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SELENIUM DIOXIDE ENTRY INTO 3-ACYLINDOLES

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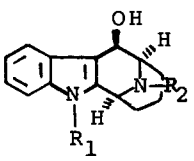
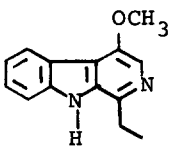
Recently we have been interested in the synthesis of alcohols 1 and 2 for study as potential antihypertensive agents. Impetus for this research stems from the need to obtain compounds which will selectively block β_1-receptor sites (heart) in the adrenergic nervous system in preference to their β_2-counterparts.[1] Alcohols 1 and 2 can be formally viewed as the reduction products of the corresponding 3-acylindoles, hence our approach toward 1 and 2 has centered on the preparation of such 3-acyl compounds. Further interest in this area has been stimulated by the recent isolation of natural products such as crenatine 3[2], dehydrocrenatine[3], crenatidine, 1-methoxy canthine-6-one 4[4]; and the 3-acylindole, borrecapine 5.[5]



1 R_1=CH_3, R_2=CH_2Ph

2 R_1=H, R_2=H



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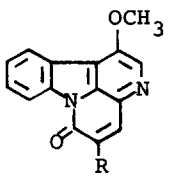

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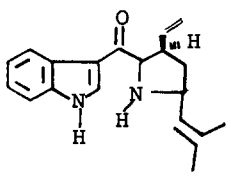

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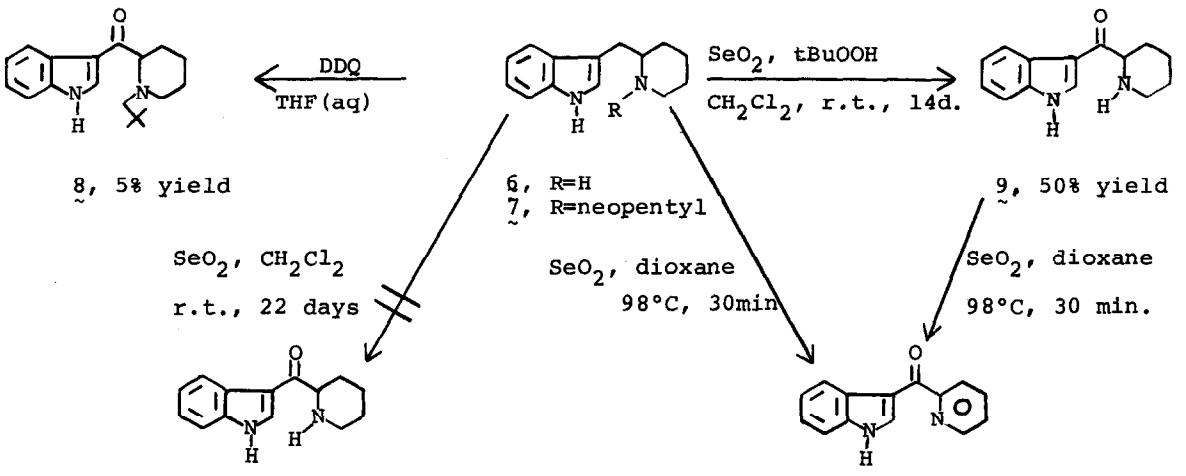
Two basic approaches to 3-acylindoles were envisaged; the first rested on the acylation of indole with acid halides[6] while the second route involved the direct oxidation of preformed 3-alkylindole intermediates. The acid halide pathway was fraught with difficulties including competing reactions between N-acylation and C-acylation[7]; moreover, this sequence was useful only for indole derivatives containing the N_a-H function.[8] The second approach appeared more promising in view of the recent report of Oikawa et al. which demonstrated that 1,2,3,4-tetrahydrocarbazole could be converted to its 4-oxo derivative in good yield with dichlorodicyanoquinone.[9] However, when the model compound 3-indolyl-2'-(N-neopentyl)-piperidyl methane (7) was treated with DDQ in aqueous tetrahydrofuran only a 5% yield of the desired 3-acylindole 8 was isolated. Similar results were observed in the case of 3-indolyl-2'-piperidyl methane 6[10].

These poor results in conjunction both with the cost of DDQ and the amount required for oxidation led to a search for another oxidizing agent. Selenium dioxide has been known for some time to oxidize activated methylene groups, although the few reported reactions of selenium dioxide with indole derivatives illustrate that selenides[11] and dimers[12] are the major products of this sequence. Despite this obstacle, the work by Sharpless[13] on allylic oxidations which employed selenium dioxide and a peroxide seemed to offer some advantages because of the catalytic amounts of selenium dioxide used in this method.

The results of the study on indolyl methyl piperidine derivatives are illustrated in Scheme I. Treatment of the indole piperidine 6 with selenium dioxide and the peroxide at room temperature gave a 50% yield of the desired 3-acylindole 9.[14] When the same sequence was carried out in the absence of the peroxide (at room temperature), no reaction occurred. In an attempt to improve the yield of this oxidation, the amine 6 was heated with selenium dioxide in refluxing

Scheme I

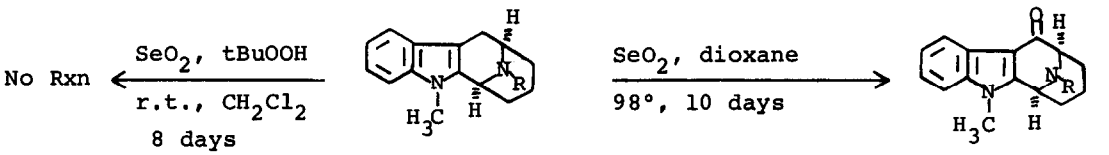


dioxane[15]; however, the product was not the 3-acylindole 9 but the indolyl pyridoketone 11,[16] isolated in 90% yield. The same ketone 11 was also obtained by oxidation of 9 with selenium dioxide in refluxing dioxane (no t-BuOOH present). Alteration of the reaction conditions provided the piperidylketone 9 by one procedure and the pyridylketone 11 by the other.

With these two methods in hand, attention was now turned to oxidation of the tetracyclic indole 12, as illustrated in Scheme II. Stirring 12 in methylene

chloride with selenium dioxide and the hydroperoxide for eight days resulted in nearly complete recovery of starting material. Since the bicyclo [3.3.1] nonane skeleton contained in the base 12 should not readily undergo aromatization (Bredt's rule) of ring C, in contrast to the situation in 6, the tetracyclic amine 12 was heated with selenium dioxide in refluxing dioxane for ten days. After workup, a 54% yield (68% based on recovered starting material) of the desired 3-acylindole 13 (mp = 188-9°, from acetone) was obtained.[17]

Scheme II



12, R=CH_2Ph
14, R=H

13, R=CH_2Ph
54% yield
15, R=H

The set of reactions in Schemes I and II clearly illustrate the potential of this method. This procedure has several distinct advantages over the dichlorodicyanoquinone approach not the least of which is cost; selenium dioxide is much cheaper than DDQ and can be used in catalytic amounts when employed in the presence of a peroxide.[13] Furthermore, the selenium dioxide method works reasonably well for the oxidation of indolyl piperidine and indolyl pyridine derivatives; whereas, DDQ does not. Further work to maximize the yields, and to explore extension of this chemistry for the synthesis of natural products 3-5 is underway in our laboratories.

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10. The method of Oikawa and Yonemitsu also gave very low yields of product when 1-alkyl-1,2,3,4-tetrahydro β-carbolines were treated with DDQ. Presumably attack on the β-carboline N-H function, followed by aromatization of ring C are competing reactions which lead to low yields of the 4-oxo derivatives.
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14. 9: mp 208-210°C (acetone); ir(KBr) 3406(broad enolic OH), 3300 and 1620 cm^{-1}(C=O); M^+228; UV(EtOH, λnm) 304, 256 and 240nm.
15. Heating the reaction in DMF or Dioxane is sufficient to convert the red selenium to black selenium which can be filtered from the medium (S. Milstein and E. Coats, Aldrichimica Acta, 11, 10 (1978).
16. This ketone has been previously reported in the literature to arise by SeO_2 oxidation of 3-indolyl-2'-pyridylmethane. G. R. Clemo and J. C. Seaton, J. Chem. Soc., 3282 (1954).
17. 13: UV(EtOH, λnm) 307(ε = 1.22 x 10^4), 267(ε = 1.77 x 10^4) and 248nm(ε = 2.0 x 10^4); ir(KBr) 3070, 2960, 2940, 1640 (C=O)cm^{-1}; Mass Spectrum M^+ at m/e 330(54.8). The carbonyl absorption in the ir spectrum of N-methyl-3-indole carboxaldehyde appears at 1635cm^{-1} very similar to that in the spectrum of 13 [B. E. Leggetter and R. K. Brown, Can. J. Chem., 31, 775 (1973)].

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