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STUDIES IN THE CHEMISTRY OF ERYTHRINA ALKALOIDE DERIVATIVES—I

PREPARATION OF ERYTHRINANE AND ERYTHRINANE-HOMOLOGUE DERIVATIVES

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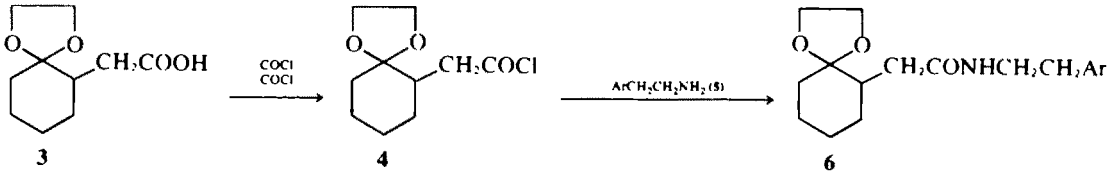
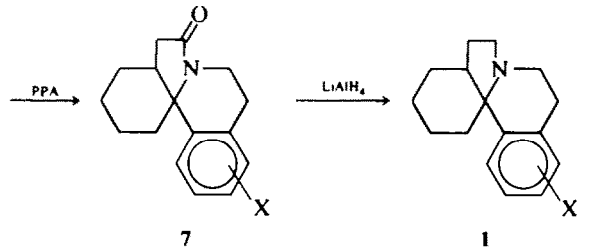
Abstract—The compounds 15-fluoro-, 16-fluoro- and 16,17-benzoerythrinane, their thienyl analogue, 1,2,3,4,4a,5,8,9-octahydro-6H-thieno[2',3'-4,3]pyrido[2,1-i]indol, the erythrinane homologue, 1,2,3,4,4a,5,6,7,9,10-decahydroisoquino[2,1-j]quinoline and its 18-fluoro and 16,17-dimethoxy derivatives were prepared. Their chemical structures and their stereochemistry were investigated. All are of the structure *cis* A/B, *cis* B/C.

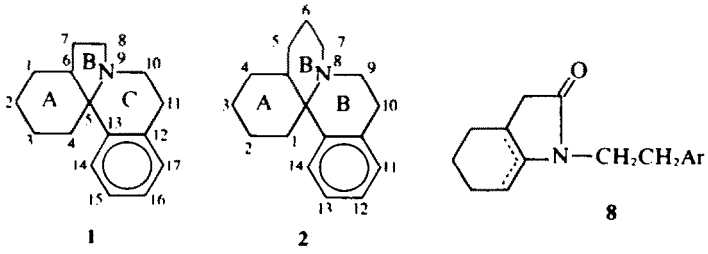
Several natural erythrina alkaloids[1-3] and erythrinane derivatives[4] are well known for their curariform activity though only few reports on synthetic erythrinane analogues are available.[5-9] In the course of our study on the effect of geometric and electronic factors on the paralytic activity of erythrinanes some representatives of the title compounds have been prepared. We were particularly interested in investigating the fluoro and thio-analogues of the natural alkaloids. Introduction of a F atom (which has a similar van der Waals radius to hydrogen) often enhances the biological activity of drugs or else causes potent antagonistic action. Typical examples are the fluorocorticoid drugs which are much more potent than the corticoids[10] and the 4-fluorophenylalanine which is phenylalanine antagonist.[11] Likewise, the introduction of thienyl instead of a phenyl ring in biologically active compounds destroyed in some cases completely or in other cases largely increased drug activity (cf. e.g. β-(2-thienyl)alanine shows phenylalanine antagonism[12] and the 3-thienyl analogue of tripelennamine has about 1.5 times the antiallergenic activity of tripelennamine.[13] We have prepared the following erythrinane derivatives: 16,17-benzoerythrinane (**1a**), 15-fluoroerythrinane (**1b**), 16-fluoroerythrinane (**1c**) and the thienyl analogue, 1,2,3,4,4a,5,8,9 - octahydro - 6H - thieno[2',3'-3,4]pyrido[2,1-i]indole (**1d**). Likewise, three representative homologues of erythrinane have been synthesized in the course of this study namely: 1,2,3,4,4a,5,6,7,9,10-decahydroisoquinolo[1,2-j]quinoline (**2a**) and its 18-fluoro- and 16,17-dimethoxy derivatives (**2b** and **2c**). Compounds **1a–1d** were synthesized by the following general route:

†Deceased on 5 April 1975.





Scheme 1.

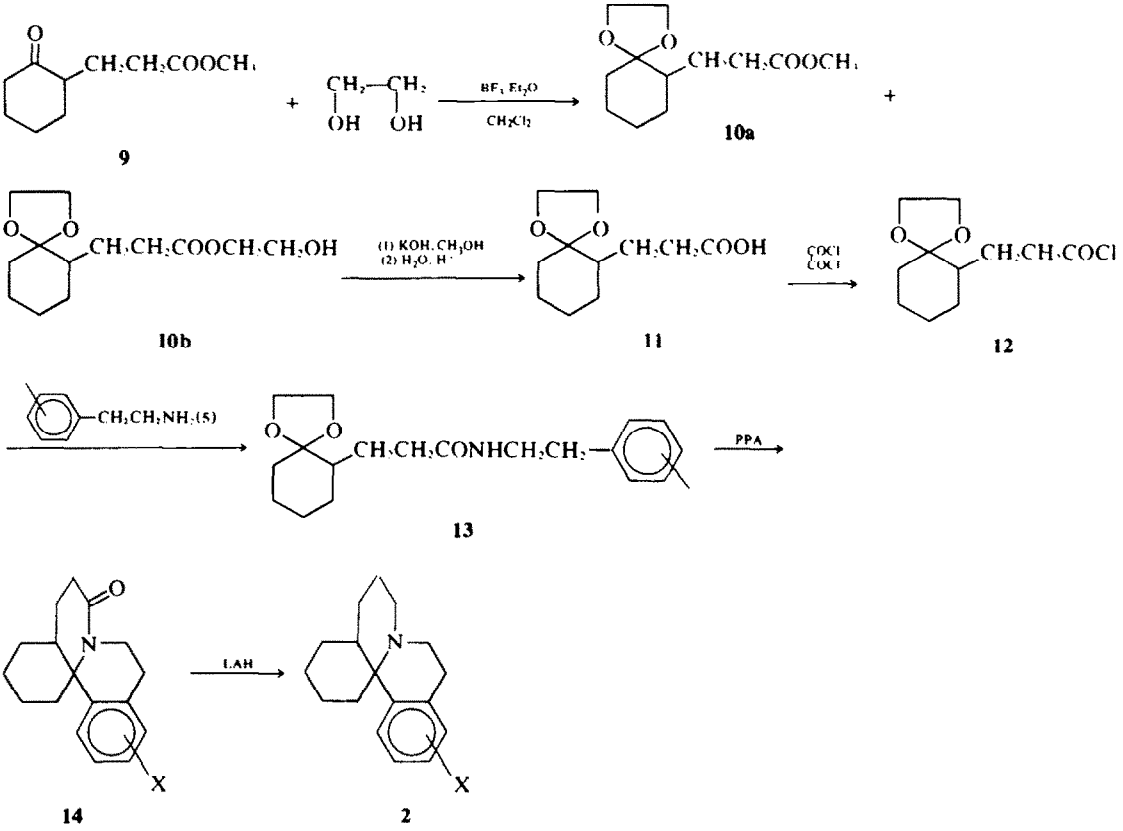


(2-Oxocyclohexyl)acetic acid ethylene ketal (**3**)[6,7] was converted to the corresponding heat sensitive chloride **4** by treatment with oxalyl chloride. The reaction of β-(1-naphtyl)-, β-(*p*-fluorophenyl)-, β-(*m*-fluorophenyl)- and β-(2-thienyl)-ethylamine (**5a–5d**) with **4** gave the amides: N[β-(1-naphthyl)ethyl]-, N-[β-(*p*-fluorophenyl)ethyl-, N-[β-(*m*-fluorophenyl)ethyl]- and N-[β-(2-thienyl)ethyl)-(2-oxocyclohexyl)acetamide ethylene ketal (**6a–6d** respectively). Large scale syntheses of amines **5** were accomplished by modification of known methods (Experimental). Mondon cyclization[6] of the amides **6a–6d** yielded the expected erythrinones **7a–7d**. Except for the sulfur containing compound the cyclization was achieved by hot (150°) PPA. Owing to the enhanced electrophilicity of the thienyl moiety, ring closure in **6d** could be affected even at room temperature in the presence of dilute HCl. The unreactivity of the products **6a–6d** towards 2,4-DNP[14] and their slow reaction with bromine solution[14] excludes their being enamidic oxindoles **8**. The structure of compounds **7a–7d** was determined from the following spectral data: IR shows a typical 5-membered lactam CO at absorption 1680 cm^{-1}[15] (CO group of the starting amides absorb at 1640–1650 cm^{-1}). NMR of **7a–7d** show downfield peaks at $\delta = 4.1$–4.4 ppm, indicating the equatorial C-10 protons.[16] Formation of the C-ring by attachment to the aromatic moiety is confirmed by the absence of one of the original aromatic protons in each of the NMR spectra of **7a–7d** (compared to **6a–6d** respectively) and by the well characterized aromatic pattern signals.

Cyclization of **6c** may lead to two possible isomers: 16-fluoro- and 14-fluoro-8-oxoerythrinane (**7c** and **7e**). Both ^1H and ^{19}F NMR spectra confirm that the isolated lactam is the 16-fluoro isomer (**7c**). The aromatic proton NMR signals are $\delta = 6.72$–7.02 (H, m, C_{15}–H, C_{17}–H), 7.26–7.45 (1H, m, C_{14}–H). The upfield signal is due to fluorine shielding which is strongest at the ortho positions;[17] this signal reflects, therefore, C_{15}–H and C_{17}–H. The downfield signal which is due to the proximity effect[18] of C_1–H and C_3–H[19] reflects C_{14}–H. Fluorine NMR spectrum, $\delta = 114.2$ (rel. $CFCl_3$, sextet, $J_1 = 9.0$ Hz, $J_2 = 6.0$ Hz, C_{16}–F) resembles that of the F atom in 15-fluoro-8-oxoerythrinane ($\delta = 114.9$ ppm). It has the X part pattern of A_2BX system with the coupling constants J_1 and J_2 corresponding to $J_{F,ortho\,H}$ and $J_{F,meta\,H}$ respectively ($J_p \sim -2$–$+2$ Hz, $J_o \sim 6$–10 Hz, $J_m \sim 6$–8 Hz[20]). The alternative isomer, 14-fluoro-8-oxoerythrinane (**7e**) should have had a different ^{19}F NMR spectrum—a quartet with the X part pattern of ABX system (the coupling with a para proton is very small), and a downfield shift due to a considerable van der Waals effect.[21]

LAH reduction of the lactams **7a–7d** afforded the respective erythrinanes **1a–1d**.

The general route followed in the preparation of the erythrinane homologues **2a–2c** is outlined in Scheme 2. 2-(β-carbomethoxyethyl)cyclohexanone (**9**)[22] was ketalized in two phase systems, with BF_3-etherate as catalyst.[23] A mixture of methyl and 2-hydroxyethyl esters of 2-(β-carboxyethyl)cyclohexanone ethylene ketal (**10a** and **10b** respectively) resulted. The latter compound is probably formed through transesterification by the glycolic solvent. The free carboxylic acid **11** (basic hydrolysis) was treated with oxalyl chloride to give the heat sensitive 3-(2-oxocyclohexyl)propionyl chloride ethylene ketal (**12**). Crude **12** was reacted with the amines: β-(*o*-fluorophenyl)-, β-phenyl, and β-(3,4-dimethoxyphenyl)ethylamine (**5e–5g** respectively) to yield



Scheme 2.

the corresponding amides: N-(β-phenylethyl)-, N[β-(p-fluorophenyl)ethyl]- and N - [β - (3,4 - dimethoxyphenyl)ethyl] - 3 - (2 - oxocyclohexyl]propionamide ethylene ketal (**13a–13c**). Cyclization by the method of Mondon[6] using PPA resulted in the formation of lactams **14a–14c**. As in the synthesis of the erythrinanes the electrodonating OMe groups caused faster ring-closure in **13c**, than in **13a** and **13b**. (1.5 hr at 100° for **13c** compared to 12 hr at 120–130° for **13a** and **13b**). It is remarkable, however, that in contrast to the formation of **5d** cyclization of **13c** could not be effected by diluted hydrochloric acid.

All three lactams **14a–14c** have the characteristic absorption at 1635 cm^{-1} (carbonyl group in 6-membered lactams[24]). NMR spectra of **14a–14c** show typical down-field signals at $\delta = 4.6$–4.9 ppm, corresponding to the equatorial C-9 proton[16c] (cf. the resonance of the equatorial proton adjacent to nitrogen in 4-oxoquinolizidine derivatives[16c]).

Finally, amines **2a–2c** were prepared by LAH reduction of **14a–14c** respectively.

The stereochemistry of the compounds **1a–1d** and **2a–2c** was elucidated by the following considerations: IR of **1a–1d**, **2a–2c** show no Bohlmann bands, which indicate *cis* fusion of the B/C rings (*trans*-fused indolizidine[25] and quinolizidine[26] derivatives are indicated by the presence of Bohlmann bands at 2700–2800 cm^{-1} in the IR). The configuration of the A/B junction was determined by the "quaternization test" as *cis*. In both erythrinane and erythrinane-homologue systems, when A/B is *cis*-fused, B/C may be either *cis* fused or *trans* fused. These two isomers (*cis* A/B, *cis* B/C and *cis* A/B, *trans* B/C) are actually conformers, due to the inversion property of the bridgehead N atom. Each of these conformers can yield on quaternization with methyl iodide the same two diastereoisomeric methiodide salts characterized by two different N-Me singlets in the NMR. When A/B is *trans*-fused, the B/C junction in the erythrinane system can only be *cis*-fused (the conformation *trans* A/B, *trans* B/C involving *trans* diaxial 5-membered-ring junction is highly improbable). Therefore quaternization of isomer *trans* A/B, *cis* B/C can only afford one methiodide salt characterized by a single N-Me singlet in the NMR. On the other hand, in the erythrinane-homologue system, although both isomers, *trans* A/B, *cis* B/C and *trans* A/B, *trans* B/C are possible, models show that in the isomer *trans* A/B, *trans* B/C, ring B can exist only as the boat conformer, which is less stable than the all-chair *trans* A/B, *cis* B/C compound. Moreover, on quaternization, both transition states and the products, *trans* A/B, *trans* B/C methidide must form unstable boat forms, with the N-Me group at the flag-pole position. Therefore, quaternization of the *trans*-fused A/B siomer is likely to give only one methiodide, characterized by a single N-Me group singlet in the NMR spectrum. Since on quaternization of **1a**, **1c**, **2a**, and **2c** there results in each case a mixture of two stereoisomeric methiodides indicated by two N-Me singlets, their A/B junctions must be *cis*-fused (and consequently must be identical in lactams **7a**, **7c**, **14a** and **14c** as well). The data of the N-Me group signals are given in Table 1. The up-field signals are assigned to the *trans* isomers, and the down-field signals to the *cis* B/C (as is known for methiodides of substituted quinolizidines[27] and substituted indolizidines[28,29]).

In order to show that each signal corresponds to a particular isomer, the *cis* A/B, *trans* B/C isomer was isolated by fractional crystallization from the mixture of the **1a** methiodides. From the mother liquer a mixture of the methiodides of **1a**, enriched with the other isomer (*cis* A/B, *cis* B/C) was obtained (10:3 in the final mixture as compared to 1:1 in the initial mixture).

These observations prove the validity of Mondon's rule[30] in the case of our homo-erythrinanes. Accordingly, *trans*-fused A/B configuration is characterized by a difference larger than 30 Hz between the chemical shifts of the aromatic protons in dimethoxyertyrhiane derivatives ($\Delta\delta = \delta_{H\text{-}14} - \delta_{H\text{-}17} > 30$ Hz), and the *cis* A/B configuration is indicated by difference smaller than 20 Hz. Correspondingly, the NMR spectra of **13c**, both A/B *cis*-fused show $\Delta\delta = \delta_{H\text{-}14} - \delta_{H\text{-}H} = 7.2$ Hz and 18.36 Hz respectively, both less than 20 Hz.

EXPERIMENTAL

M.ps were determined with a Thomas–Hoover capillary m.p. apparatus. IR spectra were recorded with a Perkin–Elmer 457 spectrophotometer and NMR spectra with a Varian T-60 and Varian HA 100D spectrometers. Mass spectra were obtained with a Varian Mat 311 mass spectrometer.

(2-Oxocyclohexyl)acetyl chloride ethylene ketal (**4**). A soln of **3**[6,7] (6.6 g, 0.033 mole) in dry benzene (50 ml) was added dropwise at room temp. to freshly distilled oxalyl chloride (21 ml) in dry benzene (75 ml). After standing overnight, the solvent was successively evaporated *in vacuo*, reintroduced and evaporated again to ensure complete removal of excess oxalyl chloride, (because of the heat-sensitivity of **4**, temp. kept below 30° throughout procedure). The crude **4**, a colourless liquid, was used without further purification for the next step. IR (neat) 1815, 1750 cm^{-1} (acyl halide C=O), NMR ($CDCl_3$) δ 3.8 (s, 4H, ethylene ketal), 2.1–2.5 (m, 2H, $CH_2C{=}O$), 1.1–2.1 (m, 11 H).

N-[β-(Naphthyl)ethyl]-(2-oxocyclohexyl)acetamide ethylene ketal (**6a**). To **5a** (11.3 g, 0.066 mole) in methylene chloride (100 ml) was added dropwise, at −20° to −10°, a soln of crude **4** (from 6.6 g **3**) in methylene chloride (50 ml). The mixture was allowed to warm to room temp. and left overnight. The solides were filtered off and the filtrate was washed with water, Na_2CO_3aq and again water, dried ($MgSO_4$) and evaporated to give an oil (quantitative yield) which solidified by tituration with petroleum (60–80°); colourless crystals, m.p. 94°–96° (from ether–hexane). NMR ($CDCl_3$): δ 7.6 (m, 7 H, ArH), 5.8† (m, 1 H, NHC=O), 4.0 (s, 4 H, ethylene ketal), 3.3–3.9 (m, 6 H, CH_2–N, $-CH_2Ar$, $CH_2C{=}O$), 1.2–2.2 (m, 7 H). IR (Nujol): 3340 (NH), 1645 (amide C=O), 1095, 956, 934, (ethylene ketal). (Found: C, 74.48; H, 7.71; N, 4.16. Calc. for $C_{22}H_{27}NO_3$: C, 74.78; H, 7.64; N, 3.96%).

8-Oxo-16,17-benzoerythrinane (**7a**). A stirred soln of **6a** (4g, 0.011 mole) in PPA was heated at 100° for 14 hr. After cooling, the dark-red soln was poured into chilled water. The mixture was extracted with $CHCl_3$ and the organic layer washed with water, $NaHCO_3$aq and again with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina (neutral, grade I Merck alumina) and eluted with $CHCl_3$–C_6H_6 (1:3 V/V) to yield

†On standing with D_2O the signal disappears.

Table 1. NMR chemical shifts of the N-methyl groups of the methiodides (δ)

	methiodides 1a	methiodides 1c	methiodides 2a	methiodides 2c
trans B/C	3.08	3.02	2.86	2.86
cis B/C	3.34	3.31	3.26	3.26

0.9 g **7a** (27.2% from **3**). The compound solidified immediately on addition of petroleum (40°–60°), m.p. 157–8° (from benzene-petroleum ether). Mass spectrum: (70 eV) *m/e* 291 (M^+). NMR ($CDCl_3$): δ 7.56 (m, 6 H, ArH), 4.32 (m, 1 H, *equatorial* C_{10}–H), 2.68 (m, 2 H, CH_2C=O), 2.86–3.41 (m, 3 H, CH_2–Ar, *axial* C_{10}–H), 2.1–1.45 (m, 9 J). IR (Nujol): 1677 cm^{-1} (lactam C=O). (Found: C, 82.56; H, 7.53; N, 5.0. Calc. for $C_{20}H_{21}NO$: C, 82.47; H, 7.2; N, 4.8%).

16,17-*Benzoerythrinane* (**1a**). A son of **7a** (1.59 g, 0.0054 mole) in dry THF was added dropwise, at room temp, to a stirred suspension of LAH (1.6 g) in the same solvent. The mixture was refluxed for 4 hr left overnight at room temp., decomposed by successive additions of cold water (1.6 ml), 15% NaOHaq (1.6 ml) and again cold water (3.5 ml)[31] stirred for 1.0 hr and filtered. The resulting semi solid was extracted several times with boiling THF until it became crystalline. The combined THF layers were evaporated, and the oily residue was taken in dry ether. On addition of a solution of HCl in dry THF the 15,16-benzoerythrinamium chloride precipitated (1.35 g, 75.8%) as a colourless solid, m.p. 209–210° (from water). Mass spectrum (70 eV) *m/e* = 277 (free amine). NMR ($CDCl_3$): δ = 7.2–8.05 (m, 6 H, ArH), 2.7–3.85 (m, 6 H, NCH_2, $ArCH_2$), 1.2–2.5 (m, 11 H). IR: No Bohlmann bands and no carbonyl bands. (Found: C, 74.23; H, 7.69; N, 4.38; Cl, 10.53. Calc. for $C_{20}H_{24}NCl \cdot 1/2H_2O$: C, 74.41; H, 7.75; N, 4.3; Cl, 10.9%).

1,2,3,4,4a,5,8,9 - *Octahydro* - 6 - *oxo* - 6H - *thieno*[2',3'-4,3]*pyrido* - [2,1-*i*]*indole* (**7d**). Crude acyl halide **4** (from 15.7 g, 0.0787 mole acid **3** and 60 ml oxalyl chlordie) was converted as above into **6d** by treatment with 10 g (0.0787 mole) **5d**[32] and 7.95 g (0.0788 mole) triethylamine. A soln of crude **6d** (3.5 g, 0.01 mole) in 10% HClaq (100 ml) and EtOH (200 ml) was stirred at room temp. for 6 days, then neutralized with Na_2CO_3aq. After evaporation of the EtOH, the mixture was extracted with methylene chloride. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give crude lactam which was purified by preparative TLC on silica gel (eluent: 0.5% MeOH in $CHCl_3$, each plate successively eluted and dried 4 times) to give colourless **7d** (0.83 g, 30.8% yield from **3**) m.p. 116–117 (from cyclohexane). Mass spectrum (70 eV) *m/e* = 247 (M^+). NMR ($CDCl_3$): δ 7.11 (d, J = 5 Hz, 1 H, AB doublet, C_{14}–H), 7.01 (d, J = 5 Hz, 1 H, AB doublet, C_{13}–H), 4.37 (m, 1 H, *equatorial* C_8–H), 2.68–3.28 (m, 3 H, CH_2–Ar and *axial* C_8–H), 2.38 (m, 2 H, CH_2–C=O), 2.28–1.4 (m, 9 H). IR (Nujol): 1680 cm^{-1} (lactam C=O). (Found: C, 67.81; H, 6.88; N, 5.51; S, 13.36. Calc. for $C_{14}H_{17}NOS$: C, 68.03; H, 6.88; N, 5.66; S, 12.9%).

1,2,3,4,4a,5,8,9 - *Octahydro* - 6H - *thieno*[2',3'-4,3]*pyrido*[2,1-*i*]*indole* (**1d**). Reduction of **7d** (0.750 g, 0.003 mole) with LAH (1.6 g) essentially as described for **1a** yielded the hydrochloride of **1d** (0.610 g, 75.3% yield) m.p. 238° (from acetone). The picrate, yellow crystals, m.p. 161–2° (from EtOH). Mass spectrum (70 eV) *m/e* = 233 (free amine). NMR ($CDCl_3$) (of the free amine) δ 6.996 (d, J = 5 Hz, 1 H, AB doublet, C_{14}–H), 6.784 (d, J = 5 Hz, 1 H, AB doublet, C_{13}–H), 2.8–3.8 (m, 6 H, CH_2–NCH_2, CH_2–Ar), 1.1–2.6 (m, 11 H). IR: No Bohlmann bands and no carbonyl band. (Found: C, 51.90; H, 4.72; N, 11.93; S, 6.62. Calc. for $C_{20}H_{22}N_4SO_7$: C, 51.94; H, 4.76; N, 12.12; S, 6.92%).

15-*Fluoroerythrinane* (**1b**). The amide **6b** was prepared in quantitative yield by treatment of crude **4** (from 6.76 g, 0.0338 mole acid **3**) with **5b** (3.4 g, 0.0338 mole). IR: 1640 (amide C=O), 3320 cm^{-1} (NH). Ring closure was afforded by heating a stirred mixture of crude **6b** (3 g) and PPA (60 g) at 135° for 12 hr. Treatment of the product by the same procedure as **7a** and preparative TLC purification on silica gel (eluent: 0.6% MeOH in $CHCl_3$) gave **7b** as an oil, (1.1 g, 46% yield from the acid **3**). Mass spectrum (70 eV) *m/e* = 259 (M^+). ^{1}H-NMR ($CDCl_3$): δ 7.34 (m, 1 H, C_{17}–H), 6.87 (m, 2 H, C_{16}–H, C_{14}–H), 4.12 (m, 1 H, *equatorial* C_{10}–H), 2.28–3.40 (m, 6 H, *axial* C_{10}–H, C_6–H, CH_2–Ar, CH_2–Ar, CH_2=C(O)), 1.26–2.24 (m, 8 H). ^{19}F-NMR ($CDCl_3$, int. $CFCl_3$): δ 114.88 (m). IR (Nujol): 1685 cm^{-1} (lactam C=O). Reduction of the lactam **7b** (1.1 g) with LAH (2.33 g) afforded the hydrochloride of **1b** (0.800 g, 68% yield), m.p. 270° (from isopropanol-ether). Mass spectrum (70 eV) *m/e* = 245 (free amine). NMR ($CDCl_3$): δ 6.92 (m, 3 H, ArH), 3.03 (m, 4 H, CH_2–N–CH_2), 2.34 (m, 2 H, CH_2–Ar), 1.14–2.12 (m, 11 H). IR: no Bohlmann bands and no CO band. (Found: C, 68.50; H, 7.18; N, 4.96; F, 6.56; Cl, 12.35. Calc. for $C_{16}H_{21}NClF$: C, 68.21; H, 7.46; N, 3.97; F, 6.74; Cl, 12.61%).

16-*Fluoroerythrinane* (**1c**). The amide **6c** (6.3 g, quantitative yield) was prepared from the chloride of acid **3** and **5c** IR (Nujol): 1640 amide C=O) 3320 cm^{-1} (NH). Cyclization of 1.18 g crude **6c** and PPA (29 g) at 130° for 12 hr gave **7c** as an oil (0.388 g, 40% yield from the acid **3**). Mass spectrum (70 eV) *m/e* = 259 (M^+). ^{1}H-NMR ($CDCl_3$): δ 7.36 (m, 1 H, C_{14}–H), 6.88 (m, 2 H, C_{15}–H, C_{17}–H), 4.08 (m, 1 H, *equatorial* C_{10}–H), 2.07–3.45 (m, 6 H, C_6–H, CH_2–Ar, CH_2C=O, *axial* C_{10}–H), 1.35–2.07 (m, 8 H). ^{19}F-NMR ($CDCl_3$, int. $CDCl_3$): δ 114.19 (d of t, $J_{F,o-H}$ = 9.0 Hz, $J_{F,m-H}$ = 6.0 Hz). IR (neat): 1680 cm^{-1} (C=O). Reduction of **7c** (2.6 g, 0.01 mole) with LAH (3.22 g) yielded **1c** which was isolated as the hydrochloride (2.2 g, 75% yield), m.p. 183° (from water). Mass spectrum (70 eV) *m/e* = 245 (free amine). NMR ($CDCl_3$): δ 7.15 (m, 1 H, C_{14}–H), 6.78 (m, 2 H, C_{15}–H, C_{17}–H), 3.01 (m, 4 H, CH_2–N–CH_2), 2.35 (m, 2 H, CH_2–Ar), 1.24–2.1 (m, 11 H). (Found: C, 63.82; H, 7.57; N, 4.63; Cl, 12.10. Calc. for the monohydrate $C_{16}H_{21}NClF \cdot H_2O$: C, 64.11; H, 7.68; N, 4.66; Cl, 11.85%).

Methiodides of **1a**. A mixture of **1a** (0.136 g) and MeI (1 g) in acetonitrile (20 ml) was refluxed for 12 hr. Evaporation of the solvent and excess MeI gave a residue (0.196 g, 94% yield) which was purified by trituration with acetone (analytical grade) to yield the mixture of the methodides of **1a**. The ratio of the two isomers *cis* A/B, *trans* B/C to *cis* A/B, *cis* B/C was 19:5; colourless powder m.p. 210–211°. Mass spectrum† (70 eV) *m/e* 277 (M^+–CH_3I)[33,34]. NMR ($CDCl_3$): δ = 7.38–8.04 (m, 6 H, ArH), 3.45–4.75 (m, 6 H, $CH_2\overset{+}{N}CH_2$, CH_2Ar), 3.079 (s, 19/8 H, $\overset{+}{N}$–CH_3, B/C *trans* isomer), 3.343 (s, 5/8 H, $\overset{+}{N}$–CH_3, B/C *cis* isomer), 1.5–2.5 (m, 11 H). (Found: C, 59.90; H, 6.3; N, 2.93; I, 30.6. Calc. for $C_{21}H_{26}NI$: C, 60.14; H, 6.2; N, 3.34; I, 30.31%). The diastereoisomer *cis* A/B, *trans* B/C was isolated by fractional crystallization from acetone, as a colourless solid, m.p. 224–5°. NMR ($CDCL_3$): δ = 3.092 (s, 3H, $\overset{+}{N}$–CH_3). (Found: C, 59.92; H, 6.48; N, 3.27; I, 29.90%).

Substituted phenylethylamines **5a–5c**, **5e**. Large scale β-(1-naphtyl)-, β-(*p*-(fluorophenyl)-, β-(*m*-fluorophenyl)- and β-(*o*-fluorophenyl)-ethylamine (**5a–5c** and **5e** respectively) were prepared by NBS bromination[35] of the appropriate toluenes, substitution of the benzylic bromine atom by a cyano group[35] and reduction of the nitriles by a modification of Brown and Suba Rao's method.[36] Data of the prepared fluorolenzyl bromides are given in Table 2.

Data of the fluorobenzyl cyanides are given in Table 3.

Reduction of *o*-fluorobenzyl cyanide was accomplished by the following way: to a solution of *o*-fluorobenzyl cyanide (13.5 g, 0.1 mole) and $NaBH_4$ (5.7 g, 0.15 mole) in dry diglyme (200 ml) a soln of newly distilled BF_3– etherate (28.2 g, 0.2 mole) in the same solvent was added at 15–17°. After standing overnight the mixture was decomposed by boiling with 5N HCl for 2 hr, then evporated to dryness, basified with conc. NaOH and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$). Evaporation of the solvent gave 10.5 g of **5e** (75.5% yield) which was purified by distillation at 80–96° (24 mm). NMR ($CDCl_3$): δ 7.2–7.8 (m, 4 H, ArH), 2.95 (m, 4 H, CH_2CH_2, A_2B_2 pattern), 1.4 (s, 2 H, NH_2). (Found: C, 68.93; H, 7.01; N, 10.20; F, 13.72. Calc. for $C_8H_{10}FN$: C, 69.06; H, 7.19; N, 10.07; F, 13.66%). The amines **5a–5c** were prepared by the same procedure as **5e**. Their data are given in Table 4.

Spectral data of **5a–5c** are as follows: Compound **5a**: NMR ($CDCl_3$): δ 7.0–7.8 (m, 7 H, ArH), 3.3 (m, 4 H, CH_2–CH_2), 1.3 (s, 2 H, NH_2). Compound **5b**: NMR ($CDCl_3$): δ 7.2 (m, 4 H, ArH), 2.8 (m, 4 H, CH_2–CH_2), 1.7 (s, 2 H, NH_2). IR (neat): 3400 (NH_2), 1600, 1500 (phenyl), 825 cm^{-1} (*para* substituted phenyl). Compound **5c**: NMR ($CDCl_3$): δ 7.2–7.9 (m, 4 H, ArH), 2.8 (m, 4 H, CH_2–CH_2), 1.3 (s, 2 H, NH_2). IR (neat) 3500 (NH_2), 785 cm^{-1} (three adjacent protons on a phenyl ring).

†On standing with D_2O the signal disappears.

Table 2. Data of the fluorolenzyl bromide isomers

Compound	Boiling point	Literature boiling point	Yield	Literature
p-fluorobenzyl bromide	92-102°(20mm)	92-102°(27mm); 93-95°(20mm)	66%	35, 38
m-fluorobenzyl bromide	87- 89°(18mm)	81(7.5mm);196-200°(760mm)	66%	40, 39
o-flurobenzyl bromide	83-92° (18mm)	195-202°(760mm)	70%	39

Table 3. Data of the fluorobenzyl cyanide isomers

Compound	Boiling point	Literature boiling point	Yield	Literature
p-fluorobenzyl cyanide	128-130°(28mm)	120-129°(25mm)	65%	35
m-fluorobenzyl cyanide	127-128°(28mm)	229-230°(760mm)	60%	39
o-fluorobenzyl cyanide	112°(18mm)	230-235°(760mm)	75.5%	39

Table 4. Data of the substituted phenylethylamines

Compound	Boiling point	Literature boiling point	Yield	Literature
β-(p-fluorophenyl)ethylamine (5b)	92-93° (17mm)	99-100° (24mm)	80%	41
β-(m-fluorophenyl)ethylamine (5c)	85-87° (17mm)	87° (15mm)	59.3%	42
β-(1-naphthyl)ethylamine (5a)	103-109° (0.2mm)	182-183° (18mm)	56%	43

β-(2-Thienyl)ethylamine (**5d**) was prepared by condensation of $MeNO_2$ with 2-thenaldehyde[37] followed by LAH reduction of the resulting β-(2-thienyl)nitroethylene.[32] $MeNO_2$ (20 ml, 0.33 mole) and 2-thenaldehyde (37 g, 0.33 mole) afforded 26 g of β-(2-thienyl)nitroethylene (51% yield) as long and yellow needles, m.p. 77–78° (lit.[37] 78–80°). Reduction of β-(2-thienyl)nitroethylene (26 g, 0.167 mole) with 19 g LAH gave 12.5 g of **5d** (60% yield) as a colourless liquid, 102–105° (25 mm) (lit.[32] 76–78° (7 mm)). NMR ($CDCl_3$): δ 7.0–7.6 (m, 3 H, ArH), 3.0 (narrow m, 4 H, $-CH_2CH_2$), 1.3 (s, 2 H, NH_2).

Methyl and 2-hydroxylethyl esters of 2-(β-carboxylethyl)cyclohexanone ethylene ketal **10a** *and* **10b**. BF_3–etherate (36 g) was added dropwise at 15–20°, to a stirred mixture of 2-(β-carbomethoxyethyl)cyclohexanone[22] (11.04 g, 0.06 mole) and, ethylene glycol (186 g) and CH_2Cl_2 (200 ml). Stirring was continued at room temp. for 5 days. The CH_2Cl_2 layer was separated, washed with water and NaOHaq dried ($MgSO_4$) and evaporated to yield a mixture of **10a** and **10b** which were isolated by fractionation. **10a**, (6.65 g, 49% yield), b.p. 110–130° (0.5 mm). NMR ($CDCl_3$): δ 3.90 (s, 4 H, ethylene ketal), 3.65 (s, 3 H, OCH_3), 2.30 (m, 2 H, CH_2–C=O), 1.50 (m, 11 H). IR (neat): 1737 (ester, C=O), 1090, 948, 925 (ethylene ketal). **10b**, (5.56 g, 36.8% yield), b.p. 130–160° (0.5 mm). (Found: C, 63.4; H, 8.9. Calc. for $C_{12}H_{20}O_4$: C, 63.1; H, 8.7%). NMR ($CDCl_3$): δ 3.90 (s, 4 H, ethylene ketal), 3.9 (m, 4 H, OCH_2–CH_2–OH), 2.98 (s, 1 H, OH, disappear in D_2O), 2.3 (m, 2 H, CH_2–C=O), 1.5 (m, 11 H). IR (neat): 3470 (OH), 1735 (C=O), 1088, 948, 923 cm⁻¹ (ethylene ketal). (Found: C, 60.18; H, 8.62. Calc. for $C_{11}H_{22}O_4$: C, 60.46; H, 8.53%).

2-(β-Carboxyethyl)cyclohexanone ethylene ketal (**11**). A soln of **10a**† (6.5 g), KOH (4 g) MeOH (110 mo) and water (6 ml) was refluxed for 2 hr. The MeOH was evaporated and mixture was diluted with water. The traces of unhydrolyzed ester were removed by extraction with ether. Chloroform was added and the mixture cooled below 0° with an ice-salt mixture acidified to a pH 1 (5N H_2SO_4). The phases were separated, the organic layer was wahed with water, dried ($MgSO_4$) and evaporated to afford **11** (5.86 g, 96.3% yield) as an oil which crystallized on standing. m.p. 59.5–60° (from cyclohexane). Mass spectrum (70 eV) *m/e* = 214 (M^+). NMR ($CDCl_3$); δ 9.187 (m, 1 H, COOH), 3.936 (s, 4 H ethylene ketal), 2.4 (m, 2H, CH_2–COO), 1.7 (m, 11 H). IR (neat): 3400–2900 (C–H , carboxylic OH), 1708 (carboxylic C=O), 1088, 945, 924 cm^{-1} (ethylene ketal). (Found: C, 61.72; H. 8.17. Calc. for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41%).

1,2,3,4,4a,5,6,7,9,10 - *Decahydro - 7 - oxoisoquinolo*[1,2-j]*quinoline* (**14a**). Compound **12** was prepared by the same procedure described for **4** using **11** (3.83 g, 0.0178 mole) and oxalyl chloride (13 ml). The crude **12** was dissolved in dry CH_2Cl_2 and added dropwise at −25 to −12° to **5f** (4.3 g, 0.0356 mole) in the same solvent (50 ml). The mixture was allowed to warm up to room temp., left overnight and filtered. The filtrate was washed with water, Na_2CO_3aq and again with water, dried ($MgSO_4$) and evaporated. The residual crude **13a** was applied in the next step without purification. [IR: 3300 (NH), 1640 (amide (C=O)), 1087, 950, 924 (ketal) NMR ($CDCl_3$): δ 3.88 (4 H, s, OCH_2CH_2O), 6.0 (1 H, m, NH–C=O)]. A soln of crude **13a** (4.3 g) in PPA (201 g) was stirred at 120° for 12 hr. After cooling the viscous mixture was poured into ice and water. Extraction with $CHCl_3$ and work-up in the usual manner afforded the expected lactam. Purification was accomplished by TLC on silica-gel (eluent: 0.6% MeOH in $CHCl_3$, every plate was eluted and dried 4 times) to give **14a** (1.16 g, 25.3% yield from **11**) as a solid, m.p. 111–112° (from cyclohexane). Mass spectrum (70 eV) *m/e* = 255 (M^+). NMR ($CDCl_3$): δ 7.137 (m, 4 H, ArH), 4.9 (m, 1 H, *equatorial* C_{10}–H), 3.749 (m, 1 H, *axial* C_{11}–H), 3.2 (m, 2 H, CH_2Ar), 2.58 (m, 2 H, CH_2C=O), 1.6 (m, 11 H). IR (Nujol): 1635 cm⁻¹ (C=O). (Found: C, 80.21; H, 8.43; N, 5.17. Calc. for $C_{17}H_{21}NO$: C, 80.00; H, 8.23; N, 5.5%).

1,2,3,4,4a,5,6,7,9,10 - *Decahydroisoquinolo*[1,2-j]*quinoline* (**2a**). Reduction of **14a** (0.780 g, 0.00306 mole) with LAH (1 g) essentially as described for **1a** gave crude **2a**. Extraction with dil HClaq basification with conc NaOHaq and extraction with CH_2Cl_2 afforded **2a**, (0.500 g, 68% yield) as an oil. IR (neat): 2660, 2680, 2720, 2750 (very small). The picrate, yellow crystals, m.p. 191–192° (from EtOH). Mass spectrum (70 eV) *m/e* = 241 (free amine). NMR ($CDCl_3$): δ 8.792 (s, 2 H, picric acid ArH), 7.3 (m, 4 H, ArH), 3.95 (m, 1 H, CH–N⁺), 3.55 (m, 2 H, CH_2N^+), 3.2 (m, 3 H, CHN^+, CH_2–Ar), 1.8–2.8 (m, 13 H). (Found: C, 58.88; H, 5.76; N, 11.53. Calc. for $C_{23}H_{28}N_4O_7$: C, 58.72; H, 5.53; N, 11.91%).

Mixture of methiodides of **2a**. **2a** (0.280 g) was quaternized with MeI (2 g) in the manner described for the methiodides of **1a**, and

†**11** was obtained also through hydrolysis of **10b** by the same procedure which is described below.

afforded a mixture of colourless methiodides of **2a** (0.400 g, 90% yield), m.p. 232–4°. The ratio of *cis* A/B *trans* B/C to *cis* A/B *cis* B/C was 20:3. Mass spectrum (70 eV) *m/e* (rel. intensity) 255 (0.2) (M^+–HI, Hofmann elimination product,[34,35] 241 (19.5) (M^+–CH_3I.[34,35] NMR ($CDCl_3$): δ 7.624 (m, 1 H, ArH), 7.284 (m, 3 H, ArH), 4.46–3.66 (m, 4 H, CH_2–N^+–CH_2), 3.62–3.06 (m, 2 H, CH_2–Ar), 3.281 (s, 9/23 H, N^+–CH_3, *cis* B/C isomer), 2.859 (s, 60/23 H, N^+–CH_3, *trans* B/C isomer), 2.75–1.419 (m, 13 H). (Found: C, 56.61; H, 7.00; N, 3.21; I, 32.80. Calc. for $C_{18}H_{26}NI$: C, 56.39; H, 6.78; N, 3.65; I, 33.15%).

11 - *Fluoro* - 1,2,3,4,4a,5,6,7,9,10 - *decahydro* - 7 - *oxoisoquinolo*[1,2-j]*quinoline* (**14b**). Crude acyl halide **12** (from 14.6 g, 0.0682 mole acid **11** and 60 ml oxalyl chloride) was converted into amide **13b** by treatment with an equimolar mixture of **5e** and Et_3N (9.73 g, 0.7 mole and 7.07 g, 0.7 mole respectively) in the manner described for **13a**. Crude **13b** (9.3 g) was cyclized with PPA (386 g) by heating at 132° for 12 hr and gave colourless lactam **14b** (0.95 g, 11% yield from the acid **11**), m.p. 125–126° (from cyclohexane). Mass spectrum (70 eV) *m/e* = 273 (M^+). ^{1}H NMR ($CDCl_3$): δ 6.96 (m, 3 H, ArH), 4.63 (m, 1 H, *equatorial* C_{11}–H), 2.2–3.3 (m, 5 H, $ArCH_2$, *axial* C_{11}–H, CH_2–C=O), 1.0–1.85 (m, 11 H). ^{19}F NMR ($CDCl_3$, int. $CFCl_3$): δ 114.36 (m). IR (Nujol): 1635 cm^{-1} (C=O). (Found: C, 74.65; H, 7.09; N, 4.78; F, 7.02. Calc. for $C_{17}H_{20}NOF$: C, 74.72; H, 7.32; N, 5.12; F, 6.96%).

11 - *Fluoro* - 1,2,3,4,4a,5,6,7,9,10 - *decahydroisoquinolo*[1,2-j]*quinoline* (**2b**). Reduction of **14b** (0.940 g, 0.00345 ml) with LAH (1.33 g) by the same procedure described for **1a**, afforded **2b** (0.880 g, 98.5% yield) as an oil. Mass spectrum (70 eV) *m/e* 259 (M^+). NMR ($CDCl_3$): δ 6.986 (m, 3 H, ArH), 2.4–3.8 (m, 6 H, CH_2–N^+–CH_2Ar), 1.05–2.4 (m, 13 H). IR (neat): 2720, 2670 cm^{-1} (very small Bohlmann's peaks). The picrate, yellow crystals, m.p. 196–7° (from abs EtOH). Mass spectrum (70 eV) *m/e* 259 (free amine). (Found: C, 56.53; H, 5.01; N, 11.17; F, 3.86. Calc. for $C_{23}H_{25}N_4O_7F$: C, 56.55; H, 5.12; N, 11.47; F, 3.89%).

1,2,3,4,4a,5,6,7,9,10 - *Decahydro* - 12,13 - *dimethoxyisoquinolo*[1,2-j]*quinoline* (**2c**). Crude **12** (from 11.8 g, 0.055 mole of the acid **11** and 50 ml oxalyl chloride) was treated with **5g** (20 g, 0.11 mole) to yield **13c** (same procedure as **13a**). A stirred mixture of **13c** (4.1 g) in PPA (125 g) was warmed at 100° for 1.5 hr affording the solid lactam **14c** by the work-up described for **14a** (1 g, 29.3% yield from the acid **11**). Mass spectrum (70 eV) *m/e* 315 (M^+). NMR ($CDCl_3$) δ 6.671 (s, 1 H, C_{13}–H), 6.551 (s, 1 H, C_{16}–H), 4.81 (m, 1 H, *equatorial* C_{11}–H), 3.846 (s, 3 H, O–CH_3), 3.826 (s, 3 H, O–CH_3), 3.8 (m, 1 H, *axial* C_{11}–H), 3.3 (m, 2 H, CH_2–Ar), 2.5 (m, 2 H, CH_2), 3.826 (s, 3 H, O–CH_3), 3.8 (m, 1 H, *axial* C_{11}–H), 3.3 (m, 2 H, CH_2–Ar), 2.5 (m, 2 H, CH_2–C=O), 1.2–2.4 (m, 11 H). IR (Nujol): 1635 cm^{-1} (C=O). Reduction of **14c** (0.540 g, 0.0017 mole) with LAH (1.07 g) afforded the amine **2c** (0.460 g, 88.8% yield) as an oil. Mass spectrum (70 eV) *m/e* 301 (M^+). NMR ($CDCl_3$): δ 6.751 (s, 1 H, C_{13}–H), 6.545 (s, 1 H, C_{16}–H), 3.847 (s, 3 H, O–CH_3), 3.826 (s, 3 H, O–CH_3), 3.55 (m, 2 H, N–CH_2), 2.86 (m, 4 H, CH_2–N, CH_2–Ar), 1.1–2.4 (m, 13 H). IR (neat): 2730, 2650 cm^{-1} (very small Bohlmann's peaks). The picrate, yellow crystals, m.p. 200–201° (from abs EtOH). Mass spectrum (70 eV) *m/e* 301 (free amine). (Found: C, 56.50; H, 5.55; N, 10.31. Calc. for $C_{25}H_{30}N_4O_9$: C, 56.60; H, 5.66; N, 10.56%).

Mixture of the **2c** *methiodides.* **2c** (0.300 g, 0.001 mole) was quaternized with MeI (2 ml) in the manner described for the methiodides of **1a**, and afforded a mixture of colourless methiodides of **2c** (0.435 g, quantitative yield), m.p. 268°. The ratio of *cis* A/B, *trans* B/C to *cis* A/B, *cis* A/B was 21:12. Mass spectrum (70 eV) *m/e* (rel. intensity) 315 (1.9) (M^+–HI Hofman elimination product,[34,35] 301 (16.3) (M^+–CH_3I[34,35]). NMR ($CDCl_3$): δ 7.198 (s, 20/55 H, C_{13}–H, *cis* B/C isomer), 7.118 (s, 35/55 H, C_{13}–H, *trans* B/C isomer), 6.767 (s, 35/55 H, C_{16}–H, *trans* B/C isomer), 6.687 (s, 20/55 H, C_{16}–H, *cis* B/C isomer), 4.48–3.70 (m, 4 H, CH_2N^+–CH_2), 3.907 (s, 3 H, OCH_3), 3.887 (s, 3 H, OCH_3), 3.567–3.06 (m, 2 H, CH_2Ar), 3.263 (s, 60/55 H, CH_3N^+, *cis* B/C isomer), 2.859 (s, 105/55 H, CH_3–N^+, *trans* B/C isomer), 2.65–1.36 (m, 13 H).

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