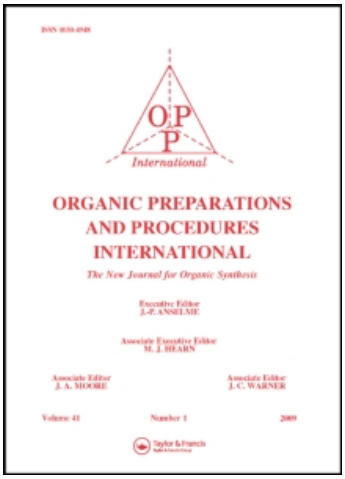

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS AND CHEMISTRY OF MELATONIN AND OF RELATED COMPOUNDS. A REVIEW

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To cite this Article Hugel, Helmut M. and Kennaway, David J.(1995) 'SYNTHESIS AND CHEMISTRY OF MELATONIN AND OF RELATED COMPOUNDS. A REVIEW', Organic Preparations and Procedures International, 27: 1, 1 — 31
To link to this Article: DOI: 10.1080/00304949509458177
URL: http://dx.doi.org/10.1080/00304949509458177

ORGANIC PREPARATIONS AND PROCEDURES INT., 27 (1), 1-31 (1995)

SYNTHESIS AND CHEMISTRY OF MELATONIN AND OF RELATED COMPOUNDS. A REVIEW

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INTRODUCTION 3
I. CHEMICAL HISTORY AND MODE OF ACTION 3
II. SYNTHESIS 5
1. *From Coffee Wax.* 5
2. *Fischer Indole Methodologies* 5
3. *From 5-Methoxytryptamine* 7
4. *From 5-Methoxyindole* 7
III. SYNTHETIC ROUTES TO TRYPTAMINE DERIVATIVES. 8
1. *Preparation of 5-Methoxytryptamine* 8
2. *Preparation of Substituted Tryptamines* 9
3. *Tryptamines via Tryptophans* 12
4. *Hydroxylation of Tryptamine Derivatives* 13
IV. SYNTHESIS OF SUBSTITUTED INDOLES 14
1. *Preparation of 5-Methoxyindoles* 14
2. *Synthetic Methods to Indole Derivatives* 16
V. MELATONIN MANIPULATIONS 18
1. *Reactions of Melatonin* 18
2. *Synthesis of Melatonin Analogues* 19
3. *Synthesis of Melatonin Metabolites* 22

4. Miscellaneous Reagents for Tryptamine Synthesis 24
REFERENCES 25

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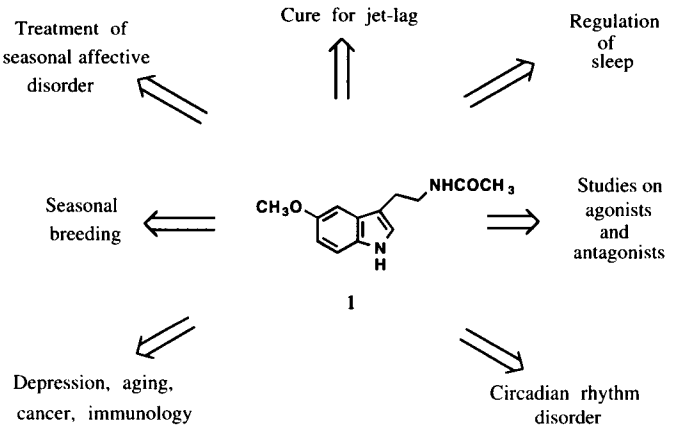
INTRODUCTION

5-Methoxy-N-acetyltryptamine (**1**), the compound known as melatonin, is a substituted indole derivative. The Fischer indole synthesis has been the chemical foundation upon which the majority of research into indole synthesis has been based. The reviews by Robinson[1] and Hughes[2] provide excellent accounts of the important aspects of Fischer indole chemistry. For information on the synthesis of tryptamines and related compounds, the reader is referred to the series of monographs on indoles edited by Houlihan.[3] Modifications of the earlier methods of indole synthesis have resulted in improvements in the preparation of tryptamines. New methods of substituted indole synthesis have emerged which have application to the production of alkoxy tryptamines. This review will provide a detailed perspective on the synthesis of melatonin and on the synthetic achievements made with respect to related tryptamine derivatives up to June1994.

I. CHEMICAL HISTORY AND MODE OF ACTION

In 1959, the dermatologist Aaron Lerner[4] isolated melatonin from the pineal gland in the brains of cattle, on the basis of its skin lightening properties in amphibia. While the actions of this compound on skin have not been found to extend to mammals, its other actions have attracted widespread interest. A key to understanding the possible role(s) of melatonin lies in the way it is produced and secreted in the pineal gland. Melatonin is secreted only during normal darkness and light exposure during the night results in termination of secretion. The most important actions of melatonin are upon reproductive activity, where it has been found to be the hormone responsible for coordinating reproductive functions with the time of the year.[5] Sheep, for example, breed normally for only about 6 months of the year (autumn and winter) due to an increased duration of secretion of melatonin during the longer nights of those seasons. Shorter durations of secretions appear to be inhibitory for reproduction in sheep. Manipulation of the melatonin levels in blood can profoundly alter the breeding dynamics of sheep.[6,7] In other species such as many rodents, the duration of melatonin secretion has

opposite effects to those observed in sheep. Thus it is clear that melatonin is a unique hormone, in that the temporal nature of its secretion is more important than the actual level. It is often referred to as the "hormone of darkness", or to the "chemical expression of darkness". In contrast to most animals, where it is intimately involved in seasonal changes in breeding, the pineal gland and melatonin appear to play a relatively minor role in reproduction in humans.[8] Because melatonin secretion in humans is controlled in the same way as in other animals, research has concentrated on its interaction with physiological systems with a temporal component. Thus it became clear that melatonin plays a role in the regulation of sleep and temperature rhythms.[9] Furthermore, because of the important role a part of the brain often termed the "biological clock" (suprachiasmatic nucleus, SCN) plays in the timing of melatonin secretion, there has also been a focus upon other biological rhythms controlled by the SCN. Thus the possible involvement of light and melatonin in seasonal affective disorder (SAD),[10] circadian rhythm disorder,[11] depression,[12] and aging[13] has been investigated. Although systematic acute and chronic toxicity tests have not been conducted on humans, it is clear from many animal and human experiments that melatonin has extremely low toxicity.[14] Pharmacological administration of the hormone has been shown to affect sleep[15] and temperature,[16] to act in concert with progestin to inhibit ovulation,[17] alleviate the symptoms of jet-lag[18] and to inhibit the growth of some cancers.[19] Whether these pharmacological actions summarized in Scheme 1 represent the spectrum of physiological roles of melatonin is not yet certain.



Scheme 1

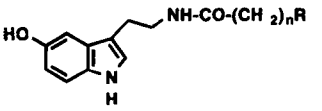
The biochemical actions of melatonin have proven difficult to establish, partly because the site of action has not been known.[20] With the availability of a high specific activity radioactive melatonin analogue [^{125}I]-2-iodomelatonin, there has been considerable interest in the location of putative melatonin binding sites in the brain. There are apparently two major brain sites where melatonin is concentrated, the SCN and the Pars tuberalis and considerable research effort is being expended to determine whether these areas contain relevant, conventional receptors for melatonin.[21] The potential applications of melatonin has stimulated interest in the study and evaluation of analogues with agonist or antagonist activity.

II. SYNTHESIS

1. From Coffee Wax

Coffee waxes, present in the outer layer of the coffee bean, represent 0.2-0.3% of the total lipids in coffee beans and contain mainly the 5-hydroxytryptamides (II) given in Table 1.[22]

TABLE 1

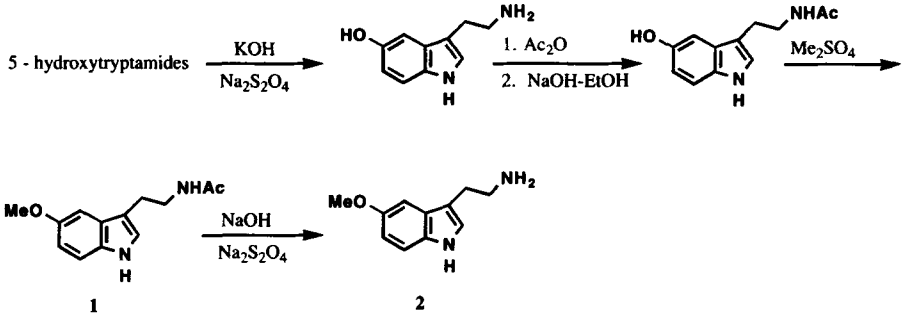


II

R	n	5-Hydroxytryptamides	Yield (%)
CH_3, CH_2OH	16	Arachidonamide	33
CH_3, CH_2OH	20	Behenamide	57
CH_3	22	Lignoceramide	10

The raw coffee beans contain 0.5-2.5g hydroxytryptamides per kilogram which corresponds to 160-70 mg of 5-hydroxytryptamine. The yield of tryptamides in the wax reaches a maximum when the ripening process of the cherry has matured. The tryptophan levels are consequently diminished. Various processes and treatments between harvesting, storage and consumption in the cup, reduce the lipid content. Italian, Turkish or ground coffee in boiled water can lead to a lipid content of a few percent.

The Hag[23] and Nestle [24] companies have developed methods outlined in Scheme 2 for the extraction, isolation and chemical derivatization of the natural tryptamides from decaffeinated coffee wax leading to melatonin and other derivatives.

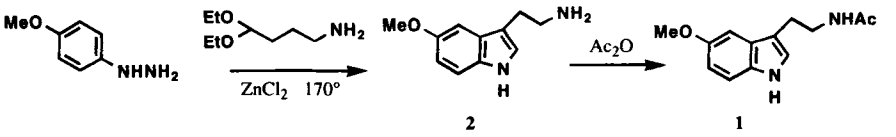


Scheme 2

2. Fischer Indole Methodologies

In 1930, thirty years before the first synthesis of melatonin was published,[25] Spath and Lederer [26] prepared crude melatonin as an intermediate in the synthesis of carbolines. This was achieved using a modified Fischer indole reaction to give 5-methoxytryptamine in 31% yield as

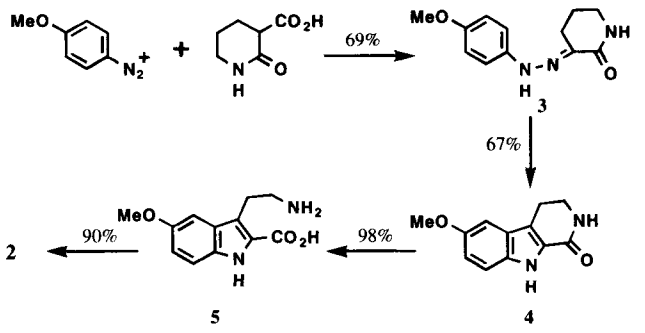
shown in Scheme 3. Subsequent acetylation provided melatonin **1.**



Scheme 3

Keglevic and coworkers[27] reacted N-acetyl-4-aminobutanal diethylacetal with 4-methoxyphenylhydrazine in 25% aqueous acetic acid at 80° for one hour and after workup and recrystallization from toluene obtained melatonin in 26% yield. This method of tryptamine formation by the indolization of 4-substituted aminobutyraldehyde arylhydrazones has been utilized to yield a variety of derivatives.[28]

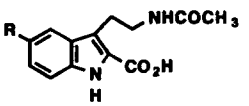
Abramovitch and Shapiro [29] employed the Japp-Klingemann reaction to form the required phenylhydrazone **3**, by coupling diazotized 4-methoxyaniline and 2-oxopiperidine-3-carboxylic acid. This was followed by Fischer indole cyclization to provide 6-methoxy-1-oxotetrahydro-ß-carboline **4.** Alkaline hydrolysis provided 5-methoxytryptamine-2-carboxylic acid **5,** which was decarboxylated under acidic conditions to yield 5-methoxytryptamine in overall 41% yield as shown in Scheme 4.

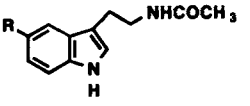


Scheme 4

The Abramovitch-Shapiro sequence appears to be the best route to 5-substituted tryptamine-2-carboxylic acids. It has been argued [30] that the yield of the decarboxylation step is strongly influenced by the nature of the substituents in the aromatic ring. The ease of decarboxylation of the 5-substituted tryptamine-2-carboxylic acids in acidic media decreases in the order OMe > Me > H >Cl > NO_2. 5,7-dimethoxy, 5-benzyloxy tryptamine-2-carboxylic acids were resistant to decarboxylation. A simple modification of the Abramovitch-Shapiro method enabled Misztal and Boksa[31] to effectively overcome this problem. Side-chain N-acylation prior to thermal decarboxylation using copper-quinoline and heat yielded the corresponding substituted N-acyl tryptamines such as melatonin and related compounds illustrated in Table 2. Note that the removal of the carboxyl group was not influenced by the R substituent.

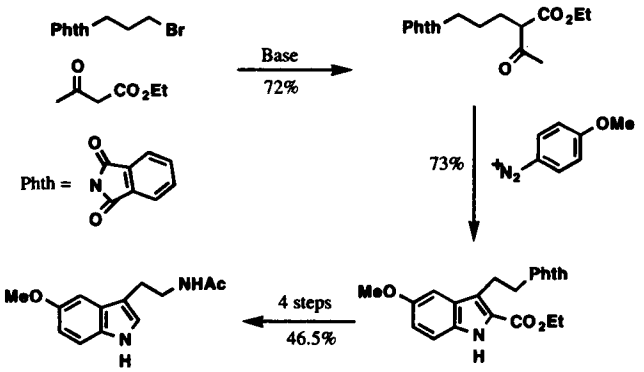
TABLE 2





R	Acylation	Decarboxylation
MeO	80 %	78 %
BnO	81 %	84 %
NO_2	85 %	86 %

Frashini and coworkers[32] used a phthaloyl protecting group for the side chain amino group of tryptamine in their synthesis of melatonin shown in Scheme 5.



Scheme 5

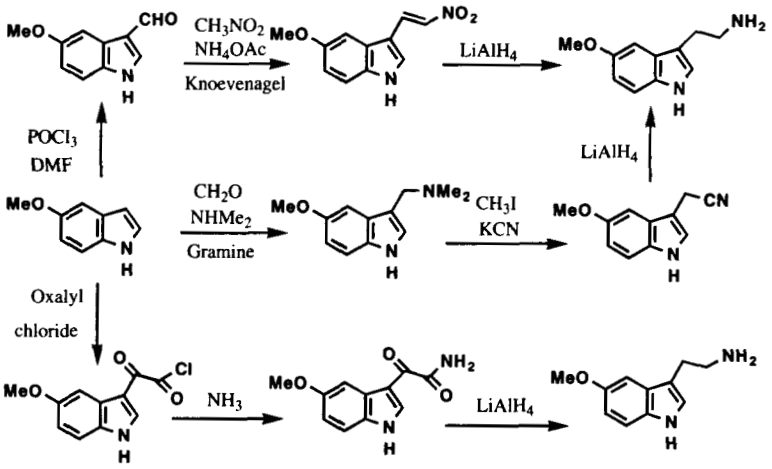
3. From 5-Methoxytryptamine

The treatment of 5-methoxytryptamine with acetic anhydride in pyridine at room temperature forms the N,N-bis acetylated derivative, which can be converted to melatonin[33] in 80% yield after washing with base.

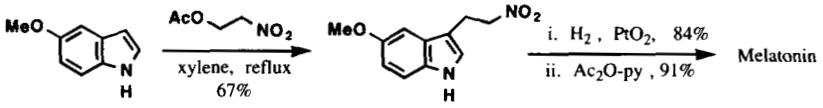
4. From 5-Methoxyindole

Melatonin has been prepared from 5-methoxyindole by a number of methods all of which depend on the fact that the indolic C-3 position is nucleophilic in character. Thus the Gramine,[25] Knoevenagel[25] and Oxalyl[34] procedures have provided ready access to 5-methoxytryptamine and therefore melatonin as outlined in Scheme 6.

Flaugh and coworkers[35] attached the ethyl acetamide side chain (Scheme 7) to 5-methoxyindole by (i) reaction with nitroethene generated in situ by the thermolysis of nitroethyl acetate, (ii)hydrogenation of the nitro group over platinum oxide and (iii) acetylation with acetic anhydride. Melatonin was obtained in 51% overall yield.



Scheme 6

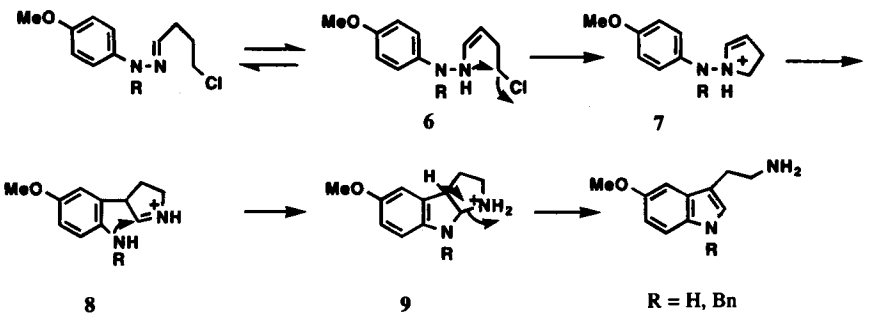


Scheme 7

III. SYNTHETIC ROUTES TO TRYPTAMINE DERIVATIVES

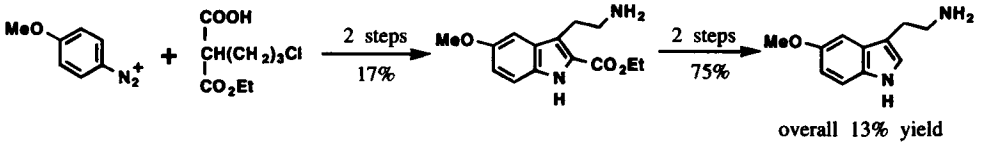
1. Preparation of 5-Methoxytryptamine

Modifications and refinements in the Lewis acids used in the Fischer indolization reaction has resulted in increased yields. For instance, the replacement of heterogeneous catalysts such as zinc chloride by homogeneous catalytic systems such as formic acid[36], dilute acetic acid[27] or the use of stoichiometric amounts of PCl_3 in benzene or dichloromethane [37] at or below room temperature requires shorter reaction times and has improved indolization yields to 70-90%. Of particular significance is that the PCl_3-anhydrous organic medium system when applied to examples where alkoxy substituted hydrazones[38] were utilized resulted in 11-37% increased yields over other methods. In the Grandberg [39] modification of the Fischer indolization, a 50% aqueous methanol solution is used. Starting with 4-chlorobutanal and 4-methoxyphenylhydrazine or its N-benzyl derivative, 5-methoxytryptamine and N-benzyl-5-methoxytryptamine were prepared in 45% and 70% yields respectively. Scheme 8 illustrates that in the Grandberg modification, the ene-hydrazine **6** undergoes cyclization to form a second ring product **7** prior to the [3,3] sigmatropic shift occurring to give **8.** A tricyclic intermediate **9** is then formed which opens to give the tryptamine derivative whereby both nitrogen atoms of the starting material have been utilized.



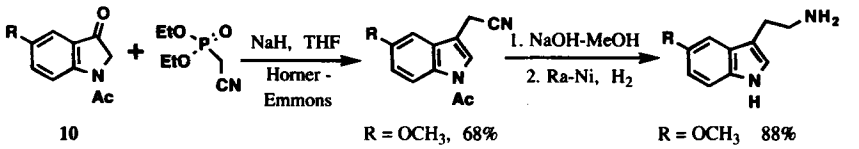
Scheme 8

Grandberg's approach was modified by Szantay and coworkers[40] who used the Japp-Klingemann reaction to form the requisite arylhydrazone. Diethyl 3-chloropropylmalonate partially hydrolyzed to the monocarboxylic acid was substituted in the synthesis as depicted in Scheme 9, instead of using the difficulty prepared 4-chlorobutanal.



Scheme 9

The application of the Horner-Emmons[41] reaction to 5-substituted-1-acetyl-3-oxo-2,3-dihydroindoles **10** as outlined in Scheme 10 leads to 5-methoxytryptamine .

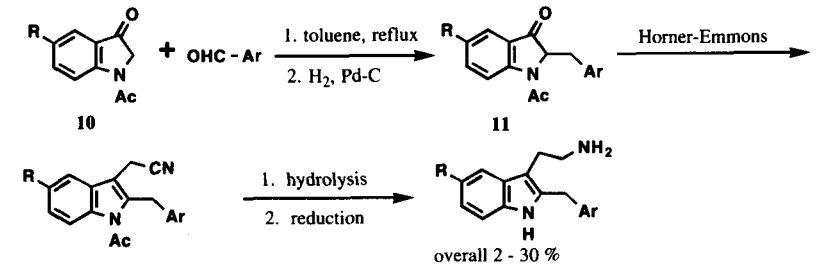


Scheme 10

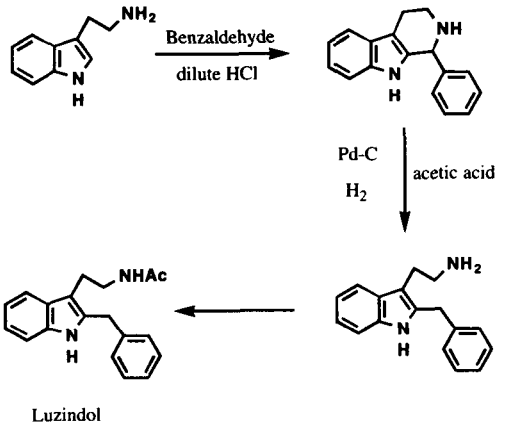
2. Preparation of Substituted Tryptamines

Condensation[42] of indolinone **10** with benzaldehyde derivatives, followed by catalytic hydrogenation gave the corresponding 2-benzyl substituted indolinones **11.** A Horner-Emmons reaction then gave the precursors of 2-substituted tryptamines as given in Scheme 11.

Starting with readily available tryptamine, Boeheringson, Dubocovich and coworkers have prepared 2-benzyl-N-acetyltryptamine[43] (Luzindol), a melatonin agonist, as detailed in Scheme 12. Alternatively, 2-benzylindole has been prepared using Fischer indole methodology and elaborated to give Luzindol in an overall yield of 19 %.[74]

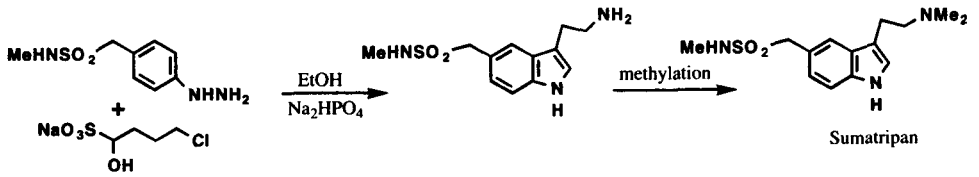


Scheme 11



Scheme 12

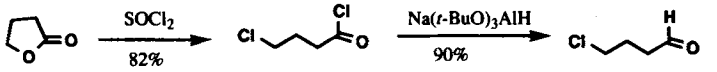
The Grandberg modification of the Fischer indole synthesis has been used for the synthesis of a wide variety of substituted tryptamines[44] some of which are potent agonists for serotonergic 5-HT_{1D} Receptors. Scheme 13 indicates that the bisulfite adduct of 4-chlorobutanal was employed in the synthesis of the tryptamine Sumatripan[45] a 5-HT_1 agonist developed to redistribute blood flow within the brain and reduce headache.



Scheme 13

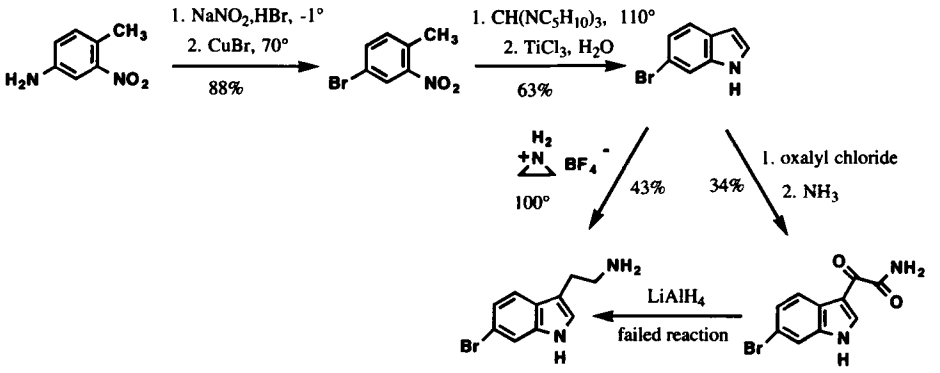
The Grandberg modification of the Fischer indole synthesis provides access to tryptamine compounds.[44,45] However the required 4-chlorobutanal for reaction with arylhydrazines is difficult to prepare. We have used the exceptionally facile reduction of acid chlorides to aldehydes with sodium

tri-*tert*-butoxyaluminohydride, developed by Cha and Brown [46] in the preparation of 4-chlorobutanal as given in Scheme 14.



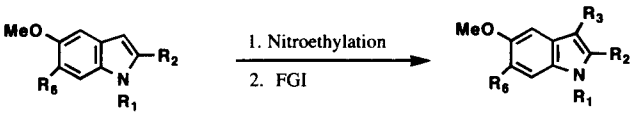
Scheme 14

The reaction of 3-bromophenylhydrazine and 4-aminobutanal diethyl acetal according to the Spath-Lederer one step protocol, provided in 60% yield a mixture of 6-bromo (36%) and 4-bromo (24%) tryptamine isomers, which could be separated efficiently on a preparative scale with ß-cyclodextrin reversed phase HPLC[47]. 6-Bromotryptamine was also prepared *via* a more tortuous route starting from 4-amino-2-nitrotoluene as given in scheme 15. Aminoethylation of 6-bromoindole with aziridinium tetrafluoroborate, followed by chromatographic purification resulted in an overall 24% yield of desired product. Treatment of 6-bromoindole with oxalyl chloride and then concentrated ammonia solution provided 6-bromoindole-3-glyoxamide. The attempted reduction to the tryptamine with lithium aluminum hydride gave a mixture of predominantly debrominated products.



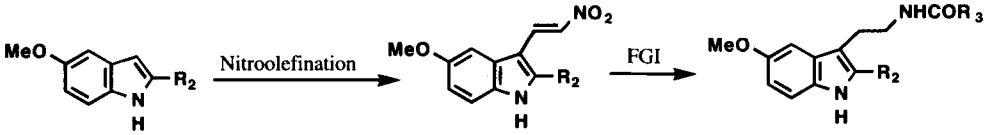
Scheme 15

Tryptamine derivatives can be prepared by side chain attachment onto indole derivatives. The selection of the method of side chain attachment depends on the type of substituents in the carbocyclic ring. Alkyl and alkoxy substituents activate the C-3 position of the indole ring (by enhancing its nucleophilic character) towards nitro-ethylation[35] as in Scheme 16 and nitro-olefination[48,49] depicted in Scheme 17. Functional group interconversion (FGI) of the nitro compounds by chemical or catalytic methods then leads to tryptamines.



R_3			
$CH_2CH_2NO_2$	$CH_2CH_2NH_2$	$CH_2CH_2NHCOCH_3$	
$R_1, R_2, R_6 = H$	67%	84%	91%
$R_1 = CH_3, R_2, R_6 = H$	66%	83%	80%
$R_2 = CH_3, R_1, R_6 = H$	51%	65%	38%
$R_6 = CH_3, R_1, R_2 = H$	58%	—	79%

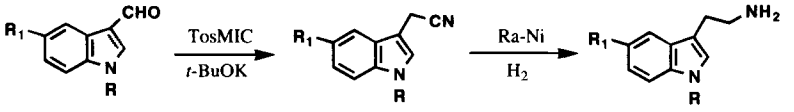
Scheme 16



R_2		R_3 = methyl	R_3 = cyclopropyl
methyl	58%	44%	45%
isopropyl	40%	30%	25%
cyclohexyl	60%	42%	—
phenyl	75%	48%	85%

Scheme 17

The readily accessible indole-3-carbaldehyde and its derivatives can be converted into tryptamines by reaction with tosyl methylisocyanide[50] (TosMIC) as shown in Scheme 18.

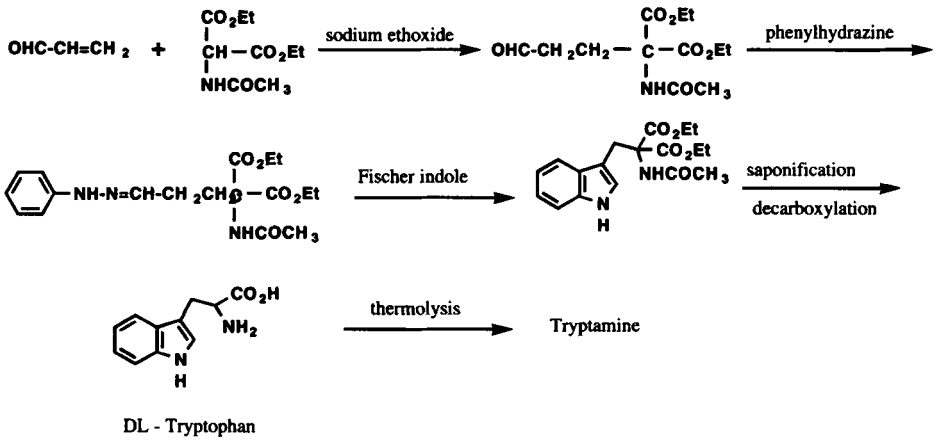


R_1 = H, Br R = Bn

Scheme 18

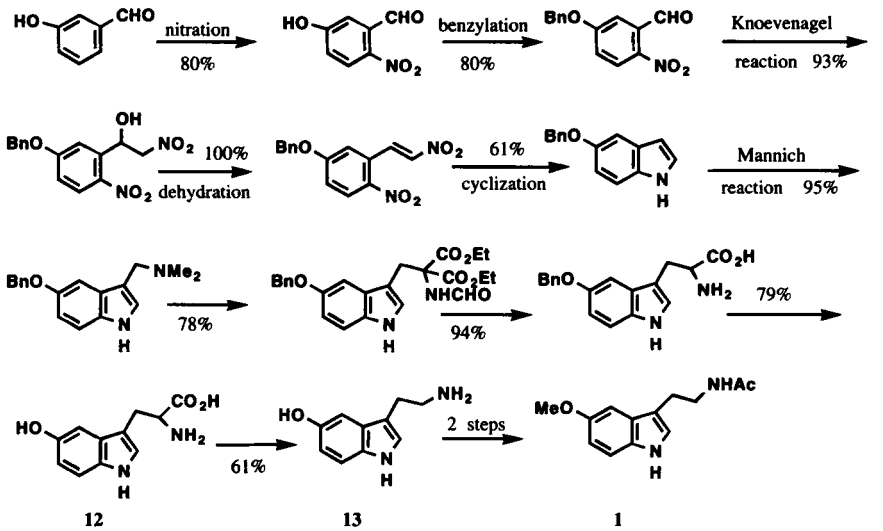
3. Tryptamines via Tryptophans

A convenient source of tryptamines is from tryptophans. DL-Tryptophan can be obtained from diethyl formylaminomalonate or from diethyl acetamidomalonate and Michael addition to acrolein. The aldehydic intermediate is reacted with phenylhydrazine to the phenylhydrazone derivative which after Fischer indole rearrangement is hydrolyzed to tryptophan as outlined in Scheme 19. Further decarboxylation of tryptophan to tryptamine is achieved by refluxing with diphenylmethane[51] or diphenyl ether[33] in a nitrogen atmosphere.



Scheme 19

The synthetic routes[52] to 5-hydroxytryptophan **12** and serotonin **13** which can be converted to melatonin **1,** are shown in Scheme 20. (S)-5-Hydroxytryptophan, an intermediate in mammalian biosynthesis of serotonin, can be obtained by enzymic resolution of the racemic compound or by fermentation with Chromobacterium violaceum.[53] Some modifications in the synthesis of 5-benzyloxyindole derivatives have been reported.[54]

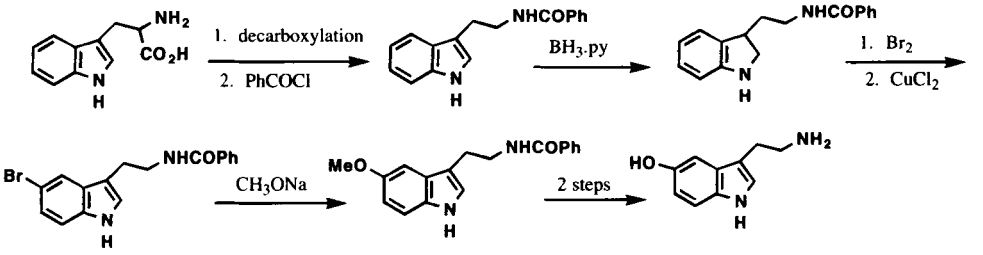


Scheme 20

4. Hydroxylation of Tryptamine Derivatives

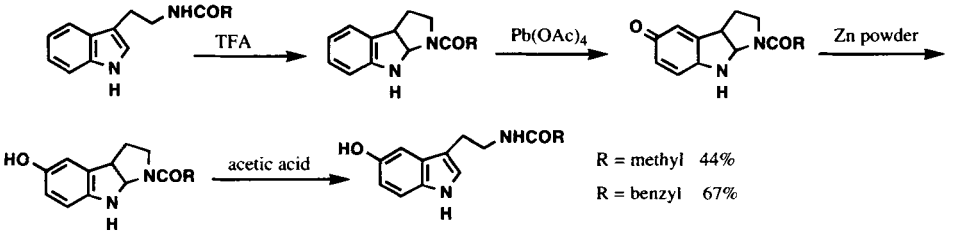
The introduction of an alkoxy or hydroxy group at C-5 of tryptamines has been achieved when the double bond between C-2 and C-3 has been blocked. Saito and Kikugawa [55] reduced the double bond and thereby directing subsequent electrophilic and nucleophilic substitution reactions to

the C-5 position in their synthesis of serotonin from tryptophan as illustrated in Scheme 21.



Scheme 21

Hino and coworkers [56] temporarily masked the indole ring double bond by the formation of a cyclic tautomer with trifluoroacetic acid (TFA) or with phosphoric acid as shown in Scheme 22. Oxidation of the aromatic ring occurred at C-5 position, and the quinone imine formation and reduction was carried out in one pot.

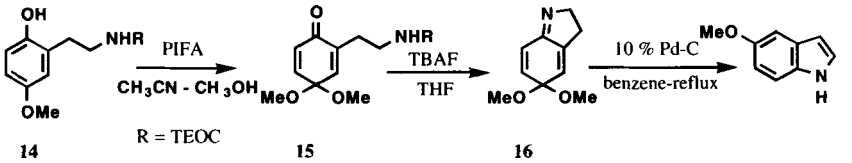


Scheme 22

IV. SYNTHESIS OF SUBSTITUTED INDOLES

1. Preparation of 5-Methoxyindoles

Kita and coworkers [57] have developed an efficient synthesis of 5-methoxyindole and other oxygenated indoles *via* the formation and reduction of quinone imines and quinone imine monoacetals. Their methodology is outlined in Scheme 23. Trimethylsilylethoxycarbonyl (TEOC) protected 2-aminoethyl-4-methoxyphenol **14** when oxidized by the hypervalent iodine reagent phenyliodine bis(trifluoroacetate) (PIFA) in acetonitrile-methanol, was converted into the benzoquinone monoacetal **15** in high yields. Upon deprotection of the TEOC group, an intramolecular cyclization occurred to form the quinone imine mono acetal **16**. 5-Methoxyindole was obtained by further treatment with 10% Pd-C.



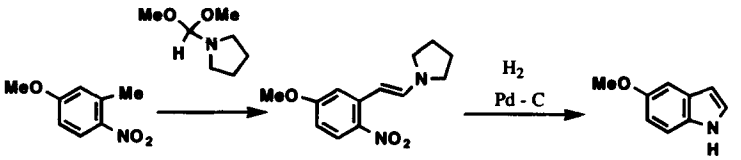
14 **15** **16**

Scheme 23

This method has been applied to the synthesis of a number of oxygenated indole derivatives as shown below.

Products	Yields (%)
5-hydroxy-6 -methoxyindole	90
5,6-dimethoxyindole	100
5-hydroxyindole	65
5-methoxyindole	100
5-hydroxy-7-bromoindole	95

The Batcho-Leimgruber [58] synthesis of 5-methoxyindole is outlined in Scheme 24. Aminomethylation of 4-methoxy-2-methylnitrobenzene by reaction with N-formyl pyrrolidine-dimethoxyacetal produces enamine **17.** Reduction to the aniline and elimination of pyrrolidine gives 5-methoxyindole in 76% yield. A wide range of benzene ring substituted indoles has been prepared by this method.

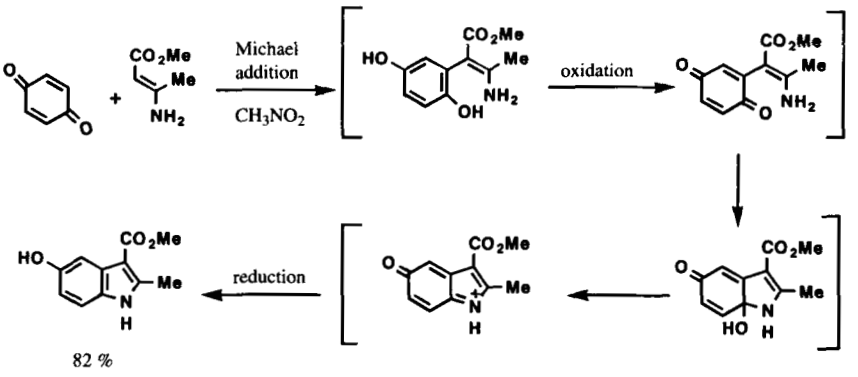


17

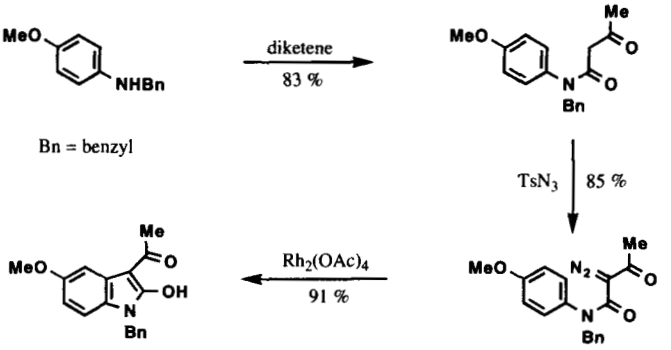
Scheme 24

Indoles bearing carboxyl and hydroxyl groups at C-3 and C-5 respectively are readily prepared by the Nenitzescu reaction[59] of enamine esters and quinones as illustrated in Scheme 25. It has been proposed that the mechanistic details of the oxidation-reduction redox process is consistent with a bimolecular sandwich electron transfer complex during the synthesis of hydroxy indoles.

Methoxyindole derivatives can also be prepared *via* rhodium carbenoid aromatic C-H insertion.[60] The synthesis of 3-acetyl-1-benzyl-2-hydroxy-5-methoxyindole is outlined in Scheme 26.



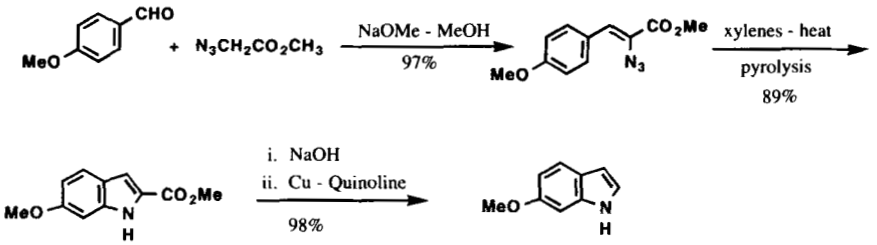
Scheme 25



Scheme 26

2. Synthetic Methods to Indole Derivatives

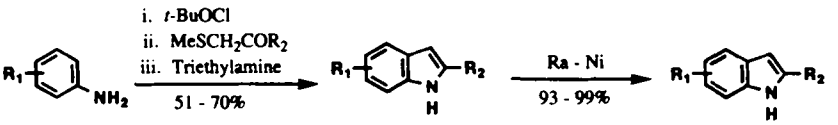
Cook and coworkers[61] applied the azide pyrolysis protocol developed by Hemetsberger[62] and Moody[63] to prepare 6-methoxyindole in 80% overall yield. The reaction sequence shown in Scheme 27 was carried out on a multi-gram scale (40g to 307g) with no chromatographic product purification required. 4-Methoxy and 4,6-dimethoxyindoles have also been prepared by this method.



Scheme 27

Substituted aniline compounds have found use in the preparation of 1-, 2-, 4-, 5-, 6-, or 7-, substituted indoles and derivatives by the Gassman [64] two step synthesis shown in Scheme 28. The

initially formed N-chloro activated aniline is reacted with a ß-keto-sulfide to form a sulfonium salt. Treatment with triethylamine results in the formation of a ylide which undergoes a [3,3]-sigmatropic rearrangement and ring closure. Raney-Nickel desulfurization in the second step provides the substituted indole product. When R_1= methoxy, the N-chloro p-anisidine is too reactive, therefore a halogen-sulfide complex is reacted with p-anisidine to form the 5-methoxyindole product.[65]

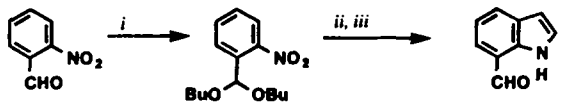


R_1 = NO_2, CO_2CH_3, halogen. CH_3, $OCOCH_3$

R_2 = Ph, CH_3

Scheme 28

Gilmore and coworkers[66] have used the Bartoli [67] methodology to prepare 7-formylindole given in Scheme 29 in 68% overall yield.

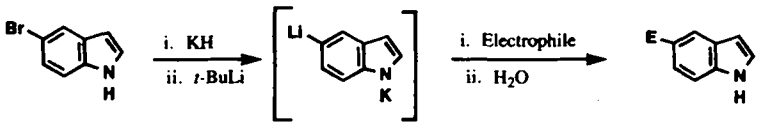


i. nC_4H_9OH /Toluene /p-TSA ii. 3 equiv. vinylmagnesium bromide /THF / -40°

iii. aqu. HCl / THF.

Scheme 29

5-Bromoindole [68,69] has been used as a precursor for the preparation of a number of 5-substituted indoles by selective halogen-metal exchange followed by reaction with electrophiles as outlined in Scheme 30.



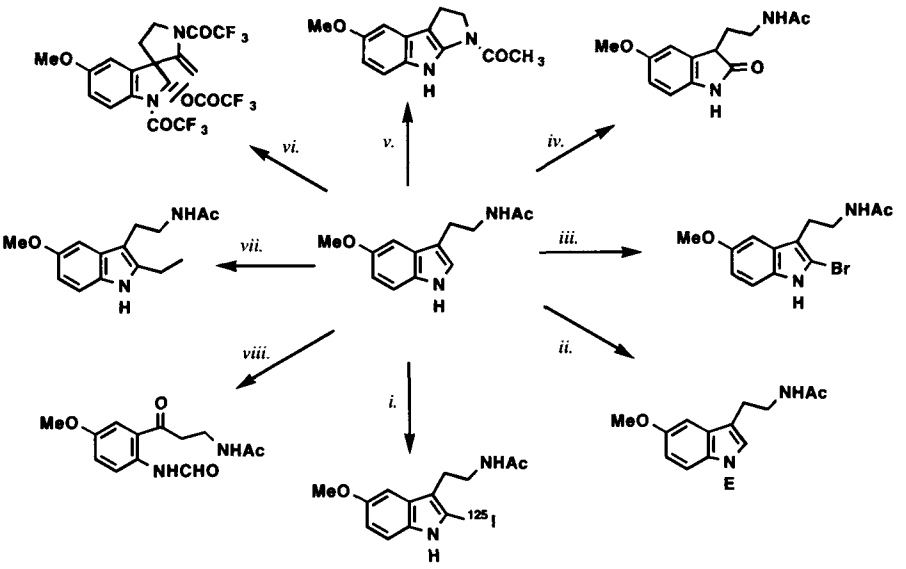
Electrophile	Substituents E (%)
DMF	CHO (57)
DMA	CH_3CO (18)
Acetone	$C(OH)(CH_3)_2$ (35)
Me_3SiNC	$CONH_2$ (32)
MeS-SMe	SMe (94)
Me_3SnCl	$SnMe_3$ (37)
$(nBuO)_3B$	$B(OH)_2$ (44)

Scheme 30

V. MELATONIN MANIPULATIONS

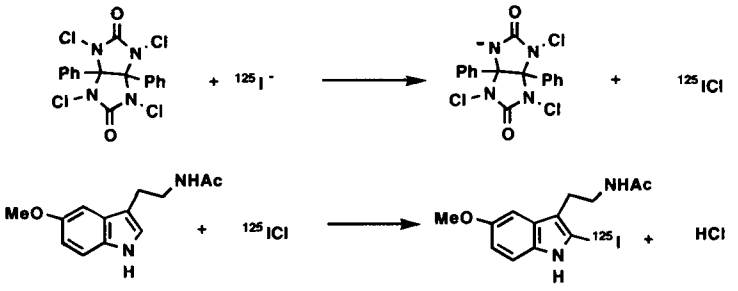
1. Reactions of Melatonin

Some of the reactions that have been carried out on melatonin are shown in Scheme 31.



Scheme 31

The localization of 2-(^{125}I)-iodomelatonin binding sites in the SCN of the human hypothalamus was possible after the synthesis of 2-(^{125}I)-iodomelatonin.[70,71] The halogen oxidizing agent,(1,3,4,6-tetrachloro-3-à, 6-à-diphenylglycoluril (IODO-GEN) was used in the preparation of the electrophilic ^{125}ICl reagent as illustrated in Scheme 32 through oxidation of radioactive iodide. Reaction with melatonin gave the product in 20-30% yield (reaction i, Scheme 31).



Scheme 32

The treatment of melatonin with two equivalents of sodium hydride and one equivalent of an electrophile, E^+, produces the indole ring N-alkylated product[72] in 60% yield (reaction ii, Scheme 31). This reaction can also be achieved using phase transfer catalysis conditions or by employing n-butyllithium as the base to deprotonate the indole and side chain nitrogens.[73] 2-Bromomelatonin was

prepared by the direct bromination of melatonin with N-bromosuccinimide (NBS) in anhydrous acetic acid at room temperature under nitrogen, followed by flash chromatography in 25-35% yield[74] (reaction iii, Scheme 31). Treatment of melatonin with a mixture of concentrated HCl and dimethyl sulfoxide produced after flash chromatography 2-oxomelatonin (N-(2-(5-methoxy-2-oxo-3-indolyl)-ethyl)acetamide) in 25% yield[75] (reaction iv, Scheme 31). Melatonin is converted into the linear tricyclic compound in 62% yield by reaction with t-butyl hypochlorite denoted by reaction v in Scheme 31. Photocyclization of N-chloroacetyl-5-methoxytryptamine afforded 47% of the angular tricyclic analogue[76] (reaction not shown in Scheme 30). The cyclization of melatonin with pentafluoropropionic anhydride, or with trifluoroacetic anhydride results in the formation of 3,3-spirocyclic indolines[77,32] (depicted by reaction vi, Scheme 31) in essentially quantitative yields, which is in marked contrast to the moderate yields obtained in other melatonin transformations. The application of the method of alkylation of tryptamines published by Fleming and Harley-Mason[78] was used to form 2-ethylmelatonin[75] (reaction vii, Scheme 31). Ozonolysis of melatonin[79] in ethyl acetate followed by catalytic hydrogenation and flash chromatography resulted in the isolation of N-acetyl-N-formyl-5-methoxykynurenamine (reaction viii, Scheme 31).

2. Synthesis of Melatonin Analogues

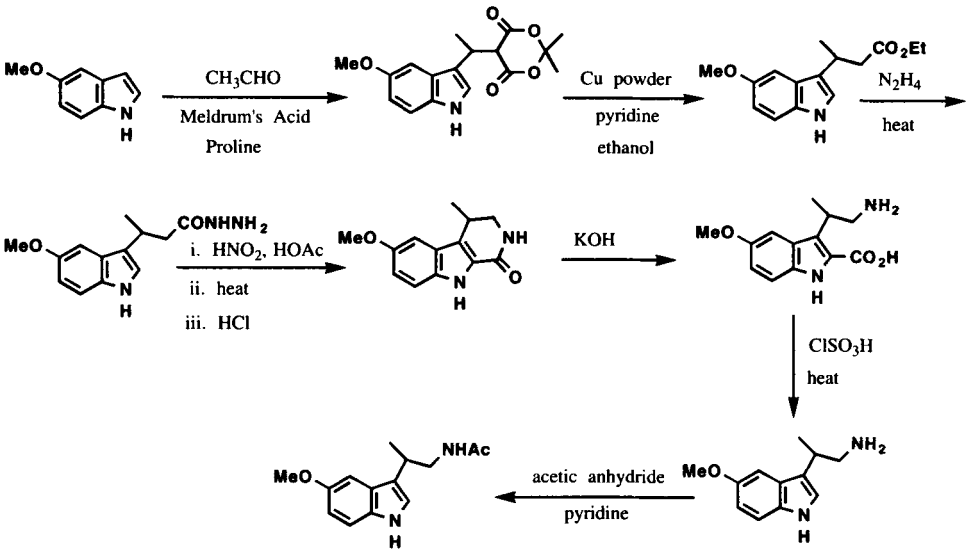
Flaugh and coworkers[80] modified the method of Oikawa and coworkers[81] in the preparation of indole-3-propionic esters. This approach was extended to prepare ß-methyl melatonin[82] as outlined in Scheme 33. An equimolar condensation of 5-methoxyindole, Meldrum's acid and formaldehyde produced the 5-methoxyindole-C-3 alkylated compound. Careful decarboxylative ethanolysis of the lactone gave the ester which when heated with hydrazine produced the hydrazide. Treatment with nitrous acid formed the azide and decomposition under Curtius conditions gave the tetrahydropyridoindole. Base hydrolysis yields the amino acid which was thermally decarboxylated using 5M methanesulfonic acid under nitrogen atmosphere. Acetylation of the amine with acetic anhydride and chromatography resulted in an overall yield of 9% of product. Other melatonin derivatives were also prepared by this method.

R-(-)- and S-(+)-3-ethoxycarbonyl-5-methyl-2-piperidone which were prepared from pulegone and 1-menthol, when reacted with the diazonium salt of p-anisidine using the Abramovitch Shapiro method of tryptamine synthesis were converted in 20% yields into S-(-)-ß-methyl melatonin and R-(+)-ß-methyl melatonin respectively.[82]

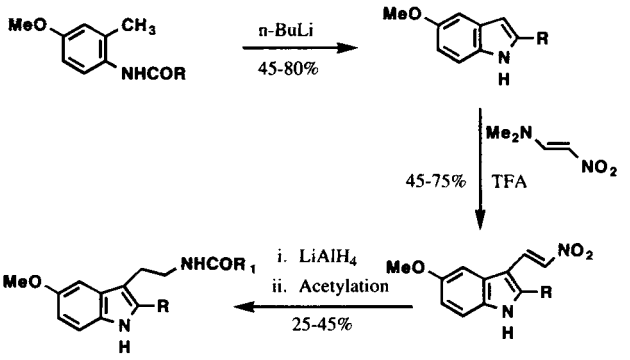
Use of the Madelung synthesis in modified form[83] provided 2-alkyl,-aryl substituted-5-methoxyindoles, which when coupled with 1-(dimethylamino)-2-nitroethylene as shown in Scheme 34 were elaborated into 2-substituted melatonin derivatives in 4-7% yield.[48]

Naphthalenic bioisosteres of melatonin including various N-acylamino substituents have been prepared. (7-methoxy-1-naphthyl)acetic acid[84] was synthesized in 6 steps from anisole and succinic anhydride *via* a Friedel-Craft acylation reaction. The synthetic pathway[85] to the naphthalenic isosteres is outlined in Scheme 35. Lithium aluminum hydride reduction of the amide to the amine resulted in low product yields therefore the amide was dehydrated to the nitrile and then reduced to

the amine. The alternative , the use of BH_3•THF to reduce the amide to the amine was not mentioned.



Scheme 33

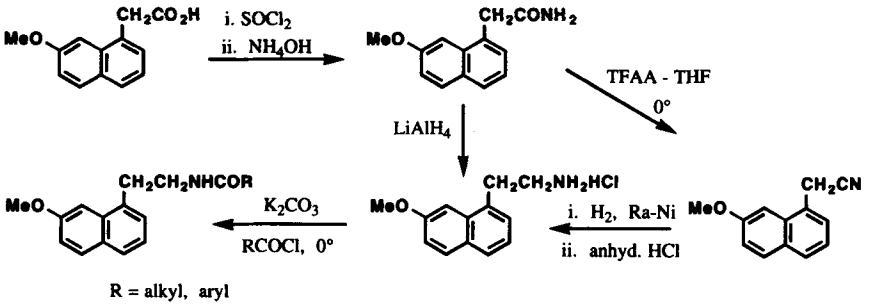


R = methyl, isopropyl, cyclohexyl, phenyl

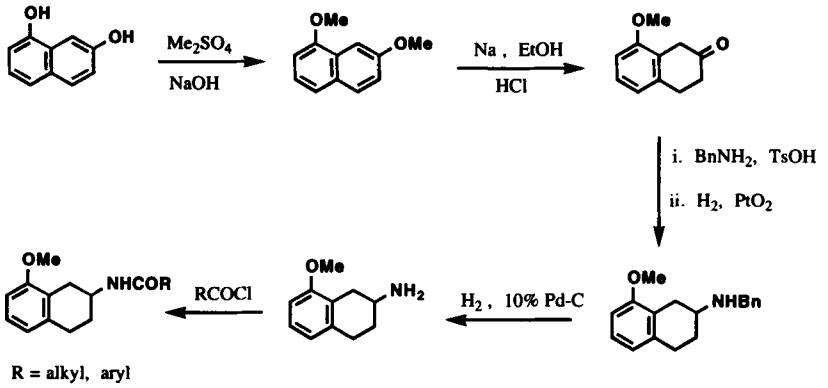
R_1 = methyl, cyclopropyl

Scheme 34

The tetralin ring structure [86] has been used as a template for non-indolic melatonin-like agents, removing the conformational flexibility of the ethyl amide side chain in melatonin. Thus 2-amido-8-methoxytetralin and derivatives have been prepared as shown in Scheme 36.

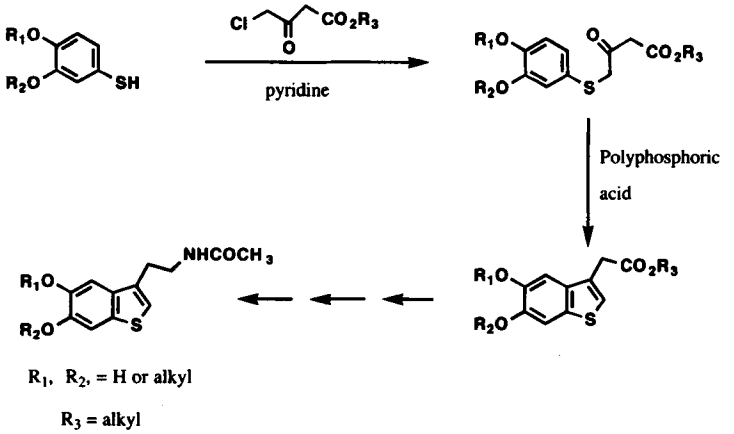


Scheme 35

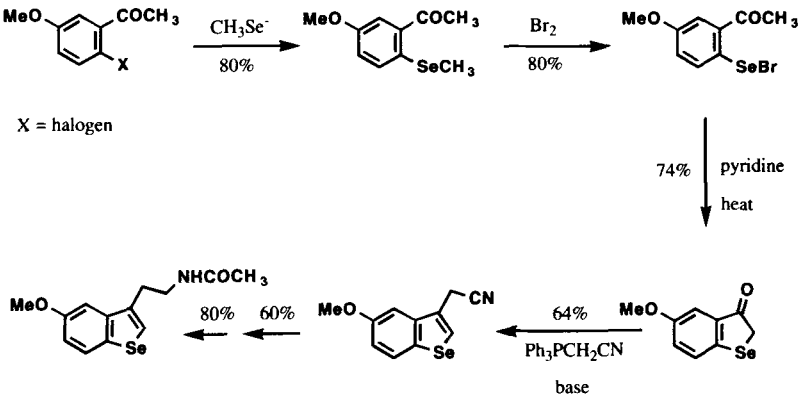


Scheme 36

Benzo(b)thiophenes[87] (27%) and benzo(b)selenophenes[88] (15%) have been synthesized as melatonin analogues are outlined in Scheme 37 and Scheme 38.



Scheme 37

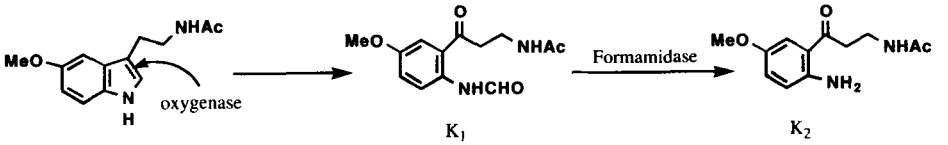


Scheme 38

The Abramovitch-Shapiro adaptation of the Fischer indole synthesis has been used to prepare[89] 6-fluoro- (17%) and 4,6-difluoromelatonin (12%). The reaction of dilute [^{18}F]fluorine gas with melatonin[90] in hydrogen fluoride at -70° yielded a mixture of radiochemically labelled 4-fluoro- (19%) and 6-fluoromelatonin (8%), which were separated by HPLC. 6-chloromelatonin[91,92] was prepared using the Batch-Leimgruber method of synthesis of 6-chloro-5-methoxyindole followed by the oxalyl route for side chain attachment. The Mannich base method of side chain elaboration has found application in the synthesis of N-succinyl-6-chloro-5-methoxytryptamine [93] and 2-iodo-5-methoxytryptamine[94]. Melatonin analogues, whereby the C-5 methoxy group has been replaced by fluoro[95], bromo[95], chloro[95] nitro[75] and amino[75] substituents have been prepared.

3. Synthesis of Melatonin Metabolites

N-formyl-N-acetyl-5-methoxykynurenamine (K_1), formed by the enzymatic 2,3-bond cleavage of melatonin by indoleamine-2,3-dioxygenase and N-acetyl-5-methoxykynurenamine (K_2), formed by the action of formamidase on K_1, are both brain metabolites of melatonin[96] as depicted in Scheme 39.

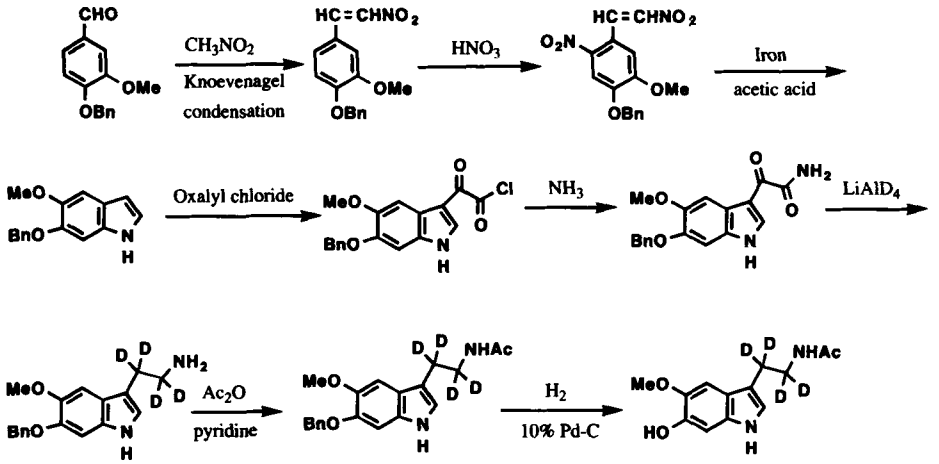


Scheme 39

Compounds K_1 and K_2 have been synthesized by ozonolysis of melatonin[79], or by chemical oxidation with singlet oxygen[97] or with m-chloroperbenzoic acid..[79] The major metabolic process for removal of melatonin is by 6-hydroxylation in liver microsomes.[98,99] The 6-hydroxymelatonin formed is excreted into the urine as sulfate (55-80%) and glucoronide (5-30%) conjugates.[99]

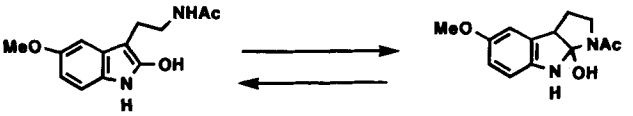
6-Hydroxymelatonin has been prepared from 6-benzyloxy-5-methoxyindole, utilizing the Mannich base methodology[100] (6 steps, 23%), or by employing the Knoevenagel condensation

route[101] (5 steps, 19%). 6-Hydroxymelatonin sulfate has been prepared[102] by reacting 6-hydroxymelatonin with chlorosulfonic acid in DMF. [$^2H_3$]-6-hydroxymelatonin sulfate was made[103] by heating the metabolite with CH_3OH-DCl. N-acetyl-6-hydroxy-5-methoxy-d_4-tryptamine has been synthesized[104] from 4-benzyloxy-3-methoxybenzaldehyde as shown in Scheme 40 in 8.5% yield.



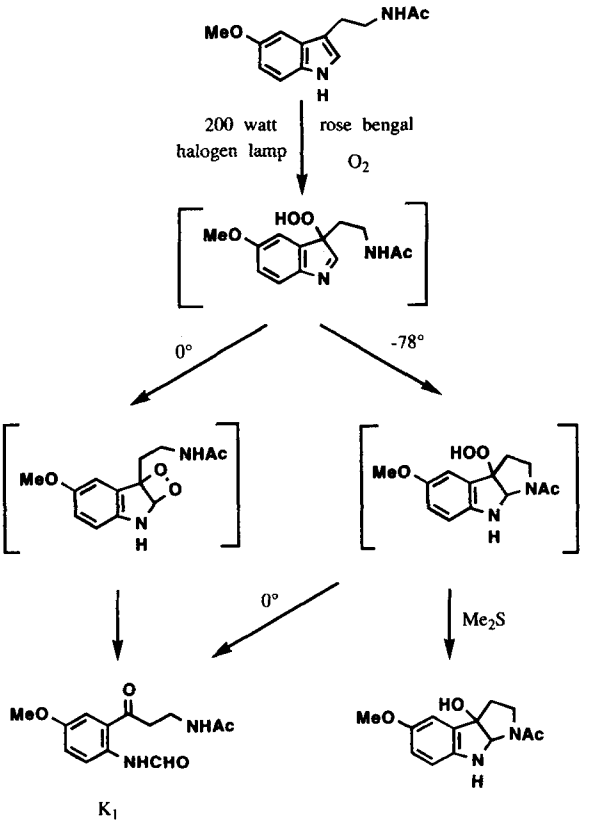
Scheme 40

A cyclic isomer of 2-hydroxymelatonin[105], identified by spectroscopic methods as 1-acetyl-1,2,3,3a,8,8a,-hexahydro-8a-hydroxy-5-methoxypyrrolo[2,3-b]indole (Scheme 41) has been found as a minor (5%) urinary metabolite in humans and in rats.



Scheme 41

The rose bengal sensitized photooxygenation[97] of melatonin as shown in Scheme 42 has produced the 3a-hydroxy cyclic isomer in 66% yield. At low temperature (-78°) the tricyclic 3a-hydroperoxy intermediate is formed which upon warming can rearrange to K_1, or be reduced with dimethylsulfide to the 3a-hydroxy tricyclic compound. At higher temperatures (0°) the dioxetane derivative is formed which collapses to give K_1. When the indole nitrogen is stabilized by acylation, the nitrogen lone-pair of electrons are no longer available to participate in breaking the C-O bond of the 1,2-dioxetane and dioxetane and epoxide indole compounds have been isolated [106] by low temperature (-30 to -40°) chromatography.

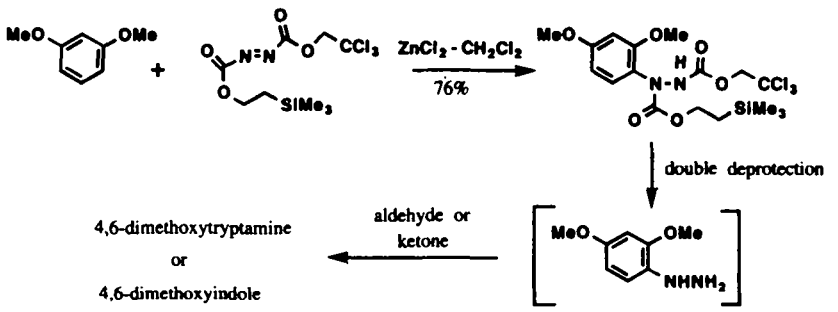


Scheme 42

4. Miscellaneous Reagents for Tryptamine Synthesis

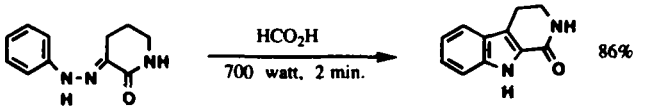
Attempts to introduce the ethylamine side chain into the indole nucleus with oxalyl chloride, followed by ammonia have either been unsuccessful owing to the difficulties in effecting complete reduction of the glyoxamide with lithium aluminum hydride or has given low product yields. Reduction of 6-bromoindole-3-glyoxylamide led to debrominated products.[47] We have reduced various indole-3-glyoxamides to tryptamines using BH_3•SMe_2[91] or BH_3•THF.[75]

Mitchell and Leblanc[107] have recently reported a mild method for the generation of alkoxyarylhydrazines which can be used for tryptamine synthesis. A doubly protected azodicarboxylate reagent was synthesized which reacted with 1,3-dimethoxybenzene by adding to the more electron deficient nitrogen of the azodicarboxylate to give the hydrazide. Removal of the trichloroethyl ester group with zinc-acetic acid and then the trimethylsilyl-ethoxycarbonyl group with fluoride provided the hydrazine which can be trapped by reaction with ketones or aldehydes as shown in Scheme 43.



Scheme 43

The Fischer indole cyclisation of arylhydrazones to the corresponding 1,2,3,4-tetrahydro-beta-carbolines has been effected by microwave heating[108] as illustrated in Scheme 44.



Scheme 44

An improved procedure for the decarboxylation of indole-2-carboxylate derivatives has been developed. Microwave accelerated decarboxylations resulted in near quantitative conversions in quinoline as solvent in 12 minutes in a sealed tube.[109]

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(Received June 28, 1994; in revised form October 17, 1994)