TRANSFER OF A FUNCTIONALIZED CARBON-FRAGMENT VIA A (SUBSTITUTED) N^5,N^{10}-METHYLENETETRAHYDROFOLIC ACID MODEL. AN APPROACH TO D,L-PYRIDINDOLOL.

Hans Bieräugel, Ronald Plemp[1] and Upendra K. Pandit*.

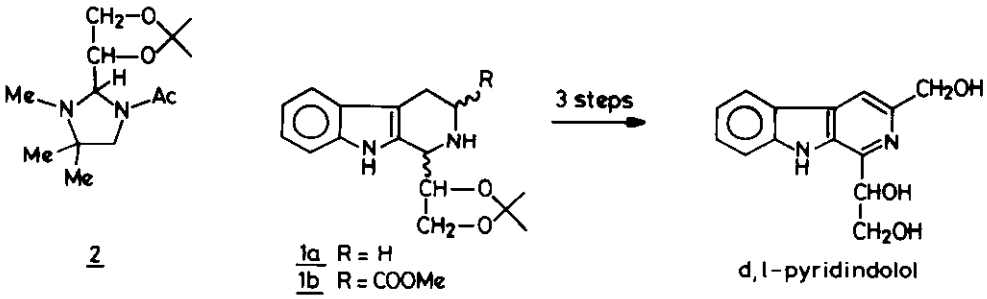
Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS AMSTERDAM, The Netherlands.

Abstract. Reaction of dl-tryptophan hydrochloride with 1-acetyl-3,4,4-trimethyl-2-[1,2-dihydroxyethyl]imidazolidine acetonide (2) leads to the formation of the β-carboline precursor of d,l-pyridindolol.

The alkaloid pyridindolol, from Streptomyces alboverticillatus, was first isolated by Umezawa and coworkers[2a-c], in 1975. These authors have also established its structure and showed that it was a specific inhibitor of bovine liver β-galactosidase. In connection with a programme on the application of folic acid models in carbon-fragment transfer reactions, we have undertaken the synthesis of a variety of indole and isoquinoline alkaloids[3], including that of pyridindolol. The recently reported total synthesis of pyridindolol by Cook et al.[4] prompts us to describe the synthesis of the β-carboline derivative (1b), which contains the complete structural framework of pyridindolol. 1b has been converted into the alkaloid in three conventional steps[4]. The emphasis of the present communication lies in the demonstration that a functionalized carbon fragment can be readily transferred via the "folic acid model" approach.

The strategy for the synthesis of the desired β-carboline precursor 1b required the C(2)-functionalized imidazolidine derivative 2 as the appropriately substituted N^5,N^{10}-methylenetetrahydrofolic acid model. The importance of the gem-dimethyl substitution pattern of the nitrogen ring has been shown previously in the synthesis and carbon-transfer reactions of N^5,N^{10}-methenyl and N^5,N^{10}-methylenetetrahydrofolic acid models[3,5].

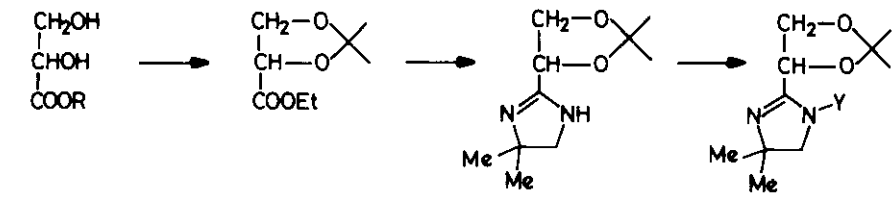
Commercially available d,l-glyceric acid (3) was esterified (Scheme I) and subsequently converted into the corresponding acetonide (4 ⟶ 5) by reaction with dimethoxypropane (toluene/p-TsOH, bath temp. 130°; 96%). The protected ester (5) was allowed to react with 1,1-dimethyl-1,2-diaminoethane, first, under reflux condi-



2

1a R = H
1b R = COOMe

d,l-pyridindolol

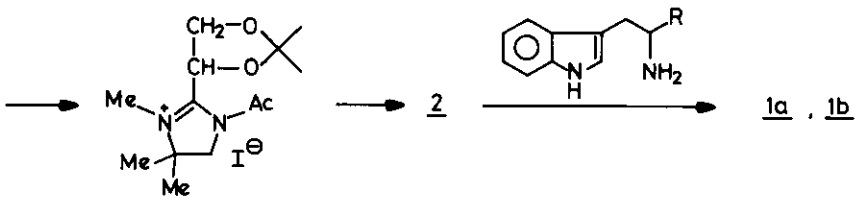


3 R=H
4 R=Et

5

6

7a Y = Ts
7b Y = Ac



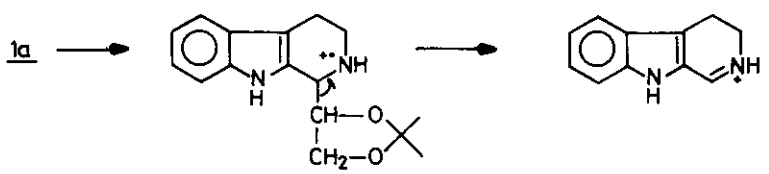
8

2

1a , 1b

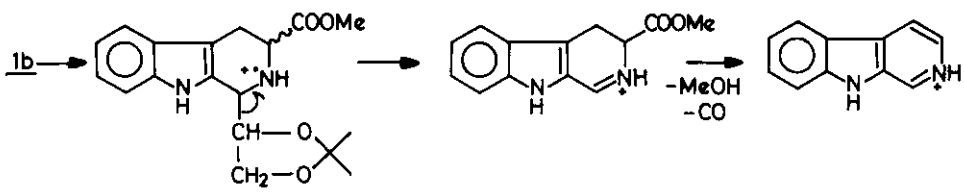
9a R = H
9b R = COOMe

Scheme I



M•• (272 , 14%)

a (171 , 100%)



M•• (330, 7.7%)

b (229 , 100%)

c (169 , 55%)

Scheme II

tions in toluene (overnight) and thereafter at 240°, whereupon the imidazoline 6 distilled over (100-113°/12 mm; 52%). Although the latter could be tosylated to 7a in 96% yield, the desired conversion of 7a to its N(3)-methyl salt proved unsuccessful, presumably owing to steric hinderance of the acetonide moiety (to methylation) in a conformation about the C(2)-C(6) bond in which the bulky acetonide and the tosyl groups are away from each other. The corresponding acetyl derivative 7b, which was readily prepared (88%) could, however, be methylated with methyl iodide to yield the salt 8 as a yellow foam (73%). Reduction of 8 with $NaBH_4$ (EtOH, 0°) gave a stereoisomeric mixture of 2 as a colourless oil (56%). The structures of 6, 7b, 8 and 2 are supported by their ^{1}H NMR spectral data (Table).

Table

^{1}H NMR data on reduced imidazole derivatives.

Compound	$Me_{O}^{O}Me$		MeCO	N(3)Me	C(2)H	C(4)Me$_2$	
2[a]	1.29 s			2.20 d 4Hz		0.88 s	1.09 s
	1.34 s	1.40 s	2.02 s	2.34 d 4Hz	b	0.92 s	1.18 s
6	1.35 s	1.38 s	-	-	-	1.21 s	1.25 s
7b	1.42 s	1.52 s	2.14 s	-	-	1.28 s	1.32 s
8	1.67 s	1.70 s	2.45 s	3.52 s	-	1.38 s	1.57 s

a. The sets of acetal and N(3) methyl signals arise from the stereoisomers of 2.

b. The proton is submerged under the multiplets arising from the dihydroxyethyl side chain moiety.

The transfer of the substituted methylene moiety from the folic acid model compound 2, to tryptamine (9a) was carried out by refluxing the two synthons in acetonitrile (AcOH, catalyst). The diastereomeric mixture of carboline 1a was obtained, after chromatography, as an oil, in 79% yield. The structure of 1a was established by its ^{1}H NMR spectra. The mass spectral data of 1a further supported the structure assigned to it (Scheme II). Particularly revealing in the mass spectrum of 1a is the peak at m/e 171 (100%) corresponding to fragment a formed upon loss of the complete side chain. Finally, in an analogous reaction to tryptamine, tryptophan ester hydrochloride (9b. HCl) was condensed with 2 to give a diastereomeric mixture of 1b in 72% yield. While the ^{1}H NMR date of 1b was consistent with the assigned structure[6], its mass spectral fragmentation pattern (Scheme II) provided additional supporting evidence. Fragmentation of the side-chain once again gave the main fragment b (m/e 229, 100%); this is followed by loss of MeOH + CO

to give the fully aromatic ion c (m/e 169).

Since the conversion of 1b into d,l-pyridindolol has been described in the literature[4], its synthesis, as described above, constitutes the formal synthesis of the racemic alkaloid. It should be noted that no effort has been spent at this stage to optimize the yields of the steps described in the sequence. Attempts to prepare pyridindolol with the natural configuration, starting from optically active glyceric acid[7] has thus far been unsuccessful, due to racemization during one or more steps of the synthetic sequence.

References.

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6. 1b, IR($CHCl_3$): 3460(NH), 3350(NH), 1730 (ester) cm^{-1}. ^1H NMR($CDCl_3$): δ 1.35, 1.41, 1.52 (3 x s, 6H, acetonide); 2.39 (s, 1H, NH, exchanges with D); 3.40-4.40 (m, overlapping with 3 singlets, 8H, including diastereomeric methoxy signals); 6.90-7.60 (m, 4H, Ar-H); 8.45-8.70 (2 broad peaks, 1H, NH).
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Received, 7th April, 1980