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THE FORMATION AND INTRAMOLECULAR ACYLATION OF A 1,2-DIHYDRO-β-CARBOLINE DERIVATIVE; A MODEL SEQUENCE FOR THE TOTAL SYNTHESIS OF FUMITREMORGINS.

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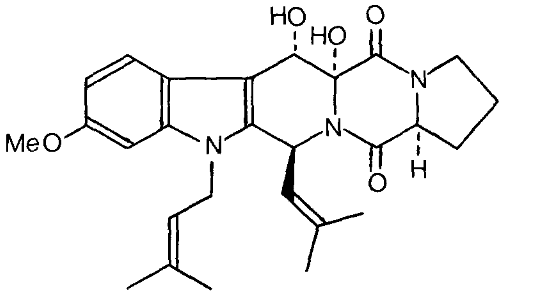
SUMMARY. The racemic 2-tosyltetrahydro-β-carbolines 4c and 4d each gave the β-carboline 5 on treatment with sodium methoxide; under similar conditions 7c furnished the pentacycle 2c.

The potent mycotoxin fumitremorgin B 1 is an attractive candidate for total synthesis. One possible approach to this goal is the regiospecific oxidation of the unsaturated precursor 2a which can be regarded as a modified 1,2-dihydro-β-carboline. Oikawa *et al*. reported briefly the preparation of model compound 2b, in poor yield, by the oxidation of the diastereoisomeric mixture 3a + 3b with DDQ.[1] We show below that 3-carboxy-β-carboline derivatives can be prepared in high yield by the base-catalysed elimination of toluene-*p*-sulphinic acid from 2-tosyltetrahydro-β-carboline-3-carboxylates in air. We describe also the preparation of model compound 3c of defined stereochemistry and an efficient synthesis of the dehydro-derivative 2c by the intramolecular acylation of an intermediate 1,2-dihydro-β-carboline.



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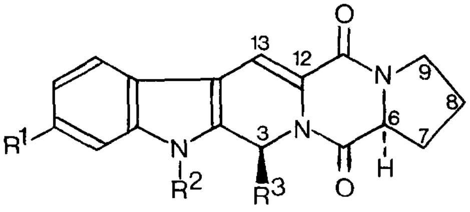
L-Tryptophan methyl ester and 3-methylbutanal reacted in refluxing benzene, in the presence of benzoic acid, to furnish the *cis*-tetrahydro-β-carboline 4a, m.p. 147°, and the *trans*-isomer 4b, m.p. 118°. These products were shown to be completely racemic by ^{1}H-n.m.r. in the presence of the chiral shift reagent tris(3-heptafluorobutyryl-*d*-camphorato)europium(III). The *cis* compound reacted with toluene-*p*-sulphonyl chloride in pyridine to give the *N*-tosyl derivative 4c, m.p. 157°, which on treatment with sodium methoxide in refluxing methanol furnished the β-carboline 5, m.p. 146°, δ($CDCl_3$) 8.86 (one-proton singlet) for H-4.[2] The *trans* compound 4d similarly furnished β-carboline

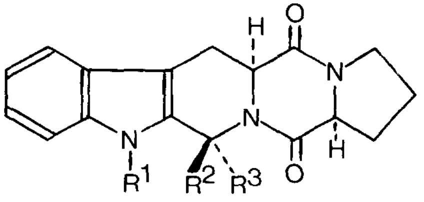
5 in quantitative yield. This smooth two-step conversion of a tetrahydro-β-carboline-3-carboxylate ester to the parent heterocycle provides a useful alternative to existing methods.[3] The intermediate 1,2-dihydro-β-carboline 6 was observed by ^{1}H-n.m.r. (δ 6.7, one-proton singlet for H-4) when the elimination of toluene-p-sulphinic acid was conducted under an atmosphere of nitrogen.[4]

For the synthesis of analogues of the fumitremorgins it was essential that racemisation of intermediates should be avoided. Massiot and Mulamba have reported that imines that are derived from aldehydes by condensation with L-tryptophanamide undergo Pictet-Spengler cyclisation at room temperature in dichloromethane, catalysed by trifluoroacetic acid, to furnish solely the cis-tetrahydro-β-carboline without detectable racemisation.[5] In order to take advantage of this observation, we prepared L-tryptophyl-L-proline methyl ester, m.p. 138°, $[\alpha]_D^{25}$ -5.6°, from the known hydrobromide salt[6] by careful treatment of the latter with alkali. The dipeptide ester was allowed to condense with 3-methylbutanal and the crude imine that was formed was subjected to cyclisation under Massiot's conditions.[5] The non-crystalline crude reaction product consisted mainly of the cis- and trans-tetrahydro-β-carbolines 7a and 7b respectively in a ratio of 85:15.[7] This mixture was heated with a catalytic amount of formic acid in 2-butanol and toluene to give a mixture of the products, 3c and 3d, of intramolecular acylation. Crystallisation furnished the desired product 3c, m.p. 293°, $[\alpha]_D^{25}$ -84°.[8]

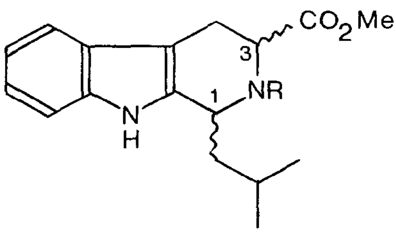
For the synthesis of the dehydro-derivative 2c, the crude mixture of 7a and 7b (see above) was treated with toluene-p-sulphonyl chloride in pyridine to furnish the cis-N-tosyl compound 7c, m.p. 246°, $[\alpha]_D^{25}$ -15.8°, in 55% yield. Treatment of the latter compound with sodium ethoxide in refluxing ethanol resulted in quantitative elimination of toluene-p-sulphinic acid, and cyclisation of the intermediate 1,2-dihydro-β-carboline, to yield the desired dehydro-compound 2c, m.p. 285°, $[\alpha]_D^{25}$ 214.7°, λ_{max} 242, 258, 364 nm., ν_{max}^{KBr} 3200, 1665, 1640, 1600, 1445, 1400, 1375, 1245 cm^{-1}.[8] When the latter reaction was performed in $[OH-^{2}H_{1}]$-ethanol, the α-proton of the proline residue in the dehydro-compound was exchanged completely for deuterium. Therefore it was necessary to consider the possibility that epimerisation had occurred at that position. The dehydro-compound was recovered unchanged following all attempts at catalytic hydrogenation, even under forcing conditions, and so correlation with the pentacycle 3c was not possible. Nor did the dehydro-compound furnish crystals that were suitable for X-ray diffraction studies. The stereochemistry that is depicted is based upon the examination of Dreiding models, which indicated that 2c must be significantly more stable than the epimer owing to severe non-bonded repulsion, between the methylene group of the isobutyl substituent and the carbonyl oxygen of the proline residue, in the latter



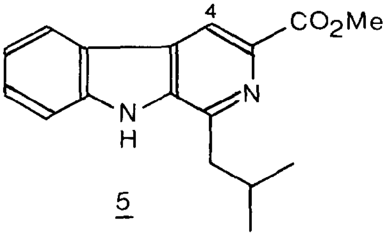
2 a; R^1 = OMe, R^2 = $CH_2CH{:}CMe_2$, R^3 = $CH{:}CMe_2$
b; R^1 = H, R^2 = $CH_2CH_2CHMe_2$, R^3 = CH_2CHMe_2
c; R^1 = R^2 = H, R^3 = CH_2CHMe_2



3 a; R^1 = $CH_2CH_2CHMe_2$, R^2 = CH_2CHMe_2, R^3 = H
b; R^1 = $CH_2CH_2CHMe_2$, R^2 = H, R^3 = CH_2CHMe_2
c; R^1 = R^3 = H, R^2 = CH_2CHMe_2
d; R^1 = R^2 = H, R^3 = CH_2CHMe_2



4 a; R = H, 1,3-*cis*
b; R = H, 1,3-*trans*
c; R = Ts, 1,3-*cis*
d; R = Ts, 1,3-*trans*



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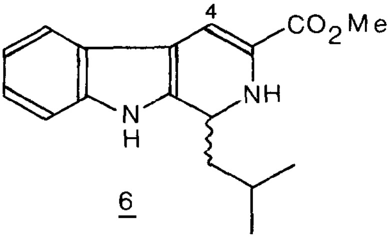

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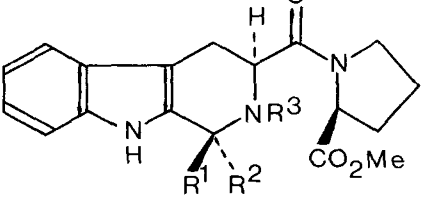

7 a; R^1 = CH_2CHMe_2, R^2 = R^3 = H
b; R^1 = R^3 = H, R^2 = CH_2CHMe_2
c; R^1 = CH_2CHMe_2, R^2 = H, R^3 = Ts

compound. The isolation of L-proline, following complete hydrolysis of the dehydro-compound in refluxing 6M hydrochloric acid, is consistent with structure 2c. In the ^{1}H-n.m.r. (d_6-DMSO) of 2c the resonances due to H-13 (δ 7.27, s) and H-3 (δ 6.04, t) appear at high frequency owing to deshielding by the carbonyls of the tryptophan residue and the proline residue respectively.

We reported earlier that derivatives of tryptophan do not undergo Pictet-Spengler cyclo-condensation with 3-methylbut-2-enal.[9] We have shown since that the imine derived from 6-methoxytryptophan methyl ester and the same aldehyde undergoes facile Pictet-Spengler cyclisation.[10] The total synthesis of natural fumitremorgins is now in progress utilising the latter observation together with the ideas that are presented in this communication.

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2. All new compounds gave ^{1}H-n.m.r., ^{13}C-n.m.r., and high resolution mass spectra that are consistent with the structures assigned. Crystalline compounds gave satisfactory elemental analyses.
3. eg. M. Cain, O. Campos, F. Guzman, and J. M. Cook, J. Am. Chem. Soc., 1983, 105, 907.
4. cf. C. J. Moody and J. G. Ward, J. Chem. Soc., Perkin Trans. I, 1984, 2895.
5. G. Massiot and T. Mulamba, J. Chem. Soc., Chem. Commun., 1983, 1147.
6. A. A. Swelim, A. I. Khodair, and S. Sallay, Bull. Fac. Sci., Assiut Univ., 1975 (Pub. 1978), 4, 233 (Chem. Abstr., 1979, 91, 21100).
7. Variable amounts of cyclo-L-prolyl-L-tryptophan were also formed owing to self condensation of the dipeptide ester.
8. Selected ^{13}C-n.m.r. chemical shifts (δ) for d_6-DMSO solutions: 2c, 166.4, 158.7, (both C=O), 121.8, 120.2, 118.1, 111.9, (arom. CH), 136.4, 136.0, 123.7, 122.3, (arom. C), 48.3(C-3), 58.1, 28.6, 21.4, 44.4, (C-6,7,8,9), 105.4(C-12), 110.3(C-13); 3c, 169.0, 165.5, (both C=O), 120.7, 118.6, 117.6, 111.2, (arom. CH), 135.7, 135.0, 125.8, 105.0, (arom. C), 49.7(C-3), 58.4, 27.7, 20.9, 44.6, (C-6,7,8,9), 55.9(C-12), 22.7(C-13).
9. D. M. Harrison, Tetrahedron Lett., 1981, 22, 2501.
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