PHOTO-INDUCED REARRANGEMENT OF 1-ETHOXY-2-PHENYLINDOLE[1]

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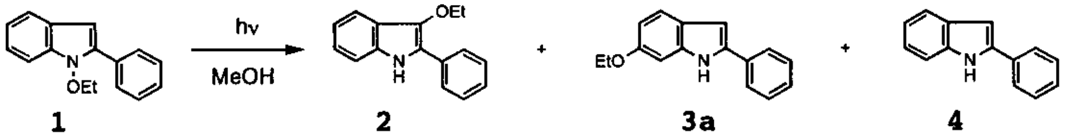
Abstract ——— Photoirradiation of 1-ethoxy-2-phenylindole in methanol afforded 3- and 6-ethoxy-2-phenylindoles. The structural determination of the latter is carried out by direct comparison of its spectral data with those of the authentic 4-, 5-, 6-, and 7-ethoxy-2-phenylindoles, whose syntheses are also included.

In our 1-hydroxyindole hypotheses,[2] we speculated that 3-, 4-, and 6-alkoxy (or hydroxy) substituted indole natural products might be originated from the corresponding 1-substituted indoles in plant leaves, where the latter could be transformed into the former by sun light.[2] Actually, about 25 years ago,[3] upon irradiation of 1-ethoxy-2-phenylindole (**1**) with Hannovia UV lamp in MeOH, we characterized 3-ethoxy-2-phenylindole (**2**) and 2-phenylindole (**4**) in 12 and 35% yields, respectively, in addition to 3% yield of unknown 2-phenylindole (unknown **3a**) containing an ethoxy group (Scheme 1).[3] The structural determination of unknown **3a** at that time was impossible not only due to the small quantity of isolation but also due to difficulty of preparing four possible authentic ethoxy-2-phenylindoles for direct comparison study.

Now, we have at last succeeded in the syntheses of authentic 4- (**5**), 5- (**6**), 6- (**3a**), and 7-ethoxy-2-phenylindoles (**3b**) applying our 1-hydroxyindole chemistry.[4] In this communication, we wish to report the structural determination of unknown **3a**.

Scheme 1

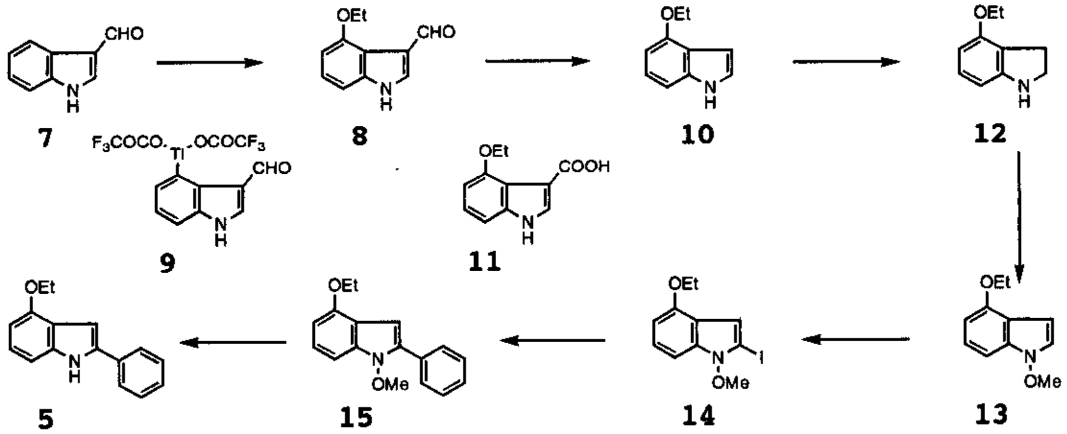


Preparation of 4-Ethoxy-2-phenylindole

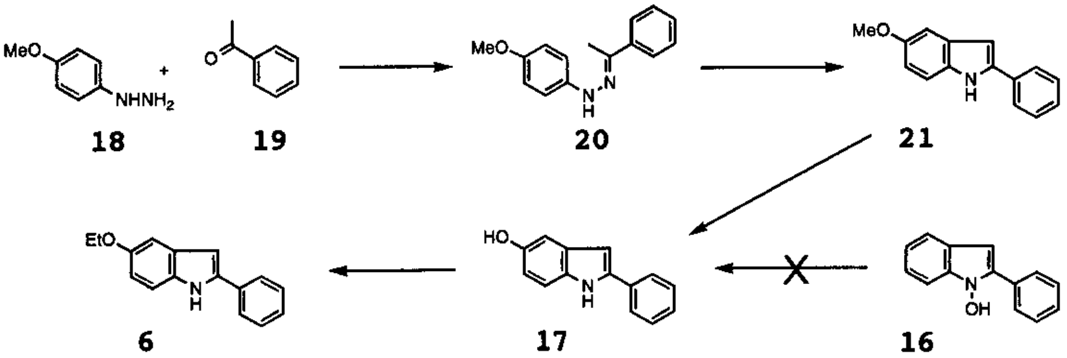
4-Ethoxy-2-phenylindole (**5**) was produced as follows (Scheme 2). According to our synthetic method for 4-substituted indoles,[5] 4-ethoxyindole-3-carbaldehyde (**8**) was obtained from indole-3-carbaldehyde (**7**) *via* (3-formylindol-4-yl)thallium bis(trifluoroacetate) (**9**) in 50% yield. Subsequent one pot reaction,[6] consisting of conversion of 3-formyl group to 3-carboxy group by sodium hypochlorite, followed by decarboxylation without isolation of the intermediate (**11**), afforded 4-ethoxyindole (**10**) in 40% yield. Reduction of **10** with $NaBH_3CN$ in

AcOH[7] afforded 2,3-dihydroindole (**12**) in 97% yield. Application of our 1-methoxyindole synthetic method to **12**, thus oxidation with 30% H_2O_2 in the presence of a catalytic amount of $Na_2WO_4 \cdot 5H_2O$,[4] followed by methylation with dimethyl sulfate,[4] produced 4-ethoxy-1-methoxyindole (**13**) in 51% yield. Regioselective lithiation[8] of **13** with *n*-BuLi and quenching of the resultant 2-lithio species with I_2 afforded 4-ethoxy-2-iodo-1-methoxyindole (**14**) in 83% yield. Palladium catalyzed Stille reaction[9] of **14** with tetraphenyltin gave 65% yield of the desired 2-phenyl compound (**15**), which was finally converted to the authentic **5** in 97% yield by catalytic hydrogenation on 10% Pd/C under atmospheric hydrogen.

Scheme 2



Scheme 3



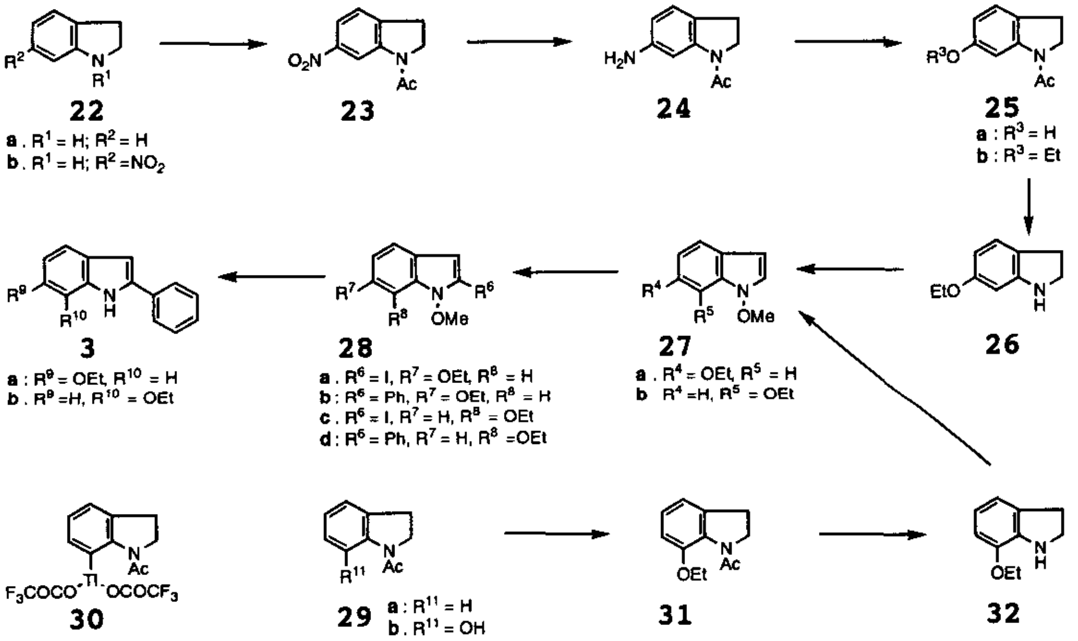
Preparation of 5-Ethoxy-2-phenylindole

Since the attempted nucleophilic substitution reaction[10] of 1-hydroxy-2-phenylindole[11] (**16**) did not generate the expected 5-hydroxy-2-phenylindole (**17**), 5-ethoxy-2-phenylindole (**6**) was produced utilizing Fischer indole synthesis as shown in Scheme 3. Heating in AcOH of the intermediate hydrazone (**20**), obtained by the reaction of 4-methoxyphenylhydrazine (**18**) with acetophenone (**19**), afforded 5-methoxy-2-phenylindole (**21**) in 40% overall yield from **18**. Demethylation of **21** with BBr_3 afforded 5-hydroxy compound (**17**) in 92% yield. Subsequent ethylation of **17** with EtI produced the authentic **6** in 89% yield.

Preparation of 6-Ethoxy-2-phenylindole

6-Ethoxy-2-phenylindole (**3a**) was produced from 2,3-dihydroindole (**22a**, Scheme 4). Nitration of **22a** to **22b** with a mixture of conc. H_2SO_4 and conc. HNO_3, followed by acetylation and subsequent catalytic hydrogenation of the resultant 6-nitro compound (**23**) on 10% Pd/C afforded 1-acetyl-6-amino-2,3-dihydroindole (**24**) in 72% overall yield. Diazotization of **24** with sodium nitrite and subsequent pyrolysis produced the desired 6-hydroxy compound (**25a**) in 36% yield. Ethylation of **25a** with EtI to **25b** proceeded in 86% yield and the following alkaline hydrolysis produced **26** in 95% yield. A series of reactions described in the preparation of **5** was successfully applied to **26** resulting in the formation of **3a** in 10% overall yield through three intermediates (**27a**, **28a**, and **28b**).

Scheme 4



Preparation of 7-Ethoxy-2-phenylindole

7-Ethoxy-2-phenylindole (**3b**) was prepared from **29a** (Scheme 4). According to our synthetic method of 7-substituted indoles,[12] **29a** was converted to 1-acetyl-2,3-dihydro-7-hydroxyindole (**29b**) in 42% yield through (1-acetyl-2,3-dihydroindol-7-yl)thallium bis(trifluoroacetate) (**30**). Ethylation of **29b** with EtI afforded 96% yield of 7-ethoxy compound (**31**), which was then hydrolyzed with aqueous 8% NaOH to give 2,3-dihydro-7-ethoxyindole (**32**) in 92% yield. A series of reactions described in the preparation of **5** was also successfully applied to **32**, resulting in the formation of **3b** in 20% overall yield through three intermediates (**27b**, **28c**, and **28d**).

Comparing the spectral data (IR, UV, ^{1}H-NMR, and MS) and melting points of four authentic samples with those of unknown **3a**, isolated from the photoirradiation of **1**, we have at last determined unequivocally that it is 6-ethoxy-2-phenylindole (**3a**). Consequently, we have established that various 1-substituents of indoles, including 1-alkoxy group, have the possibility of migration to 3-, 4-, and/or 6-positions upon photoirradiation.[3] These results could be explained by sigmatropic [1,3], [1,5], and [1,7] rearrangements.

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