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OXIDATION OF 1-ACYLINDOLES WITH MOLYBDENUM PEROXO COMPLEX (MoO_5·HMPA): PREPARATION OF 1-ACYL-trans- AND cis-2,3-DIHYDROXYINDOLINE DERIVATIVES

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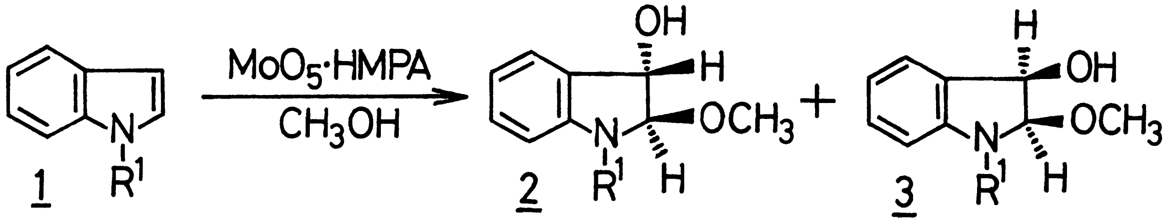
Oxidation of 1-acylindoles with MoO_5·HMPA in methanol gave a mixture of 1-acyl-trans- and cis-2,3-dihydroxyindoline derivatives in good yields, while 1-acyl-2-substituted indole was oxidized to a corresponding 2-hydroxyindoxyl.

Although several mehtods have been reported for the preparation of 1-acyl-2,3-dihydroxyindoline derivatives by the oxidation of 1-acylindoles,[1)] most of these methods are limited to the oxidation of 1-acyl-2,3-disubstituted indoles and yields are usually poor.

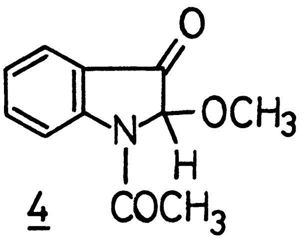
It is known that readily available molybdenum peroxo (MoO_5) complexes are excellent mild oxidizing reagents. The reagents have been utilized in the epoxidation of olefins,[2)] the hydroxylation of enolate anions,[3)] carbanions[4)] and N-silyl amides,[5)] and in the oxidation of dihydropyrane.[6)] However, the use of MoO_5 complexes for the oxidation of indole nucleus has not been reported. We now wish to report that oxidation of 1-acylindoles with MoO_5·HMPA in methanol gives rise to 1-acyl-2,3-dihydroxyindoline derivatives in good yields, and that oxidation is affected by the presence of a substituent at 2-position of indole.

A solution of 1-acetylindole (1a) (3 mmol) in dry methanol (30 ml) was allowed to react with MoO_5·HMPA (3.3 mmol) under nitrogen at room temperature for a week,



a) $R^1=COCH_3$, b) $R^1=COC_6H_5$, c) $R^1=CO_2CH_3$, d) $R^1=SO_2C_6H_4-CH_3(p)$

and concentrated under reduced pressure to give a syrup, from which 1-acetyl-*trans*-3-hydroxy-2-methoxyindoline (2a) and *cis*-isomer (3a) were obtained in 56% and 15% yields, respectively, by using a silica-gel column chromatography. The structure of 2a was determined by its elemental analysis and spectral data, and by conversion of 2a with CrO_3-pyridine-H_2O[7] into 1-acetyl-2-methoxyindoxyl (4).[8] The elemental and spectral data of 3a were strikingly similar to those of 2a, and CrO_3 oxidation of 3a also gave 4. The stereochemistry of hydroxy and methoxy groups in 2a and 3a was confirmed by comparison of the coupling constants between 2-H and 3-H of the corresponding O-acetates, (5) and (6) [$J_{2,3}$=0 Hz for 5, $J_{2,3}$=6 Hz for 6].[9]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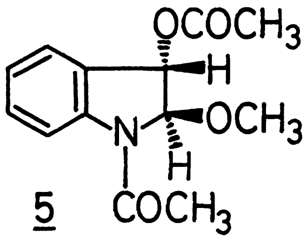
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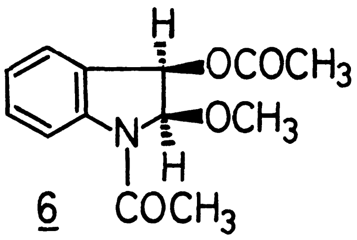
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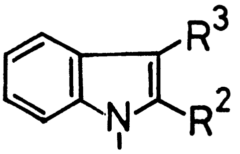
Similarly, 1-benzoylindole (1b), 1-methoxycarbonylindole (1c), and 1-tosylindole (1d) gave the corresponding indolines, (2b-d) and (3b-d) in good yields; the structures were determined by their elemental and spectral data. The results are shown in Table 1.

Table 1. Physical Data of 1-Acyl-3-hydroxy-2-methoxyindolines

	Yield (%)[a]		Product 2[b]		Product 3[b]	
Reactant	2	3	Mp (°C)	NMR (δ)[c]	Mp (°C)	NMR (δ)[c]
1a	56	15	98-99	5.01 (s,2-H) 4.80 (d,3-H)[d]	121-122	5.0-5.4 (m,2-H and 3-H)
1b	56	18	178-180	5.13 (s,2-H) 4.82 (s,3-H)	116-117	5.45 (d,2-H)[e] 5.28 (d,3-H)
1c	69	19	98-100	5.35 (s,2-H) 4.78 (d,3-H)[d]	102-104	5.43 (d,2-H)[e] 5.18 (dd,3-H)
1d	69	7	oil	5.23 (s,2-H) 4.60 (s,3-H)	oil	5.27 (d,2-H)[e] 4.70 (d,3-H)

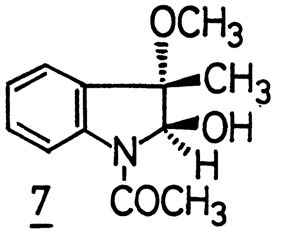
a) Isolated yield. b) All *trans*-isomers showed smaller Rf-values than the corresponding *cis*-isomers. c) Measured in deuterochloroform using tetramethylsilane as internal standard. d) The coupling with hydroxy proton was observed. e) Coupling constant $J_{2,3}$=6 Hz.

Treatment of 1-acetyl-3-methylindole (1e) with MoO_5·HMPA under the same conditions gave a mixture of 1-acetyl-trans-2-hydroxy-3-methoxyindoline (7) and the cis-isomer (8) in 75% yield, which could not be separated by chromatography and recrystallization.[10] The structures were assigned as 7 and 8 on the basis of their spectral data and the conversion to oxindole (9)[11] by oxidation with CrO_3-pyridine. The reaction of 1-acetyl-2,3-dimethylindole (1f) with MoO_5·HMPA afforded a mixture of 1-acetyl-trans- and cis-2,3-dihydroxy-2,3-dimethylindoline, (10) and (11)[12] in 51% yield. In contrast, 1-acetyl-2-methylindole (1g) was oxidized with MoO_5·HMPA to give 1-acetyl-2-hydroxy-2-methylindoxyl (12)[13] in 63% yield.



1e-g

e) $R^2=H, R^3=CH_3$
f) $R^2=R^3=CH_3$
g) $R^2=CH_3, R^3=H$



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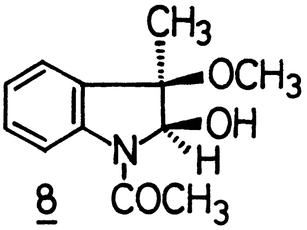

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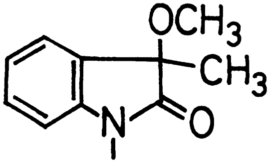

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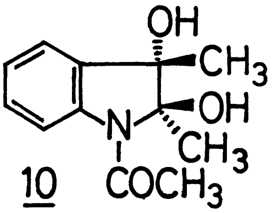

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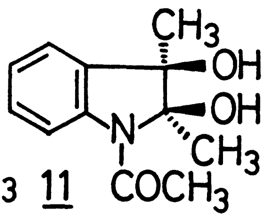

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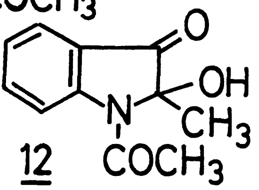

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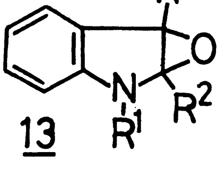

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The 2,3-epoxides (13) are expected to be produced initially by the oxidation of 1 and the methoxy derivatives, 2 and 3 or 7 and 8, should be formed by the subsequent methanolysis of 13 from 1a-d and 1e, respectively. Further studies are being continued to clarify these oxidation mechanisms.

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