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SYNTHETIC STUDIES IN THE β-CARBOLINE AREA
NEW ENTRY INTO 4-SUBSTITUTED AND 3,4-DISUBSTITUTED β-CARBOLINES

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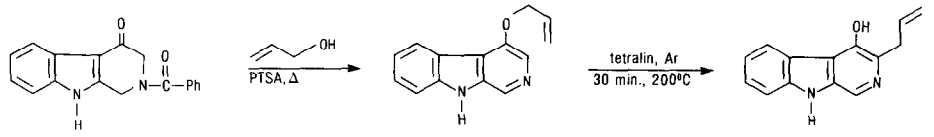
Summary: The [3,3] sigmatropic rearrangement of the allyl ether 2 to provide 3 represents a new synthetic entry into 3,4-disubstituted β-carbolines. In keeping with the interest in such substituted β-carbolines, the hydrazine mediated conversion of 4-oxo-tetrahydro β-carboline 1b into 4-amino β-carboline 2b is also described, as well as the analogous reaction in the isoquinoline series.

The discovery of the potent affinity of both 3-substituted[1-5] and 3,4-disubstituted β-carbolines for benzodiazepine receptors has stimulated renewed interest in the synthesis of these compounds.[2-5,6] The lability of agents such as β-carboline-3-carboxylic acid ethyl ester to *in vivo* hydrolysis[7] has been overcome by preparation of the t-butyl ester,[8] while the 3,4-disubstituted β-carboline DMCM reported by Braestrup[2] has also been shown to be somewhat resistant to esterase hydrolysis.[9] For these reasons an investigation directed toward preparation of 3,4-disubstituted β-carbolines was initiated recently in our laboratory. This has resulted in the successful functionalization of position-3 of the β-carboline nucleus by way of the Claisen rearrangement of the corresponding allyl substituted ether (position-4). The synthesis began with 2-benzamido-4-oxo-1,2,3,4-tetrahydro β-carboline 1[10] which was subsequently heated with allyl alcohol under the conditions illustrated below:



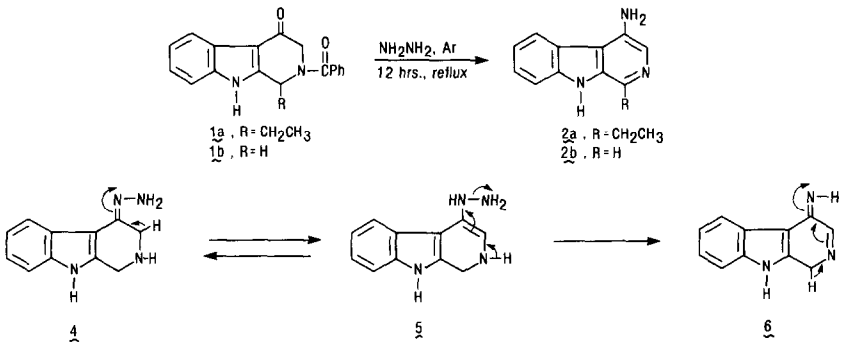
1 2 3, 84% yield

The formation of 2 was straightforward since hydrolysis of the benzamide function, allyl enol ether formation and oxidation to the fully aromatic β-carboline all occurred in a one pot reaction. The desired [3,3] sigmatropic rearrangement to provide 3 was effected in 84% yield by heating 2 at 200°C in tetralin. To our knowledge this is the first example of the occurrence of such a rearrangement in ring C of a β-carboline, and it has stimulated interest in other 4-substituted β-carbolines. In this vein, the [3,3] sigmatropic rearrangement of the 4-amino analog[11] was felt to be of importance and research directed toward a simple synthesis of 4-amino β-carbolines was begun.

Earlier during the synthesis of the β-carboline alkaloid crenatine[10], it was found that 1-ethyl-4-oxo-1,2,3,4-tetrahydro β-carboline 1a could be converted into 1-ethyl-4-amino

β-carboline 2a upon heating 1a in hydrazine, as illustrated in Scheme I. The yield and ease of this sequence prompted further study of this reaction, as outlined in Schemes I-IV. The proposed mechanism for this conversion is shown for 1b at the bottom of Scheme I. Removal of the benzamide moiety from 1b with hydrazine, with simultaneous formation of the hydrazone 4, followed by the steps indicated (4-6) would result in the generation of ammonia accompanied by 4-amino β-carboline 2b. Indeed, on heating 1b in refluxing hydrazine for 12 hours, a 70% yield of the 4-amino β-carboline 2b was realized.

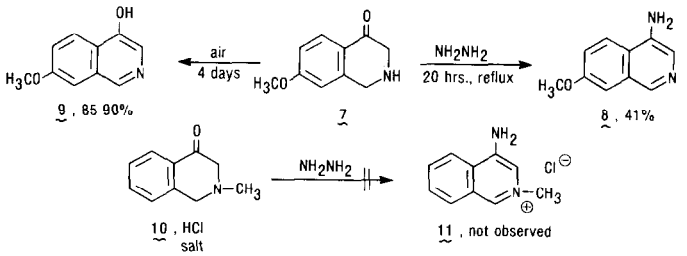
Scheme I



Attention now turned to the reaction of hydrazine with 4-oxo-7-methoxy-1,2,3,4-tetrahydroisoquinoline 7, prepared by the method of Mann.[12] As illustrated in Scheme II, treatment of the 4-oxo-tetrahydroisoquinoline 7 with hydrazine gave the desired 4-amino-7-methoxyisoquinoline 8 albeit in only 41% yield. Although no attempts to maximize the yield of this transformation have been made, the low yield may be due in part to the inherent lability of 7 toward oxidation. When 7 was simply allowed to stand as a solid for several days in the air a nearly quantitative conversion into 4-hydroxy-7-methoxyisoquinoline 9 occurred. Nonetheless, the hydrazine mediated conversion of 7 into 8 may provide an alternate pathway to analogs of chloroquin.[13]

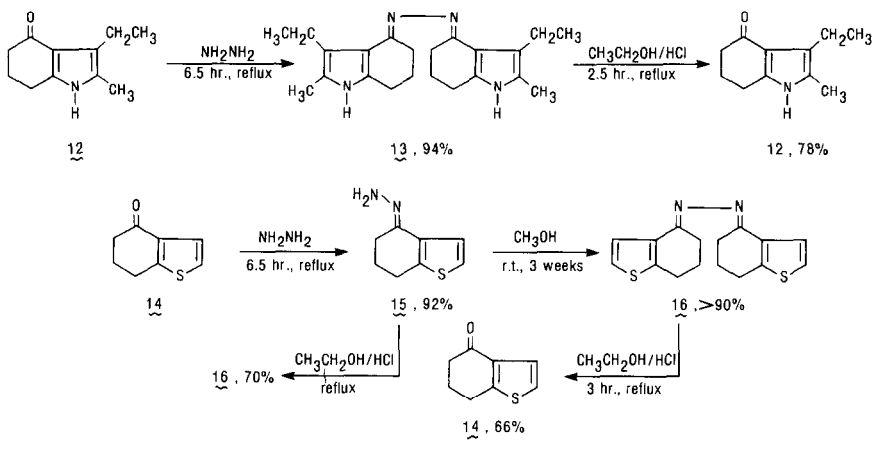
Examination of the proposed mechanism outlined in Scheme I clearly demonstrates that an acidic hydrogen (2-position, N-H) should facilitate the reaction. In concert with this, Mann et al[12] reported that 2-methyl-4-oxoisoquinoline hydrochloride 10 gave no trace of the desired isoquinoline cation 11 when heated in refluxing hydrazine even over extended periods of time (Scheme II). In a similar study to determine the effect of an acidic N-H (intermediate 5, Scheme I) on the progress of the reaction, the 3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole 12 was heated with hydrazine, however, only the azine derivative 13 was isolated from the reaction mixture. In another attempt, 4-oxo-4,5,6,7-tetrahydrothiophene 14 gave the hydrazone 15 in 92% yield, while as illustrated in Scheme III, extended reaction times gave the azine 16 in high yield. However, none of the desired 4-aminoindole or 4-aminothiophene derivatives, respectively, were formed in this sequence. These results demonstrate the necessity of a γ-acidic hydrogen to drive the amination-oxidation to completion.

Scheme II



As described above, it had been shown that 10 was not converted into 11 in refluxing hydrazine, however, it has been reported [12] that the phenylhydrazone derivative of 10 did give the 2-methyl-4-aminoisoquinolinium salt 11 when this compound was heated in ethanolic hydrogen chloride. The difference in reactivity is probably due to the stability of the anilinium ion ($PhNHNH_2$,CH_3CH_2OH, HCl) vs that of the amide anion which would result from the reaction of 10 with hydrazine. Since Mann et al[12] had achieved some success with hot ethanolic hydrogen chloride, the two azines 13 and 16 (Scheme III) were heated in refluxing ethanolic hydrogen chloride, however, only the two starting ketones 12 and 14 were isolated. This resulted from hydrolysis of the azine derivatives 13 and 16, respectively, on workup. In a similar attempt, the hydrazone 15 in the thiophene case was heated in ethanolic hydrogen chloride for several hours, however, only the crystalline azine 16 (72% yield) was isolated from this sequence.

Scheme III

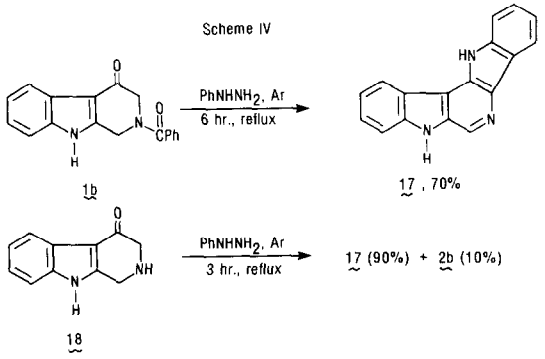


Although 4-amino β-carboline 2b could be prepared in good yield via the reaction of 1b with hydrazine and the corresponding 4-aminoisoquinoline synthesized by a similar route, the work of Mann[12] using phenylhydrazine (CH_3CH_2OH, HCL, 10 → 11) seemed a viable alternative.

In this vein, 2-benzoyl-4-oxo-1,2,3,4-tetrahydro β-carboline 1b was heated for six hours with excess phenylhydrazine. The compound produced cleanly by this sequence in 70% yield was the undesired, but interesting, 3,4-indolosubstituted β-carboline 17 (Scheme IV).[14] This base 17 can be viewed as the product of a Fischer indole cyclization[15] of 1b with phenylhydrazine. Since the necessary removal of the benzoyl group with phenylhydrazine may have retarded the formation of 4-amino β-carboline 2b in favor of the formation of the Fischer product 17, the 4-oxo-1,2,3,4-tetrahydro β-carboline 18 was subjected to reaction in

refluxing phenylhydrazine. In this case some of the desired 4-amino ß-carboline 2b was formed (10%) supporting the mechanistic (acidic N-H, intermediate 5, Scheme I) hypothesis put forth earlier. The major product, however, was the Fischer indole derivative 17 which comprised the remainder (90%) of the mixture.

Scheme IV



1b

17, 70%

18

In summary, the hydrazine mediated amination-oxidation of 4-oxo-1,2,3,4-tetrahydro ß-carbolines proceeds smoothly in refluxing hydrazine to provide the corresponding 4-amino ß-carbolines. For the reaction to proceed in a practical sense, the substrate requires the presence of an acidic hydrogen (N-H) in the ring undergoing reaction, furthermore the sequence can be extended to 4-oxo-1,2,3,4-tetrahydroisoquinolines. In the 4-oxo-tetrahydro ß-carboline series and presumably in the 4-oxo-tetrahydroisoquinolines, hydrazine appears to be a superior reagent for this transformation since it cannot be diverted into the Fischer indole product (i.e. 17). Studies directed toward the aza Cope rearrangement of the nitrogen analog of 2 are in progress.

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