ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED 5-HYDROXY-TRYPTOPHAN DERIVATIVES

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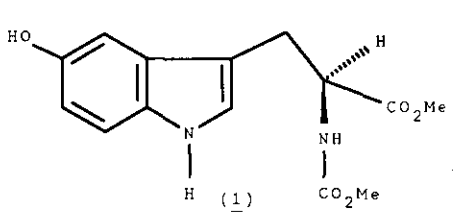
Abstract - 5-hydroxytryptophan was converted to pyrroloindole (3), which on deprotonation with LDA and subsequent reaction with alkyl halides gave the C-2 alkylated derivatives (6-9) cleanly with retention of configuration. Reversion to the 5-hydroxytryptophan skeleton was then achieved by stirring in trifluoroacetic acid and deprotection by treatment with sodium in liquid ammonia followed by saponification.

In this laboratory we have developed a method for the substitution at the α-position of tryptophan, with clean retention of configuration.[1] This method has recently been extended to encompass the diastereoselective introduction of substituents at the β-position of tryptophan,[2] and the preparation of α-substituted derivatives of aspartic acid.[3] The general methodology is based on the pioneering studies of Hino on the formation and derivatization of cyclic tautomers of tryptophan namely the hexahydropyrrolo[2,3b]indoles.[4,5] In continuation of our studies in this area we have now extended our investigation to include the asymmetric α-

alkylation of 5-hydroxytryptophan and report below our preliminary results in this area.

Our interests in 5-hydroxytryptophan were twofold. Firstly, we wished to probe the effect of the 5-hydroxy group on the acid mediated tautomerization of the tryptophan skeleton to the hexahydropyrroloindole system, with particular emphasis on the configuration and conformation of the cyclic tautomer. Secondly, given the potential of (±)-α-fluoromethyl-5-hydroxytryptophan as a time dependent inhibitor of aromatic acid decarboxylase,[6] we were interested in developing a general asymmetric alkylation of 5-hydroxytryptophan.

The methoxycarbamate (1) of L-5-hydroxytryptophan methyl ester was suspended in 85% phosphoric acid at room temperature and, after complete dissolution, worked up with 15% aqueous potassium carbonate and extracted into dichloromethane to give the cyclic tautomer (2). This somewhat unstable substance was immediately converted into the crystalline derivative (3) by reaction with benzenesulphonyl chloride in pyridine in 65% yield. The cyclic tautomer (2) had been previously obtained by Hino, by Fremy's salt oxidation of the corresponding cyclic tautomer of tryptophan followed by



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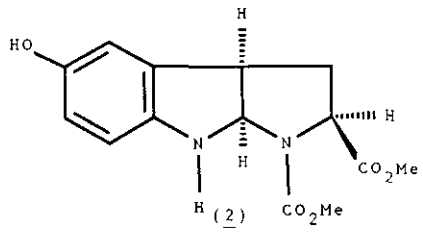

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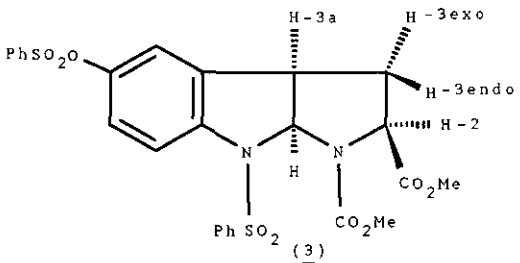

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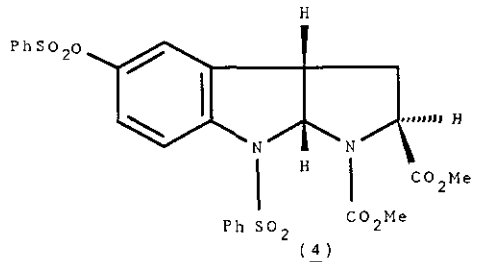
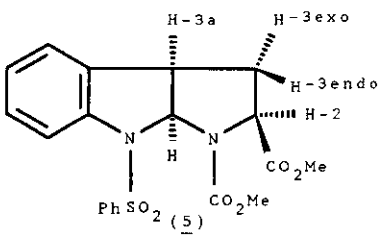


(4)

reduction of the quinoneimine.[7] Although the isolated yield of 3 was somewhat lower than in the simple tryptophan series (typically 85%) it was obtained as a single diastereoisomer, uncontaminated by the exo-ester (4). Thus the 5-hydroxy group did not drastically affect the preference for the CO_2Me-endo configuration. As in the simple tryptophan series the CO_2Me configuration was readily discernible by the chemical shift of the ester methyl group at C-2 (δ 3.31) indicative of shielding by the aromatic ring current and so the indicated configuration, rather the alternative (4). Nevertheless the conformation of 3 is different from that of 5, which lacks the sulphonyl group at C-5. Thus, in 5 the ester had δ 3.05 in the ^1H nmr

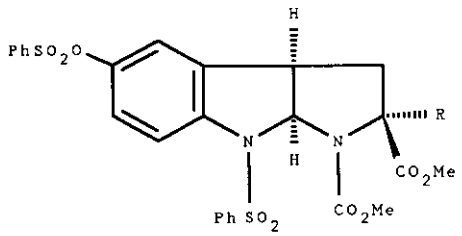


(5)

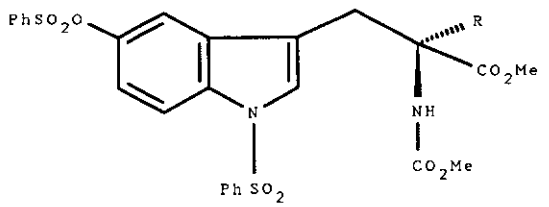
spectrum whereas in 3, although the ester group is evidently shielded, it is clearly not so to the same extent as in 5. Furthermore, in 5 H-3_{endo} is a simple geminal doublet in the ^1H nmr spectrum indicating that the torsion angles H2-C2-C3-H3_{endo} and H3_{endo}-C3-C3a-H3a are approximately 90° as is found crystallographically in various derivatives,[1,8] whereas in the ^1H nmr of 3, H-3_{endo} appears as a ddd indicating extensive coupling to H-2 and H-3a as well as to H-3_{exo} and so a different conformation of the pyrroloindole system. It is evident that the sulphonyloxy group at C-5 has a substantial effect on the conformation of 3.

We next turned to the chemistry of 3 and were delighted to discover that despite the modification of conformation due to the sulphonyloxy group no change in the diastereoselectivity of alkylation at C-2 was observed. Thus, deprotonation of 3 with lithium diisopropylamide in THF at -78 °C followed by quenching led, in each case, to clean alkylation at C-2 in high yield

by quenching led, in each case, to clean alkylation at C-2 in high yield and, within the limits of nmr detection, formation of a single diastereoisomer resulting form alkylation on the exo-face of the bicyclic nucleus (Table). The configuration at C-2 in each of the alkylated derivatives (6-9) is verified by the chemical shift of the shielded C-2 endo-CO_2Me (Table, column 3). Treatment of 6-8 with neat trifluoroacetic acid at room temperature resulted in rapid essentially quantitative ring opening to the 5-hydroxytryptophan derivatives (10-12).



(6) R = Me
(7) R = CH_2Ph
(8) R = $CH_2CH{=}CH_2$
(9) R = $CH_2OCH_2CH_2SiMe_3$



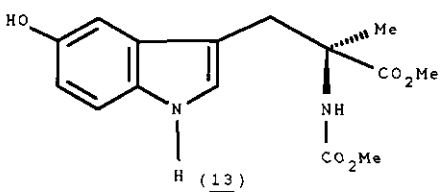
(10) R = Me
(11) R = CH_2Ph
(12) R = $CH_2CH{=}CH_2$

Table: Alkylation and Ring Opening of Pyrroloindoles

Electrophile	Alkylation (Yield %)	δ(CO_2Me) Pyrroloindole	Ring Opening (Yield %)
MeI	6 (75)	3.19	10 (95)
$PhCH_2Br$	7 (70)	3.26	11 (97)
$CH{=}CH_2CH_2Br$	8 (70)	3.20	12 (93)
$Me_3SiCH_2CH_2OCH_2Cl$	9 (65)	3.24	------

The two benzenesulphonyl groups could be removed reductively, in one pot, by treatment with sodium in liquid ammonia as illustrated by the conversion

of 10 to 13 in 63% isolated yield. Finally, cleavage of the ester and carbamate groups was achieved by heating to reflux with 5M aqueous potassium hydroxide followed by neutralisation and ion exchange chromatography giving 14 in 67% yield.[9,10]



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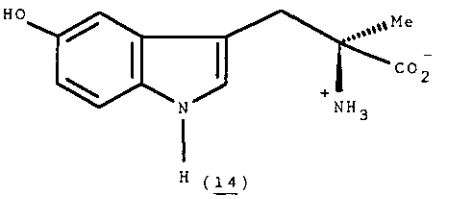

(14)

In conclusion, we have developed a protocol for the α-alkylation of 5-hydroxytryptophan with clean retention of configuration. In the course of our experiments we have also demonstrated that the 5-hydroxy group has no discernible effect on the configuration of the ring closed tautomer but that, after sulphonylation, it does provoke a conformation change in the later species.

ACKNOWLEDGEMENT

We thank the Universiti Brunei Darussalam Research and Consultancy Committee for financial support to LLBL and Messrs Milan Bruncko and Swaminathan Natarajan (UIC) for assistance with optical rotations and ion exchange chromatography.

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9 All new compounds gave spectra and microanalyses *and /or high* resolution mass spectral data in agreement with the assigned structures.

10 Specific rotations $[\alpha]_D$ in $CHCl_3$ for key compounds, all of which were either viscous oils or foams, are as follows: 3 +108.5°(c=1.2), 6 +120.8°(c=1.4), 7 +122.6°(c=1.6), 8 +135.7°(c=0.30), 9 +97.6°(c=0.58), 10 +24.8°(c=1.57), 11 +18.6°(c=1.5), 12 +34.2°(c=1.8), 13 +36.4°(c=0.33), 14 -71.4°(c=0.4, MeOH).

Received, 7th December, 1992