO-d_6/TMS): 11.40 (1H, b, NH), 8.11 (4H, m), 7.55 (2H, m), 7.43 (4H, m, 2 x Ph), 8.06 (1H, dd, J = 5.3 and 1.5 Hz), 7.85 (1H, dd, J = 7.8 and 1.5 Hz), 7.08 (1H, dd, J = 7.8 and 5.3 Hz, arom.), 7.47 (2H, b, 2 x COOH), 6.01 (2H, s, 2 x CH/ tartrate), 3.53 (3H, s, COOMe), 3.52 (1H, s, 12b-H), 3.20 - 1.30 (14H, m, 7 x CH_2), 1.78 (1H, m), 1.40 (1H, m, CH_2/Et), 0.99 (3H, t, J = 7.9 Hz, CH_3/Et); ^{13}C-nmr (75 MHz, $CDCl_3$ + DMSO-d_6): 173.8, 169.4, 164.9 (3 x C=O), 132.9, 129.4, 129.1, 128.0 (Ph), 145.7, 137.6, 133.7, 128.1, 120.7, 114.8, 109.8 (azaindole), 72.2 (CH/tartrate), 65.6 (N-CH), 55.8, 53.0 (2 x N-CH_2), 50.9 (OCH_3), 38.7 (C/q/), 31.3, 29.6, 27.7, 27.5, 20.6, 20.5 (6 x CH_2), 7.6 (CH_3); Anal. Calcd for monohydrate $C_{38}H_{43}N_3O_{11}$: C, 63.59; H, 6.04; N, 5.85. Found: C, 63.3; H, 5.54; N, 5.53.

To the mother liquor (+)-O,O'-dibenzoyl-D-tartaric acid monohydrate (5.65 g, 15 mmol) was added at 5°C, while stirring. Isolation of the salt as above resulted in (+)-(1*R*,12b*R*)-10 x DDBT salt monohydrate (10.2 g, 95%), mp 144 - 146 °C; $[\alpha]_D$ = +122.6° (c = 0.8, ethanol - DMF 2:1); ir, ^{1}H- and ^{13}C-nmr spectra are identical with those of (-)-10.

Determination of the optical purity of (+)- and (-)-10. Racemic base [(±)-10] (35 mg) was dissolved in $CDCl_3$ (1 ml). To this solution Eu(tfc)$_3$ {tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato],europium derivative} (10 mg) was added and the ^{1}H-nmr spectrum was recorded at 300 MHz. The following peaks were splitted most significantly: COOMe (3.63 and 3.61 ppm) and 12b-H (3.52 and 3.45 ppm). The same experiment was carried out with both enantiomeric bases [(+)-and (-)-10] (liberated from the corresponding DBT salts as described below): no peak duplication was observed in both cases (detection limit of the other enantiomer approx. 5%).

(1*S*,12b*S*)- and (1*R*,12b*R*)-11-Aza-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propionic acid [(-)- and (+)-10a]. Dibenzoyltartrate [(-)-10 x LDBT] (3.0 g, 4.3 mmol) was dissolved in a mixture of 1N $NaHCO_3$ (15 ml) and benzene (45 ml) while stirring. The layers were separated, the aqueous phase was extracted twice with benzene (10 ml each), then the combined organic phases were washed with water (2 x 10 ml). The benzene solution was dried over anh. Na_2SO_4, then evaporated to dryness. The resulting oil was refluxed in ethanolic NaOH solution (0.1 g NaOH/45 ml 95% EtOH) for 2 h. To the solution acetic acid (0.6 ml) was added to set the pH to 4, then the solvent was removed under reduced pressure and the residue was crystallized with water at 5°C to give acid (-)-(1*S*,12b*S*)-10a (1.06 g, 75 %), mp 262 - 265 °C; $[\alpha]_D$ = + 103 ° (c = 1, 10% AcOH); ir: 3290 (NH), 3000 - 2200 (NH^+), 1680 (C=O), 1590 (C=C), 1270 (COOH), 772 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, pyridine d_5/TMS): 11.00 (1H, b, COOH), 8.80 (1H, b, NH), 8.40 (1H, dd, J = 4.8 and 1.4 Hz), 7.80 (1H, dd, J = 7.1 and 1.4 Hz), 7.07 (1H, dd, J = 7.1 and 4.8 Hz, arom.), 3.38 (1H, b, 12b-H), 3.20 - 1.30 (16H, m, 8 x CH_2), 1.00 (3H, t, J = 6.2 Hz, Me); Anal. Calcd for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.78; H, 8.03; N, 12.26.

The enantiomeric acid was prepared by the same procedure starting from (+)-10 dibenzoyltartrate to yield (+)-(1*R*,12b*R*)-10a (1.13 g, 80%), mp 264 - 267 °C; $[\alpha]_D$ = - 99° (c = 1, ethanol); ir and ^{1}H-nmr are identical with those of (-)-10a; Anal. Calcd for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.70; H, 7.76; N, 12.63.

Ethyl (1*S*,12b*S*)- and (1*R*,12b*R*)-11-Aza-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propionate [(-)- and (+)-(12)]. Dibenzoyltartrate [(-)-10 x LDBT] (8.1 g, 11.5 mmol) was converted to the corresponding base as described above. The resulting oil (4.1 g) was dissolved in abs. ethanol (40 ml) and to this solution sublimed potassium-tert-butoxide (0.41 g) was added below 5°C. The mixture was stirred at room temperature for 10 h, then cooled to 5°C again and acidified with 0.2 ml acetic acid. After evaporation of the solvent, the residue was crystallized with water to yield (-)-(1*S*,12b*S*)-12 (3.62 g, 88%), mp 118 - 120°C; $[\alpha]_D$ = -139.7° (c = 1, ethanol), ir: 3150 (NH), 2810, 2750 (N-CH_2), 1726 (C=O), 1163 (C-O-C), 1612, 1588, 777 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$/TMS): 8.50 (1H, b, NH), 8.18 (1H, dd, J = 4.8 and 1.4 Hz), 7.75 (1H, dd, J = 7.9 and 1.4 Hz), 7.0 (1H, dd, J = 7.9 and 4.8 Hz, arom.), 4.00 (2H, q, J = 7.1 Hz, CH_2/OEt), 3.30 (1H, br s, 12b-H), 3.20 - 1.30 (16H, m, 8 x CH_2), 1.18 (3H, t, J = 7.1 Hz, CH_3/OEt), 1.1 (3H, t, J = 6.2 Hz, CH_3); Anal. Calcd for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.97; H, 8.35; N, 11.70.

The enantiomeric ethylester (+)-(1*R*,12b*R*)-12 was prepared by the same procedure starting from (+)-10 x DDBT, mp 121 - 123°C; $[\alpha]_D$ = +139.6° (c = 1, ethanol), ir and ^{1}H-nmr are identical with those of (-)-12; Anal. Calcd for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.99; H, 8.46; N, 12.32.

Ethyl (3*S*,16*S*)-12-Aza-14,15-dihydro-14-hydroxylaminoeburnamenine-14-carboxylate (13) dibenzoyltartrate and base To a suspension of sublimed potassium tert-butoxide (2.21 g, 20 mmol) in dimethylformamide (10 ml), cooled to 0°C, tert-butyl nitrite (0.47 ml, 4 mmol) then ethyl ester (-)-12 (2.21 g, 6.2mmol) and further quantity of tert-butyl nitrite (1.1 ml, 9.5 mmol) was added while keeping the temperature below 5°C. The mixture was stirred at room temperature for 2 h, then was neutralized by addition of acetic acid (1.2 ml). The dark solution was evaporated under reduced pressure and the residue was solidified with aqueous $NaHCO_3$ solution and filtered off. The crude product (2.4 g) was dissolved in a mixture of ethyl acetate (25 ml) and water (25 ml), and to the solution (-)-O,O'-dibenzoyl-L-tartaric acid (3.75 g, 10.5 mmol) was added to result in the precipitation of crude salt (3.5 g, 76%) which was finally recrystallized from ethanol-water 1:1 mixture to give pure (-)-(3*S*,16*S*)-13 x LDBT salt (1.75 g, 38%), mp 154 - 155 °C; $[\alpha]_D$ = -139.7° (c = 1, ethanol); ir: 3540 (OH), 3500 - 2200 (NH and NH^+), 1726 (C=O), 1266, 1112 (C-O-C, 1026 (N-OH), 1602, 716 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, DMSO-d_6/TMS): 8.30 - 6.80 (13H, m, arom.), 5.90 (2H, s, CH/tartrate), 5.00 (4H, b, hetero), 4.10 (2H, q, J = 7.1 Hz, CH_2/OEt), 3.90 (1H, br s, H-3), 3.20 - 1.30 (14H, m, 7 x CH_2), 1.18 (3H, t, J = 7.1 Hz, CH_3/OEt), 0.90 (3H, t, J = 6.2 Hz, CH_3).

The corresponding base was prepared with ethyl acetate and 1 M $NaHCO_3$ by standard procedures to give base (-)-13 (88 %), mp 130°C; $[\alpha]_D$ = -64.2° (c = 1, ethanol); ir: 3420 (OH), 3160 (NH), 2798, 2753 (N-CH_2), 1719 (C=O), 1289, 1153 (C-O-C), 993 (N-OH), 769 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$/TMS): 9.00 (1H, b, N-OH), 8.20 (1H, dd, J = 5.7 and 1.4 Hz), 7.86 (1H, dd, J = 7.9 and 1.4 Hz), 7.1 (1H, dd, J = 7.9 and 5.7 Hz. arom.), 4.20 (2H, q, J = 7.1 Hz, CH_2/OEt), 3.40 (1H, bs, H-3), 3.30 - 1.30 (14H, m, 7 x CH_2), 1.18 (3H, t, J = 7.1 Hz, CH_3/OEt), 1.00 (3H, t, J = 7.1 Hz, CH_3); *Anal. Calcd for $C_{21}H_{28}N_4O_3$: C, 65.60; H, 7.34; N, 14.57. Found: C, 65.86; H, 7.34; N,* 14.01.

Ethyl (3*S*,16*S*)-12-Aza-apovincaminate (14) dibenzoyltartrate and base. A solution of dibenzoyl-tartrate (-)-(3*S*,16*S*)-13 x LDBT (7.43 g, 10 mmol) in acetic acid (74 ml) was heated at 100°C for 2 h. The solution was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (200 ml) and extracted first with sat. $NaHCO_3$ (200 ml) then with 1N Na_2CO_3 solution (40 ml). After drying over anh. Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on Merck silica gel (particle size 0.063 - 0.200 mm) with acetone. The pure fractions were evaporated and the residue was crystallized with ether to yield crude base (-)-14 (0.53 g, 14%). This was dissolved in ethyl acetate (20 ml) and to the solution (-)-O,O'-dibenzoyl-L-tartaric acid monohydrate (0.51 g, 1.4 mmol) was added. After stirring for 1 h the precipitate was filtered off and washed with cold ethyl acetate to give dibenzoyltartrate (-)-(3*S*,16*S*)-14 x LDBT (0.82 g, 1.2 mmol, 12%), mp 164 - 165°C; $[\alpha]_D$ = - 35.7° (c = 1, EtOH); ir: 2800 - 2200 (NH^+), 1729 (C=O), 1641 (C=C), 1266, 1115 (C-O-C), 1601, 1595, 714 (arom.) cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6/TMS): 8.10 (4H, m), 7.50 (2H, m), 7.37 (4H, m, 2 x Ph), 8.27 (1H, dd, J = 5.0 and 2.0 Hz), 7.22 (1H, dd, J = 7.8 and 2.0 Hz), 7.09 (1H, dd, J = 7.8 and 5.0 Hz, arom.), 5.92 (2H, s, 2 x CH/tartrate), 5.79 (1H, s, C=CH), 4.80 (1H, s, H-3), 4.40 (2H, m, CH_2/OEt), 3.68 - 1.03 (10H, m, 5 x CH_2), 1.31 (3H, t, J = 7.5 Hz, CH_3/OEt), 1.82 (2H, m, CH_2/Et), 0.76 (3H, t, J = 6.4 Hz, CH_3/Et); ^{13}C-nmr (75 MHz, DMSO-d_6): 170.4, 165.6, 162.9 (3 x C=O), 133.1, 130.0, 129.8, 128.2 (Ph), 146.5, 143.9, 126.8, 125.6, 119.8, 117.2, 105.4 (azaindole), 129.6, 123.2 (C=C), 72.9 (CH/tartrate), 62.1 (CH_2/OEt), 55.8 (N-CH), 50.6, 44.4 (2 x N-CH_2), 39.4 (C/q/), 27.0, 26.4, 17.8, 15.6 (4 x CH_2), 14.0 (CH_3/OEt), 8.0 (CH_3); Anal. Calcd for $C_{39}H_{39}N_3O_{10}$ C, 66.00; H, 5.54; N, 5.92. Found: C, 65.62; H, 5.55; N, 5.79.

The corresponding base was prepared with ethyl acetate and 1 M $NaHCO_3$ by standard procedures to give base (-)-14 (70 %), mp 110 - 111°C; $[\alpha]_D$ = + 185.9° (c = 0.5, ethanol); ir: 2808, 2723 (N-CH_2), 1729 (C=O), 1680 (C=C), 1257, 1175 (C=C), 1608, 770 (arom.) cm^{-1}; ^{1}H-nmr (60 MHz, $CDCl_3$/TMS): 8.20 (1H, dd, J = 5.0 and 2.0 Hz), 7.70 (1H, dd, J = 7.8 and 2.0 Hz), 7.00 (1H, dd, J = 7.8 and 5.0 Hz, arom.), 5.90 (1H, s, C=CH), 4.45 (2H, q, J = 7.5 Hz, CH_2/OEt), 4.20 (1H, bs, H-3), 3.50 - 1.10 (12H, m, 6 x CH_2), 1.40 (3H, t, J = 7.5 Hz, CH_3/OEt), 1.04 (3H, t, J = 6.4 Hz, CH_3/Et); Anal. Calcd for $C_{21}H_{25}N_3O_2$ C, 71.77; H, 7.17; N, 11.96 . Found: C, 71.6; H, 7.35; N, 11.79.

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REFERENCES

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1. M. Lounasmaa and A. Tolvanen, 'The Alkaloids: Eburnamine–Vincamine Alkaloids', Vol. 42. ed. by A. Brossi, Academic Press, New York, 1992, pp.1 - 116.
2. (a) Cs. Lörincz, K. Szász, and L.Kisfaludy, Arzneim. Forsch., 1976, 26, 1907. (b) N. Neuss, "Indole and Biogenetically Related Alkaloids", ed. by J. D. Phillipson and M. H. Zenk, Academic Press, London, 1980, pp.294.
3. (a) H. Hammer and E. Winterfeldt, Tetrahedron, 1981, 37 3609; (b) Synthelabo S. A., Japan Patent, 58105988

(1981) (Chem.Abstr., 1983, 99, 158404p); (c) L. Diatta and C. Warolin (Synthelabo S. A.), S. African Patent, ZA 8108413 (1981) (Chem. Abstr., 1983, 99, 139924s).

4. N. Aktogu and F. Clemence (Roussel-UCLAF), Eur. Pat. Appl., EP 287,468 (1988) (Chem. Abstr., 1989, 110, 231945t).
5. P. Lardenois (Synthelabo S. A.) Fr. Demande, 2,456,743 (1980) (Chem. Abstr., 1981, 95, 97842y).
6. For the novel triaza-polycycles the C.A. ring-numbering systems of the corresponding carba analogues have been adopted.
7. O. Seide, Ber., 1924, 57, 1802.
8. R. R. Lorenz, B. F. Tullar, C. F. Koelsch, and S. Archer, J.Org.Chem., 1965, 30, 2531.
9. M. M. Robison and B. L. Robison, J. Am. Chem. Soc., 1955, 77, 457.
10. L. Velluz, G. Muller, and A. Allais (Lab. Francais de Chimiotherapie), Fr. Patent, 1,261,179 (1961) (Chem. Abstr., 1962, 57, 2274b).
11. Cs. Szántay, L. Szabó , and G. Kalaus, Tetrahedron, 1977, 33,1803.
12. E. Wenkert and B. Wickberg, J. Am. Chem. Soc., 1965, 87, 1580.
13. L.Szabó , Gy. Kalaus, and Cs. Szántay, Arch. Pharm., 1983, 316, 629.
14. L. Szabó, J. Sápi. Gy. Kalaus, Gy. Argay, A. Kálmán, E. Baitz-Gács, J. Tamás, and Cs. Szántay , Tetrahedron, 1983, 39, 3737.
15. L. Czibula , A Nemes, Gy. Visky, M. Farkas, Zs. Szombathelyi, E. Kárpáti, P. Sohár, M. Kessel, and J. Kreidl, Liebigs Ann. Chem., 1993, 221.
16. A. Nemes, L.Czibula, Gy. Visky, M. Farkas, and J. Kreidl, Heterocycles, 1991, 32, 2329.

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