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STUDIES IN THE CHEMISTRY OF ERYTHRINA ALKALOIDE DERIVATIVES—II

SYNTHESIS AND STEREOCHEMISTRY OF DECAHYDRO-3-METHYL-6H-PYRIDO[2,1-i]INDOLE

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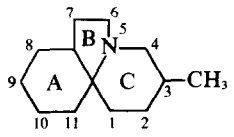
Abstract—1,2,3,4,7,7a,8,9,10,11-Decahydro-3-methyl-6H-pyrido[2,1-i]indole was prepared as an example of an erythrinane derivative lacking the aromatic moiety. The stereochemical structure of this compound and its 6-oxo derivative were found to be predominantly *cis* A/B, *trans* B/C, axial CH_3 and *cis* A/B, axial CH_3, respectively.

In the course of our study of the structure-activity correlations in alkaloids we synthesized the title compound (**1**) as an example of the parent compound lacking an aromatic moiety.



1

The synthesis of **1** is outlined in Scheme 1.

Treatment of N - (1 - cyclohexenyl)piperidine with ethyl bromoacetate in methanol[1] afforded a mixture of the esters **3a** and **3b** (**3b** results from **3a** by transesterification). Ketalization of the esters followed by hydrolysis gave 2 - carboxymethylcyclohexanone ethylene ketal (**4**).[2,3] The temperature sensitive (2 - oxocyclohexyl)acetyl chloride ethylene ketal (**5**) (from **4** and oxalyl chloride, below 30°) was converted into amide **7** with 2 - methyl - 3 - butenylamine (**6**). The amine **6** was obtained from phthalimide and methacrolein by a process developed previously in our laboratory.[4] On warming **7** with PPA a mixture of 1,4,7,7a,8,9,10,11 - octahydro - and 1,2,7,7a,8,9,10,11 - octahydro - 3 - methyl - 6H - pyrido [2,1 - i]indole (**8** and **9** respectively) resulted. The structures of **8** and **9** were determined from their NMR spectra; compound **8** has a narrow signal at 5.66 ppm characteristic of vinylic protons while the proton of **9** shows up at 6.53 ppm, a typical vinylic enamide hydrogen absorption. Furthermore, in both compounds the Me groups show singlets at 1.63 ppm (characteristic of vinylic Me groups). Since **8** isomerized to **9** on silica gel, it was difficult to separate the two isomers by TLC. Therefore, the mixture of the unsaturated compounds was subjected to catalytic hydrogenation (with Adams' catalyst) to yield the saturated lactam **10**, which was purified by preparative TLC on silical-gel. The characteristic peak of **10** at 1678 cm^{-1} in the IR which is typical of all the examined erythrinone derivatives[2,3,5] indicates the presence of a 5-membered lactam structure. The NMR spectrum of **10** reveals the disappearance of the singlet at $\delta = 1.63$ ppm that was present in the starting materials (characteristic of the vinylic Me groups in both isomers). Instead, a typical Me doublet ($\delta = 0.9645$ ppm, $J = 7.1$ Hz) is formed indicating complete reduction of both double bonds. Reduction of **10** with LAH gave decahydro - 3 - methyl - 6H - pyrido[2,1 - i]indole (**1**).

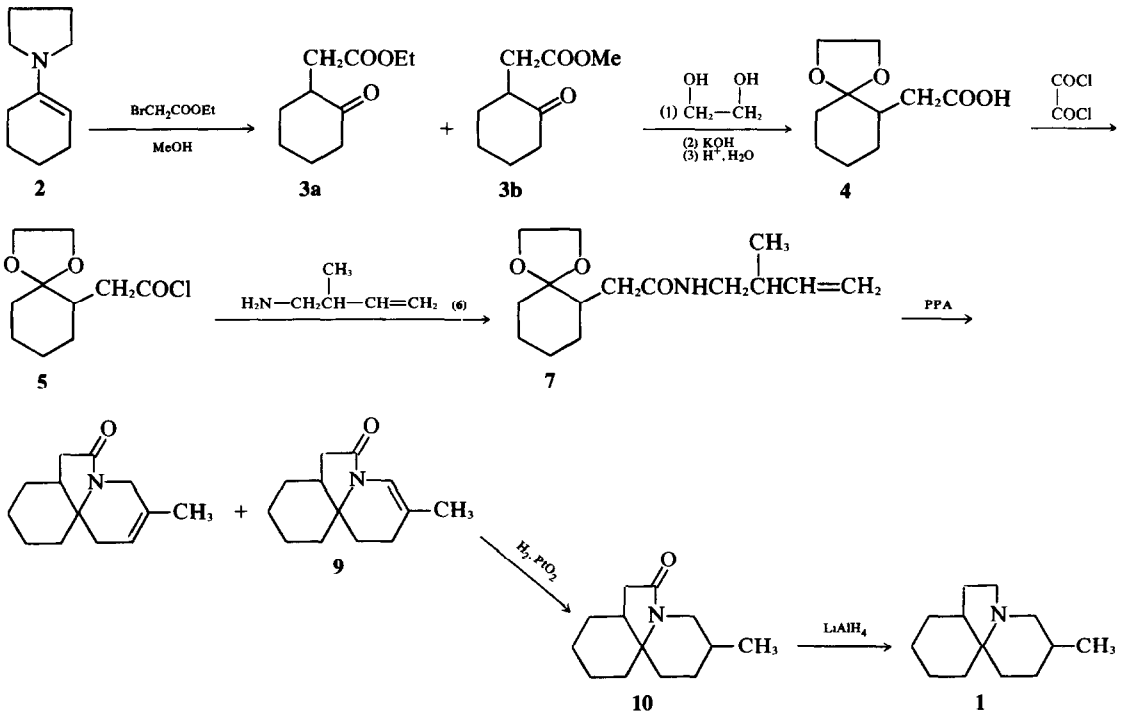
Structure determination of **1**. Four isomeric structures may be written for compound **1**:

(1) *trans*-fused A/B, *cis*-fused B/C, axial-CH_3 (α isomer)
(2) *trans*-fused A/B, *cis*-fused B/C, equatorial-CH_3 (β isomer)
(3) *cis*-fused A/B, *cis*-fused B/C, axial-CH_3 (γ isomer)
(4) *cis*-fused A/B, *cis*-fused B/C, equatorial-CH_3 (δ isomer)

The existence of a structure *trans*-fused A/B, *trans*-fused B/C must be excluded, since diaxial fusion is improbably in small ring systems. The presence of the *trans*-ring fusion implies a rigid molecular structure for the α and β isomers; therefore, quaternization of each of the isomers with methyl iodide should yield only one methiodide. Each quaternary salt is expected to have a single N-Me singlet in the NMR spectrum. When A and B rings are *cis*-fused, B/C ring-fusion can be either *cis* or *trans*. However, because of the ease of inversion at the bridgethread nitrogen, the *cis* B/C and *trans* B/C fused isomers are mutually interconvertible as in the parent compound, indolizidine.[6] In addition, the *cis* A/B, *cis* B/C structure, being flexible, can flip over into a second *cis* form in analogy to *cis*-decaline.[7] It thus follows that those isomers in which ring A and ring B are *cis*-fused may have the following three interchangeable conformations, i.e. for the γ isomer:

(i) *cis* (1) fused A/B, *trans* fused B/C, axial-Me
⇅ N inversion
(ii) *cis* (1) fused A/B, *cis* (1, Neq) fused B/C, axial-Me
⇅ Flipping
(iii) *cis* (2) fused A/B, *cis* (2, Nax) fused B/C, equatorial-Me

†Deceased on 5 April 1975.



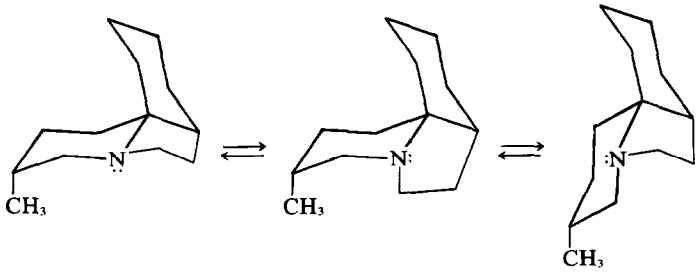
Scheme 1.

and for the δ isomer:

(i) *cis* (1) fused A/B, *trans* fused B/C, equatorial-Me
⇃↾ N̈ inversion
(ii) *cis* (1) fused A/B, *cis* (1, N̈eq) fused B/C, equatorial-Me
⇃↾ Flipping
(iii) *cis* (2) fused A/B, *cis* (2, N̈ax) fused B/C, axial-Me.

Upon quaternization with methyl iodide each of the γ and δ isomers is expected to form two diastereoisomeric methiodides,[8-10] one, *cis*-fused A/B, *cis*-fused B/C and the other *cis*-fused A/B, *trans*-fused B/C isomer. Indeed, the reaction of **1** and methyl iodide gave a mixture of two methiodides identified by two N–C$\underline{H}_3$ singlets in the NMR spectrum ($\delta_1 = 3.25$, $\delta_2 = 3.32$ ppm). Compound **1** must, therefore, have *cis*-fused A/B structure (vis γ or δ). It shows a Bohlmann band[11] in the IR (ν_{max} 2790 cm^{-1}) which is typical for *trans*-fused indolizidine derivatives[11] and indicates that rings B and C in **1** are predominantly *trans*-fused. The conformation of the C-3 Me group is assigned from the NMR pattern of the axial C-4 proton δ 2.10 (1H, dd, $J_{gem} = 11.4$ Hz, $J_{H_4,H_3} = 2.8$ Hz). The axial C-4 proton in **1** is expected to couple more strongly with an axial C-3 proton than with an equatorial one (cf. coupling constants in piperidine derivatives: $J_{ax,ax} = 10$–12 Hz, $J_{ax,eq} = 1.9$–3.0 Hz[13]). To prevent the blotting out of the signals of C-4 protons by those of C-6 protons (also adjacent to the N atom) the dideuterated analogue 6-d_2 of **1** was prepared by LAD reduction of **10**. The vicinal coupling constant of $J_{H_4,H_3} = 2.8$ Hz fits within the frequency range of $J_{ax,eq}$. Consequently, the C-3 proton in **1** must be equatorial and the C-3 Me group—axial. Double resonance experiments confirmed the assignment of the C-4 methylene protons; irradiation at 2.64 ppm changed the signal pattern at $\delta = 2.10$ ppm from doublet of doublet into a single narrow doublet. (The higher upfield signal at $\delta = 2.10$ ppm corresponds to the axial α proton, and the lower upfield signal at $\delta = 2.64$ ppm to the equatorial α proton[14]). It can be thus concluded that **1** has the structure of the γ isomer, and it exists mainly as the *cis* A/B, *trans* B/C, axial-CH_3 conformer (i) (cf. Fig. 1).

Structure determination of **10**. Considerations similar to those given for **1** indicate that the C-3 Me in **10** is axial; δ 2.858 (1 H, dd, $J_{gem} = 13$ Hz, $J_{H_4,H_3} = 3.0$ Hz), (the theoretical values reported for $J_{ax,eq}$ are 1.9–3.0 Hz, and for



conformer (ii) conformer (iii)

Fig. 1.

$J_{ax,ax}$ = 10–12 Hz[13]). The higher upfield signal δ = 2.858 ppm corresponds to the axial C-4 proton and the lower upfield signal, δ = 3.699, to the equatorial one.[15] It is therefore obvious that the lactam **10** has the same structure as the γ isomer of **1**, however, owing to the presence of the C–N function with considerable π character[16] the number of conformers is limited to two, viz:

(i) *cis* (1) fused A/B (C_{11} axial to ring C), axial-Me
⇅ Flipping
(ii) *cis* (2) fused A/B (C_{11} equatorial to ring C), equatorial-Me

since the C-3 Me group has been proven to be axial, lactam **10** exists predominantly in (i) conformation (see Fig. 2).

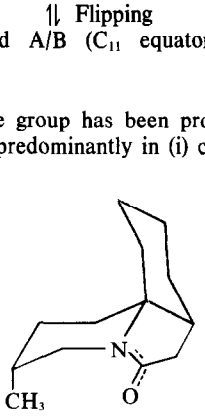


Fig. 2.

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 - *Carbethoxymethylcyclohexanone* (**3a**) *and* 2 - *carbometoxymethylcyctohexanone* (**3b**). Cyclohexanone (147 g, 1.5 mole) and pyrrolidine (174.2 g, 2.46 mole) was converted by the procedure of Szmuszkovicz[1] to N - (1 - cyclohexenyl)pyrrolidine (192.5 g, 85% yield), and subsequently reacted with ethyl bromoacetate in MeOH to give a mixture of **3a** and **3b**. The respective Et and Me groups show up in the NMR spectrum of the mixture: δ 4.15 (q, J = 7 Hz, 2 H, CH_2–O), 1.27 (t, J = 7 Hz, 3 H, CH_3CH_2–) and δ 3.69 (s, 3 H, OCH_3). IR (net) 1722 (ketone C=O), 1745 (ester C=O). This mixture was hydrolyzed without being separated.

Ethylene ketal of N - (2 - *methyl* - 3 - *butenyl*)(2 - *oxocyclohexyl*)*acetamide* (**7**). A soln of 2 - carboxymethylcyclohexanone ethylene ketal[2,3] (13.7 g, 0.0685 mole) in dry benzene (50 ml) was added dropwise, at room temp to a stirred solution of oxalyl chloride (60 ml) in dry benzene (100 ml). After standing overnight at room temp the solvent was evaporated below 30°. The last traces of oxalyl chloride were removed by several additions of benzene followed, each time, by evaporation. The residue, 2-oxocyclohexylacetyl chloride ethylene ketal (**5**), a colorless, temp sensitive liquid, was used in the next step without further purification, IR(neat): 1750 and 1815 cm^{-1} (acyl halide C=O), NMR δ 3.8 (s, 4 H, OCH_2CH_2O) 2.1–2.5 (m, 2 H, CH_2–C=O), 1.1–2.1 (m, 11 H). A solution of the whole bulk of **5** in dry methylene chloride (50 ml) was added dropwise at −30 to −10° to a stirred and cooled mixture of **6**[4] (5.85 g, 0.0685 mole) and triethylamine (6.9, 0.0685 mole) in 100 ml of the same solvent. The mixture was allowed to warm slowly to room temp and left overnight. The mixture was filtered and the filtrate washed successively with water, Na_2CO_3 aq and water, dried ($MgSO_4$) and evaporated to yield 13 g (70.9% yield) of **7** as a colorless crystals, m.p. 65° (from ether–petroleum ether 40–60°).

Mass spectrum (70 eV) *m/e* 267 (M^+). NMR ($CDCl_3$): δ 5.86 (m, 1 H, N<u>H</u>C(=O)), 5.8 (m, 1 H, C<u>H</u>=CH_2), 5.2 (narrow m, 1 H, CH=C(<u>H</u>)H) *trans* to H), 5.0 (m, 1 H, CH=C(<u>H</u>)H) *cis* to H), 4.0 (s, 4 H, ethylene ketal), 3.3 (m, 2 H, CH_2N), 1.3–2.8 (m, 10 H), 1.1 (d, J = 7 Hz, 3 H, C–CH_3). IR (Nujol): 3340 (NH), 1637 cm^{-1} (amide C=O). (Found: C, 67.30; H, 9.19; N, 5.19. Calc. for $C_{15}H_{25}O_3N$: C, 67.41; H, 9.36; N, 5.24%).

1,2,3,4,7,7a,8,9,10,11 - *Decahydro* - 3 - *methyl* - 6 - *oxo* - 6<u>H</u> - *pyrido*[2,1 - i]*indole* (**10**). A stirred mixture of crude **7** (6.2 g) and PPA (155 g) was heated at 100° for 16 hr. After cooling, the mixture was poured into iced water and extracted with methylene chloride. The organic layer was washed successively with water, $NaHCO_3$ aq and water, dried ($MgSO_4$) and evaporated to yield a ≈ 1:1 mixture of **8** and **9**.

NMR δ 6.53 (narrow m, C(=O)N–C<u>H</u>=C of **9**), 5.66 (narrow m, C=C<u>H</u> in **8**), 1.63 (s, CH_3–C=C in both **8** and **9**).

The crude mixture of **8** and **9** was used without separation. A soln of this mixture in abs EtOH (50 ml) was hydrogenated at room temp, over Adams' catalyst (initial press 45 psi, 18 hr). After removal of the catalyst the solvent was evaporated. The residue was purified by preparative TLC (Absorbent: Merck silica-gel, eluent: 0.5–0.6% MeOH in chloroform, each plate eluated twice) to afford (1.87 g, 38.9% yield) as an oil which crystallized on standing; platelets, m.p. 77–78° (from petroleum–ether 40–60°).

Mass spectrum (70 eV) *m/e* 207 (M^+). NMR ($CDCl_3$): δ 3.692 (dd, J_{gem} = 13 Hz, J_{vic} = 2 Hz, 1 H, *equatorial* C_4–H), 2.863 (dd, J_{gem} = 13 Hz, J_{vic} = 3 Hz, 1 H, *axial* C_4–H), 2.5–1.1 (m, 16 H), 0.964 (d, J = 7.1 Hz, 3 H, CH_3). IR (Nujol): 1678 cm^{-1} (C=O). (Found: C, 75.15; H, 10.09; N, 6.83. Calc. for $C_{13}H_{21}NO$: C, 75.36; H, 10.14; N, 6.76%).

1,2,3,4,7,7a,8,9,10,11 - *Decahydro* - 3 - *methyl* - 6H - *pyrido*[2,1 - i]*indole* (**1**). To a stirred suspension of LAH (2.79 g) in dry THF (50 ml) a soln of **10** (1.87 g, 0.009 mole) in 30 ml of the same solvent was added dropwise at room temp. After refluxing for 4 hr, the mixture was left overnight at room temp and subsequently treated with cold water (2.8 ml), 15% NaOH aq (2.8 ml) and again cold water (9 ml).[17] The mixture was filtered and the amorphous solid extracted several times with boiling THF. The combined organic soln was dried ($MgSO_4$) and evaporated to afford **1** (1.03 g, 55% yield) as a yellowish oil with a typical odor of an amine. Mass spectrum (70 eV) *m/e* 193 (M^+). NMR ($CDCl_3$): δ 3.0 (m, 1 H, N–CH_2), 2.62 (m, 2 H, N–CH_2), 2.24 (m, 1 H, N–C<u>H</u>$_2$), 2.1–1.1 (m, 16 H), 0.922 (d, J = 6.7 Hz, 3 H, CH_3). IR (neat): 2790 cm^{-1} (a Bohlmann peak). The amine was converted into the picrate, yellow crystals, m.p. 146–146.5 (from ethanol). (Found: C, 53.72; H, 6.00; N, 13.17. Calc. for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.16; N, 13.26%).

N - *Methyl* - 3 - *methyldecahydro* - 6<u>H</u> - *pyrido*[2,1 - i]*indolinium iodide* (**11**). A mixture of **1** (0.08 g) and MeI (2 ml) in acetonitrile (10 ml) was refluxed for 12 hr. Evaporation of the solvent and excess MeI left semisolid **11** which was purified by trituration with acetone, (A.R. grade), to give colorless crystals, m.p. 248°. Mass spectrum (70 eV) *m/e* 207 (M^+–HI, Hofmann elimination product[18,19]), 193 (M^+–CH_3I[18,19]). NMR ($CDCl_3$): δ 3.4–4.4 (m, 3 H, CH_2N^+–), 3.326 (s, 60/23H, N^+–CH_3, *cis* B/C isomer), 3.256 (s, 9/23 H, N^+–CH_3, *trans* B/C isomer), 2.8–3.25 (m, 1 H, N^+–CH_2–), 1.2–3.7 (m, 16 H), 1.057 (d, J = 6.4 Hz, 3 H, CH_3–C). (Found: C, 50.11; H, 7.71; N, 4.47; I, 38.00. Calc. for $C_{14}H_{26}NI$: C, 50.14; H, 7.76; N, 4.17; I, 37.91%).

6,6 - *Dideuterio* - 1,2,3,4,7,7a,8,9,10,11 - *decahydro* - 3 - *methyl* - 6<u>H</u> - *pyrido*[2,1 - i]*indole* (**1a**), was prepared in the same manner as **1**. The lactam **10** (0.130 g) was treated with LAD (0.508 g) in dry THF to give 0.120 g of **1a** (quantitative yield). Mass spectrum (70 eV) *m/e* 195 (M^+), IR (neat), 2055, 2170 cm^{-1} (C–D).

REFERENCES

[1]J. Szmuszkovicz, *Adv. Org. Chem.* **4**, 1 (1964).
[2]A. Mondon, *Chem. Ber.* **92**, 1461 (1959).
[3]V. Bockelheide, M. Müller, J. J. Jack, T. T. Grossnickle and G. Chang, *J. Am. Chem. Soc.* **81**, 3955 (1959).
[4]E. D. Bergmann and Y. Migron, *Org. Prep. Proced. Int.* **8**, 75 (1976).

[5]M. Müller, T. T. Grossnickle and V. Boekelheide, *J. Am. Chem. Soc.* **92**, 2959 (1959).
[6]H. S. Aaron and C. P. Ferguson, *Tetrahedron Letters* 6191 (1968).
[7]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, p. 231. Interscience, New York (1965).
[8]T. Moynehan, K. Schofield, R. Jones and A. J. Katrizky, *J. Chem. Soc.* 2637 (1962).
[9]W. Meyer and N. J. Sapianchiay, *J. Am. Chem. Soc.* **86**, 3343 (1964).
[10]B. Lüning and C. Lundin, *Acta Chem. Scand.* **21**, 2136 (1967).
[11]A. E. Theobald and R. G. Lingard, *Spectrochim. Acta* **24A**, 1245 (1967).
[12]F. Bohlmann, *Angew. Chem.* **69**, 541 (1957); *Chem. Ber.* **91**, 2157 (1958).
[13]H. Booth, *Progress in Nuclear Magnetic Resonance Spectroscopy* (Edited by J. W. Emsley), p. 338. Pergamon Press, Oxford (1969).
[14]H. Hamlow, S. Okuda and N. Nakagawa, *Tetrahedron Letters* 2553 (1964).
[15]F. Bohlmann and D. Schumann, *Ibid.* 2435 (1965).
[16a]J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Vol. 1, p. 553. Pergamon Press, Oxford (1965); [b]R. M. Moriarty, *J. Org. Chem.* **29**, 2748 (1964); [c]W. A. Szarek, S. Wolfe and J. K. N. Jones, *Tetrahedron Letters* 2743 (1964).
[17]V. M. Mičovič and M. L. J. Mihailovič, *J. Org. Chem.* **18**, 1190 (1953).
[18]M. Hesse, W. Vetter and H. Schmid, *Helv. Chem. Acta* **48**, 674 (1965).
[19]M. Hesse and H. Schmid, *Liebigs Ann.* **698**, 85 (1966).