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TRANSFER OF FUNCTIONALIZED CARBON FRAGMENTS VIA SUBSTITUTED 5,10-METHYLENETETRAHYDROFOLATE MODELS. Approach to dihydroindole and indole alkaloids.

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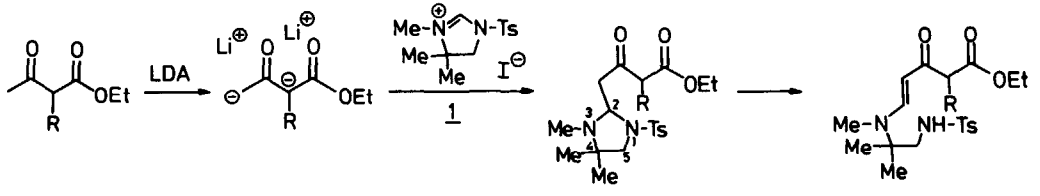
Abstract: 4-(2-N(1)-tosyl-N(3)-methyl-4,4-dimethylimidazolidyl)-3-ketobutanoate reacts with tryptamine, in the presence of acetic acid, to give primary "carbon transfer" products, which can be conveniently converted to synthetically useful indole and dihydroindole derivatives.

Tetrahydrofolate coenzymes are involved in the biological transfer of a one carbon unit at different oxidation levels[2]. Models of folate coenzymes have been developed in this laboratory which can transfer a =CH- [3] or a $-CH_2-$ [4] unit via mechanisms analogous to those operative in the biochemical processes. Since, in principle, models incorporating a wide variety of sophisticated substituents at the transferable carbon can be constructed[5a,b], such models provide the opportunity of transferring substituted carbon fragments to suitable substrates.
In this communication, the application of this concept to a synthetic approach to dihydroindole and indole alkaloids is presented.

The strategy of the synthesis involved the construction of substituted 5,10-methylenetetrahydrofolate analogues 3a,b and transfer of the "multifunctionalized carbon fragments" to tryptamine, followed by appropriate cyclization steps. The imidazolidine derivatives 3a,b were obtained in high yields by addition of imidazolinium salt 1 to anions 2a,b, prepared in situ from the corresponding β-keto esters[6]. The reaction mixtures contained small amounts of enamino ketones 4a,b, which were readily recognized by their characteristic NMR spectra (vinyl protons). These are derived from the primary reaction products (3a,b) during the workup of the mixture[7].

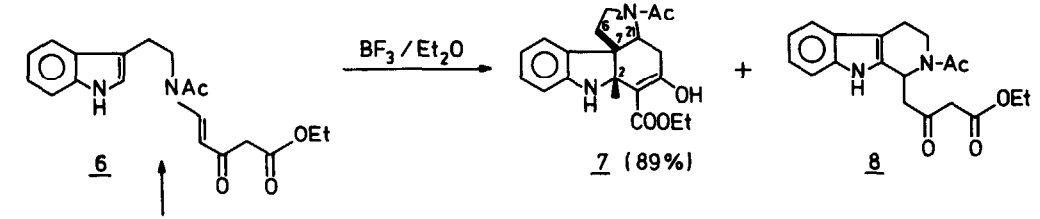
The critical step in the synthetic scheme is the transfer of C(2) and the attached fragment of 3a,b to tryptamine. This reaction was accomplished by refluxing a mixture of tryptamine and 3a,b in acetonitrile, in the presence of acetic acid. Following chromatographic separation, the "transfer-products 5a,b" [8] were obtained in 50-60% yields. The formation of 5a,b is visualized as an exchange reaction of the amine moiety in 4a,b -produced by the acid-cata-



2a R = H
2b R = Et

3a R = H (83%)
3b R = Et (72%)

4a R = H
4b R = Et



6

7 (89%)

8

5a R = H (56%)
5b R = Et (60%)

9a R = H (95%)
9b R = Et (90%)

10a R = H
10b R = Et

lyzed ring-opening of 4a,b- by tryptamine, as the acceptor reagent.

The enaminoketone ester 5a was converted to the dihydroindole derivative 7 -a potential vindoline intermediate- by acetylation of the amine function and treatment of the acetyl derivative 6 with BF_3/Et_2O (R.T. 15 min.). Under the latter conditions, the product consisted exclusively (according to the NMR spectrum) of 7 (89%; m.p. 189-191°). When a higher temperature (90°) was employed, both 7 and 8 were formed in the reaction in low yield (12%). The ratio of 7/8 in the product mixture was shown by NMR to be 70/30. The structure and stereochemistry of 7 was established by NMR and Nuclear Overhauser differential spectra[9]. Especially informative, regarding the stereochemistry, was the differential spectrum in which the C(2)-H [10] was irradiated, whereby the C(21)-H [10] and one of the C(6) [10] protons were found to display a Nuclear Overhauser effect.

The stereochemistry at C(21)-H in 7 is opposite to that found in the related intermediate prepared by Büchi[11] and Takano[12] and in the corresponding alkaloids. It should be pointed out that the C(21)-H in the α-configuration is the thermodynamically favoured form in the so called "Büchi intermediate" [11,12] and presumably in 7 and that epimerisation at this centre is possible via the cleavage and re-formation of the N(4)-C(21) bond (reversal of a Michael adduct). In this context it is noteworthy that in Takano's synthesis[12], the last step -a Li/NH_3 reduction- converts a mixture of C(21)-epimeric compounds to a single product with a C(21)-H α-configuration. These considerations lead us to regard compound 7 as the kinetic product and its formation suggests that the stereochemistry at the C(2), C(7) and C(21) centres may be controlled by an intramolecular 1,4-cycloaddition reaction[13].

The approach involving the conversion of the "carbon fragment transfer products" (5a,b) to β-carboline derivatives of synthetic interest is illustrated by the reaction 5a,b → 9a,b. This cyclization step proceded in high yield (9a, 95%; 9b, 90%) when 5a,b were allowed to react with HCl/EtOH, at room temperature, for 15 min. The structure of the crystalline salts 9a and 9b was attested by their spectral data [9a, m.p. 177-179°; IR(KBr): 1735, 1710 cm^{-1}, NMR(DMSO): δ 5.07 m, C(2)-H carboline ring; 9b, m.p. 155-158°, IR(KBr): 1735, 1700 cm^{-1}, NMR(DMSO): δ 5.05 m, C(2)-H carboline ring]. When 9a was treated with excess of $NaBH_4$ in ethanol (16 h), a crystalline product (m.p. 205-210°), consisting of a stereoisomeric mixture corresponding to 10a [IR(KBr): 3270, 1610 cm^{-1}; FD mass spectrum mol. wt = 256] was isolated in 69% yield. A similar reaction of 9b (reaction time, 5 days) led to the crystalline isomeric mixture 10b [m.p. 200-220°, 30%, IR(KBr): 3260, 1602 cm^{-1}; FD mass spectrum mol. wt = 284]. The latter product (10b) could also be prepared in two separate steps, involving $NaBH_4$ reduction of 9a to the corresponding alcohol [m.p. 157-160°; FD mass spectrum mol. wt = 330; 66%] and cyclization of the latter to

10b (CH_3COOH/CH_3CN, Δ) in 84% yield.

Conversion of intermediates of the type 7 and 10a,b to the corresponding alkaloids is currently in progress.

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Satisfactory spectral data have been obtained for all new compounds described in this communication.

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7. 3a,b were converted to 4a,b upon mild treatment with acid or base.
8. The Z-configuration of 5a,b was attested by the coupling constants of the vinylic protons. (5a J = 7 Hz, 5b J = 7 Hz).
9. Salient chemical shifts in the NMR of 7 (C_6D_6): δ 4.20 [1H, 2, C(2)-H], 3.43 [1H, dxd J = 12 Hz, J = 4Hz, C(21)-H].
Details of the NMR spectra and the NOE experiments shall be presented elsewhere.
10. The numbering system used is one based on a biogenetic interrelationship of indole alkaloids as proposed by J. LeMen and W.I. Taylor, Experientia 21, 508 (1965).
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13. Mechanistic aspects of the formation of 7 shall be discussed in a forthcoming paper.

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