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OXIDATIVE DIMERIZATION OF Nb-ACYLTRYPTOPHANS
TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF DITRYPTOPHENALINE

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Abstract : First total synthesis of ditryptophenaline **1** is described and the absolute configuration was determined

We have previously described effective oxidative dimerization of Nb-methoxycarbonyltryptamine **3** by proflavine-sensitized photooxygenation in formic acid and obtained rac- and meso-folicanthines by subsequent reduction1). In an extension of this novel dimerization, we investigated the mechanistic sequence of the reaction and obtained evidences for the dimerization of **3** via photosensitized electron transfer reaction. As part of our effort to define the scope and limitation of the oxidative coupling reaction, we intended to synthesize ditryptophenaline which was produced by several strains of Aspergillus flavus and characterized by Büchi2). We now report the first total synthesis of this substance and determined the absolute configuration.

Irradiation3) of **3** in O_2-saturated formic acid containing other acridine dye such as acridine orange instead of proflavine for 2 hr also provided **5** (a and b)1) and **7**4) in 17% and 40% yields, respectively, together with **4**5) in 27% yield, whereas the similar reaction without light or in a solvent like methanol or trifluoroacetic acid did not give **5**. Using methylene blue or toluidine blue which is $^1O_2$ sensitizer and belongs to thiazine dye, gave only traces of **5** under similar conditions, suggestive of the indolyl radical cation intermediate **8** by electron transfer mechanism6).

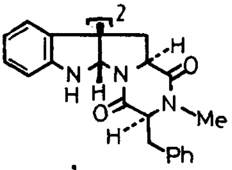
In fact, the dimers **5a** and **5b** were obtained (28%) by irradiation of **3** in formic acid containing chloranil, which has been found to function as a photosensitizer forming radical cation by electron transfer7) along with **6a**8) (16%). Nb-Methoxycarbonyltryptamine **3** quenches the fluorescence of acridine orange at 575 nm in formic acid9). The quenching follows Stern-Volmer kinetics, with $kq\,\tau_s \simeq 10.1\ M^{-1}$. These data suggested that the dimer **5** might be derived by coupling reaction of the tricyclic radical **9** formed via **8b** which arised from the electron transfer from **3** to the singlet excited state of proflavine (path a) as shown in Scheme 1. The reaction of **9** with $^3O_2$ would result in the formation of **7** while we cannot rule out $^1O_2$ as an intermediate in competitive pathway (path b). The 2,3-dimer **6** might be formed by the radical addition of **9** to **3** followed by deprotonation.

Sensitized photooxygenation of **3** by dicyanoanthracene (DCA), which is an electron transfer sensitizer for photooxygenation of olefins6), in acetonitrile or methanol failed to form dimers although **3** quenches efficiently the fluorescence of DCA in these solvents. However, irradiation of oxygen-saturated formic acid solution of **3** and DCA for 3.5 hr led to **5** (11%) and **4** (25%), indicating that the radical cation **8** might be stabilized in formic acid6b).

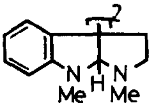
In order to increase the yield of **5**, other reaction conditions to generate the radical cation **8** by one electron oxidants such as $FeCl_3$-pyridine-O_2, $CuSO_4$-O_2-MeOH, pyridine N-oxide-CuCl-MeOH10), $TiCl_4$11), $Ph_3\overset{+}{C}\,BF_3^-$ -hv-O_2 12), were investigated, but no coupling product **5** was obtained in any cases.

On the other hand, **5** was obtained in 30% yield when a mixture of **3** and chloranil in formic acid was kept for 22 hr at room temperature without light. Furthermore, the oxidation of **3** with thallium (III) trifluoroacetate (TTFA) (1/2 equivalent)-$BF_3\cdot Et_2O$13) in acetonitrile for 70 min in an ice-salt bath gave two products which were readily separated chromatographically. The major product was shown to consist of two diastereoisomers **5c** and **5d** (31%) which were further separated by preparative TLC to give less polar dimer **5c**, mp 207.5-210.5° and more polar dimer **5d**, mp 295-299°8). These products were identified by comparison with authentic samples1) as **5a** and **5b** after Na-formylation with formic acid, respectively. Structure **6b** was assigned to the minor component, isolated in 18% yield, on the basis of spectral data and comparison with **6a** after formylation.

In light of these results, we intended to synthesize **1** by analogous oxidative coupling of cyclo-L-N-methylphenylalanyl-L-tryptophanyl **10**14) prepared by L-N-methylphenylalanine and L-tryptophan. As was the case with model compound **3**, irradiation of **10** in formic acid with proflavine, chloranil, DCA or DDQ under a wide variety of conditions, were carried out but gave no dimeric compound. Instead, 3a-hydroxypyrroloindole **11a** (10%) and **11b** (10%) and small amount of their O-formyl derivatives were obtained15). An alternate reagent, TTFA, could again be employed successfully to produce the desired dimer **1** in 3% yield which was easily crystallized from methylene chloride-methanol to give mp 196-203°16) (lit2) mp 204-205°) identical through spectral (IR, UV, NMR, $[\alpha]_D^{33}$ -318.1 (c 0.46, CH_2Cl_2), high resolution mass) and chromatographic comparison with authentic sample of the natural material. Since relative configuration of **1** has been reported2), our total synthesis established the absolute configuration of **1** as shown in the chart.



1



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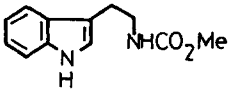

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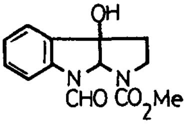

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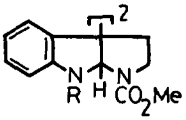
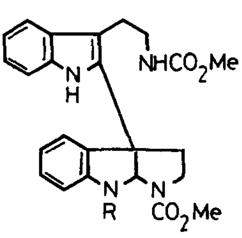
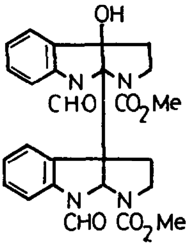


5

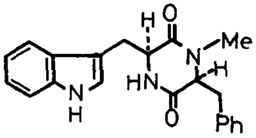
a, R=CHO, rac-, less polar
b, R=CHO, meso-, more polar
c, R=H , rac-, less polar
d, R=H , meso-, more polar



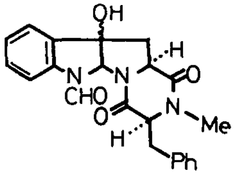
6 a, R=CHO
b, R=H



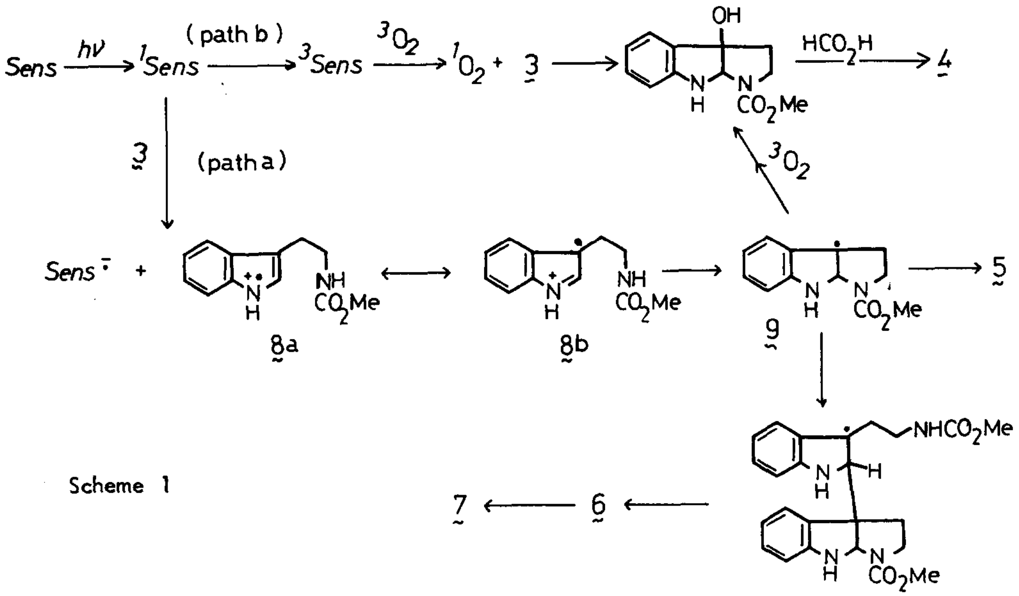
7



10



11 a, less polar
b, more polar



Scheme 1

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References and Notes

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2. J.P. Springer, G. Büchi, and J. Clarady, Tetrahedron Lett., 1977, 2403.
3. A 500 W halogen lamp was used with a liquid filter of $NaNO_2$ ($\lambda > 360$ nm).
4. 7a : amorphous, less polar isomer ; λmax (EtOH) nm 251.5, 280sh, 287sh ; νmax (KBr) cm^{-1} 3300, 1685 ; m/z 506 (36) M^+ ; δ ($DMSO$-d_6) 3.68 (s, 6H. Me), 5.74 (s, 1H, NCHN), 8.69, 8.88 (2 s, 2H, NCHO). 7b : mp 247°, more polar isomer ; λmax (EtOH) nm (ε) 249 (23800), 279.5 (4800), 287sh (4300) ; νmax (KBr) cm^{-1} 3410, 1720sh, 1704, 1662 ; m/z 506 (12) M^+ ; δ (DMSO-d_6) 3.68 (s, 6H, Me), 6.19 (s, 1H, NCHN), 8.76, 8.88 (s, 2H, NCHO).
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8. Elemental analysis and spectral data support the structures. The compound 6a was converted to 7 by proflavine-sensitized photooxygenation in formic acid.
9. Fluorescence spectra were recorded on MPF-4 Hitachi spectrofluorometer. For a HCOOH solution of acridine orange (3.67×10^{-5} M) was quenched by 3 (λexc 483 nm, λem 575 nm).
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13. TTFA has been reported to act as an efficient one-electron oxidant for certain aromatic compounds. E.C. Taylor, J.G. Andrade, G.J.H. Rall, and A. Mckillop, J.Am.Chem.Soc., 102, 6513 (1980).
14. 10, mp 130° (dec) (benzene) ; $[\alpha]_D^{20}$ -152° (c 0.7, 95% EtOH).
15. 11a : less polar, mp 251.5-253.5° (dec) ; λmax (EtOH) nm (ε) 242.5 (8900), 302.5 (2500) ; ν max (KBr) cm^{-1} 3410, 3320, 1680, 1650 ; m/z 364 (23) M^+ ; δ (DMSO-d_6) 0.84 (t, 1H, J = 12 Hz) and 2.10 (q, 1H, J = 6 and 12 Hz) (CH_2), 2.94 (s, 3H, NMe), 3.24 (m, 2H, CH_2Ph), 3.52 (q, 1H, J = 6 and 12 Hz, CH), 4.39 (m, 1H, CH-CH_2Ph), 5.20 (s, 1H, NCHN). 11b : more polar, mp 188-191° (dec) ; λmax (EtOH) nm (ε) 240.5 (8600), 300 (2600) ; ν max (KBr) cm^{-1} 3380, 3340, 1615 ; m/z 364 (25) M^+ ; δ (DMSO-d_6) 1.00 (t, 1H, J = 12 Hz) and 2.23 (q, 1H, J = 6 and 12 Hz) (CH_2), 2.84 (s, 3H, NMe), 3.30 (s, 2H, CH_2Ph), 4.35 (m, 2H, 2 x CH), 5.12 (d, 1H, J = 2 Hz, NCHN), 5.88 (s, 1H, NH or OH, exchangeable).
16. The CD spectrum of the synthetic sample, ($c = 4.15 \times 10^{-5}$, EtOH) $[\theta]$ (nm) -56.4×10^3 (250), -8.60×10^3 (275), -41.7×10^3 (308), was superimposable with that of the natural product.

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