CARBON TRANSFER VIA N^5,N^{10}-METHYLENETETRAHYDROFOLATE MODELS.☼

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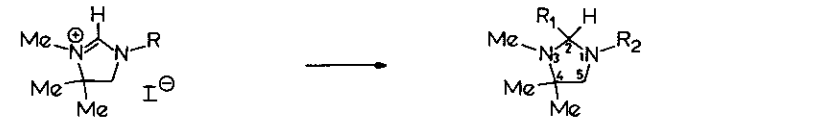
Abstract.- 1-Acyl or 1-tosyl-3,4,4-trimethylimidazolidine derivatives react with tryptamine or 2-(3,4-dimethoxyphenyl)ethylamine, under acidic conditions, to yield tetrahydro-β-carboline or tetrahydroisoquinoline derivatives.

In connection with our current programme on the development of synthetic methodology based upon the utilisation of coenzyme models, we have recently reported the synthesis of and carbon-transfer reactions from the N^5,N^{10}-methenyltetrahydrofolate models 1a,b[2]. We now present results describing the transfer of synthetically useful carbon fragments from the related N^5,N^{10}-methylenetetrahydrofolate models 2a-e.

The methylenetetrahydrofolate models (2a-e) can be conveniently prepared from 1a-b[2] by, either reduction with sodium borohydride, (as in the case of 2a,b), or the addition of the appropriate Grignard reagent (as for 2c-e). Relevant data for these models is described in Table I.

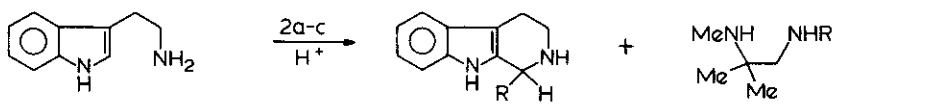
As substrates for the transfer of C(2) - and the associated carbon fragments - tryptamine (3) and 2-(3,4-dimethoxyphenyl)ethylamine (6) (Scheme A) were selected, in view of the potential application of the reaction to the synthesis of indole and isoquinoline alkaloids. When a mixture of the coenzyme models (2a-c) and tryptamine was heated (CH_3CN, reflux) in the presence of acetic acid, the corresponding β-carboline derivatives 4a-b[3] were obtained in 40-60% yield. Besides, the diamino derivatives 5a,b were isolated in good yields. The structures of 4a-c were attested by their NMR spectra. The mechanism of formation of the tetrahydro-β-carbolines can be rationalized via the sequence described in Scheme B. It is proposed that under acidic conditions the imidazolidine derivative 2 undergoes ring-opening to the iminium salt 9 (Scheme B), which can react with the "substrate" primary amine to

☼Dedicated to Professor H. Umezawa on the occasion of his 65th birthday.



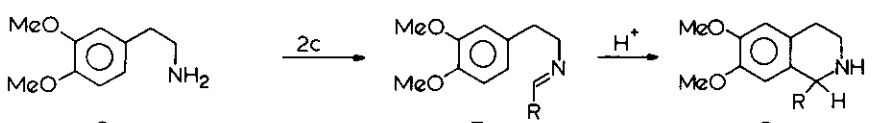
1a R = $COCH_3$
1b R = $SO_2C_6H_4(p)CH_3$

	R_1	R_2
2a	H	$COCH_3$
2b	H	$SO_2C_6H_4(p)CH_3$
2c	(p)$MeOC_6H_4$	$COCH_3$
2d	$CH_2C_6H_5$	$SO_2C_6H_4(p)CH_3$
2e	CH_3	$SO_2C_6H_4(p)CH_3$



4a R = H
4b R = p(MeO)C_6H_4

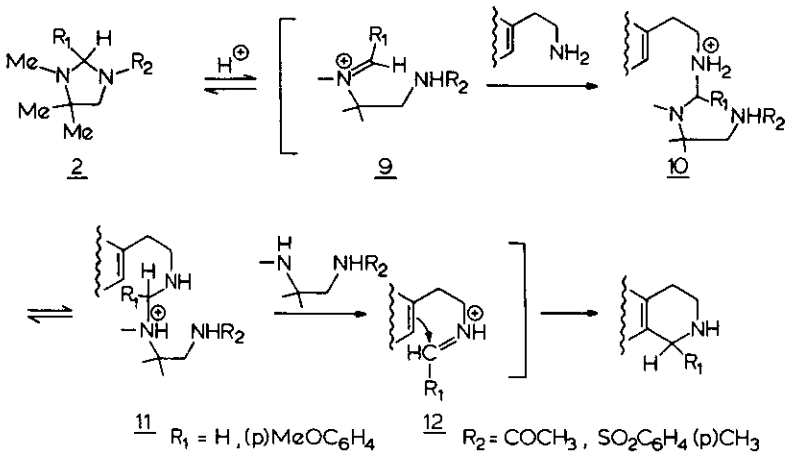
5a R = $COCH_3$
5b R = $SO_2C_6H_4(p)CH_3$



6 7 8

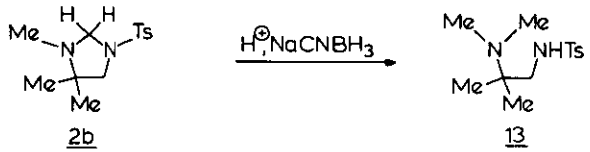
R = p(MeO)C_6H_4

Scheme A



11 R_1 = H, (p)$MeOC_6H_4$ 12 R_2 = $COCH_3$, $SO_2C_6H_4$ (p)CH_3

Scheme B



Scheme C

give the ammonium salt 10, in the primary step. Support for the acid-catalyzed ring-opening is derived from the recently reported equilibrium between 1,3-dimethylimidazolidine and N-methyl-N-(2-N-methylamino)ethyl-N-methylenium trifluoroacetate[4] and other analogies[5]. Furthermore, when 2b was reduced with sodium cyanoborohydride, in the presence of acetic acid, the diaminoethane derivative 13 was obtained in excellent yield (Scheme C). The transfer of a proton involving the conversion of 10 to 11 followed by expulsion of the diamine moiety, would constitute an adequate rationalization for the formation of iminium salt 12, which would cyclize via a nucleophilic attack of the indole moiety, to complete the formation of the β-carboline system.

The reaction of the β-phenylethylamine derivative 6 with 2a or 2b under the previously described conditions, resulted in complex mixtures, from which no isoquinoline 8 (R=H) has been isolated thus far. When, however, 6 was heated with 2c (CH_3CN, reflux, CH_3COOH), the imine 7 was obtained in good yield (> 60%). The structure of 7 was proven by its identity with the Schiff base prepared from 6 and benzaldehyde. Imine 7 can be cyclized to 8 under acidic conditions.[6] The formation of 7 would follow the steps proposed in Scheme B and, in fact, its isolation supports the involvement of intermediate 12 in the sequence leading to the β-carbolines.

The demonstrated utility of N^5,N^{10}-methylenetetrahydrofolate models in the synthesis of the aforementioned heterocyclic systems is capable of application to the synthesis of indole and isoquinoline alkaloids. In this connection, it should be emphasized that the particular merit of the reported synthetic approach lies in the fact that the use of the relatively unstable aldehydes, required in the Pictet-Spengler procedure for related synthesis, is avoided. The synthesis of alkaloids and other natural products, via the folate model method, is being actively investigated and our results on these studies will be presented elsewhere.

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TABLE I

Data on imidazolidines 2a-e.

	Yield	m.p.	$C_2(H)$	$N_3(Me)$	$C_4(Me)_2$	$C_5(H)_2$
2a	66%	oil	4.22(m)	2.28(s)	1.07(s)	3.37(m)
					1.10(s)	
2b	92%	59-60°	4.08(s)	2.12(s)	0.92(s)	3.17(s)
2c	90%	86-93°[a]	4.62(s)[a]	2.08(s)	0.97(s)	3.28(d) J=11 Hz
			4.87(s)[a]		1.18(s)	3.89(d) J=11 Hz
2d	63%	123-125°	4.30(t)	2.11(s)	0.32(s)	2.53(d) J=13 Hz
					0.85(s)	3.19(d) J=13 Hz
2e	12%	oil	3.85(q)	2.08(s)	0.44(s)	3.19(d) J=16 Hz
					1.07(s)	3.29(d) J=16 Hz

NMR spectra were run in $CDCl_3$. Chemical shifts are reported in δ(TMS≡δ 0.0).

[a] Two amide conformers.

References.

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3. The reaction of tryptamine with 2d gave a mixture in which the presence of the β-carboline 4c (R=$CH_2C_6H_5$) was indicated. The optimization of this reaction with respect to the formation of 4c is being studied.

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