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# MODELS OF FOLATE COENZYMES—IX[1]

## SYNTHESIS OF D,L-PYRIDINDOLOL

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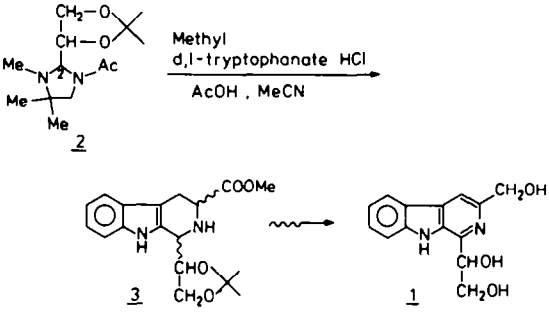
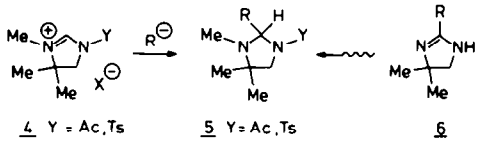
**Abstract**—Reaction of the acetonide of 1-acetyl-3,4,4-trimethyl-2-[1,2-dihydroxyethyl] imidazolidine – a substituted $N^5$,$N^{10}$-methylenetetrahydrofolate model – with d,l-tryptophan hydrochloride, in the presence of acetic acid, leads to the formation of the known β-carboline precursor of d,l-pyridindolol in one practical step.

The β-carboline alkaloid, pyridindolol **1**, has been isolated from *streptomyces alboverticillatus* by Umezawa and coworkers[3a–c] and shown to be a specific inhibitor of liver β-galactosidase. The total synthesis of pyridindolol has been recently described by Cook *et al.*[4] As part of our continued interest in the study of the carbon-fragment transfer reaction via models of folate coenzymes,[5] we have utilized this approach in the synthesis of d,l-pyridindolol.[6] The present communication describes in detail both the synthesis of the required imidazolidine derivative **2** which is regarded as a 5, 10-methylenetetrahydrofolate (THF) model and its utilization in the preparation of the known pyridindolol precursor **3**,[4] in one practical step (Scheme A).




Scheme A.

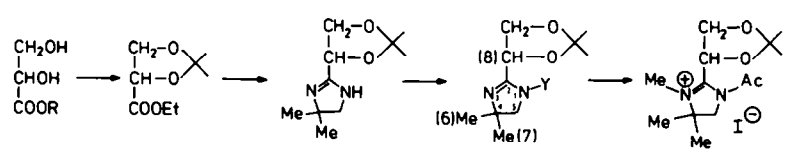
Two approaches for the synthesis of 2-substituted imidazolidine derivatives containing unsymmetrically substituted ring nitrogens are available. In one of these the available imidazolinium salt (**4**, a 5, 10=CH–THF model) is allowed to react with the desired nucleophile ($R^-$) to yield the corresponding imidazolidine (**5**, a 5,10–CHR–THF model). The second approach involves the construction of the imidazoline system (**6**) carrying the desired substituent (R) at the 2-position, followed by derivatization of the nitrogens and subsequent reduction (Scheme B). For the



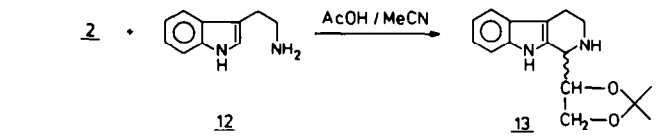
Scheme B.

synthesis of pyridindolol the required imidazolidine derivative (**2**) contained functionalization which did not allow its accessibility via salts of type **4**. Consequently, the second mentioned procedure was followed (Scheme C). Commercially available d,l-glyceric acid (**7a**) was esterified and the 1,2-dihydroxy function in the ester (**7b**) was protected as the corresponding acetonide (**7**). Reaction of the latter protected ester with 1,1-dimethyl - 1,2-diaminoethane led to imidazolidine **9**. While **9** could be tosylated, subsequent methylation of **10a** proved unsuccessful. In contrast, the acetyl derivative of **9**, namely **10b**, readily yielded the salt **11** upon methylation. The difference in the reactivities of **10a** and **10b**, towards methylation, can be explained by the screening of $N^-3$, by the acetonide moiety, from a reaction with an electrophile. This results from a conformation of the acetonide (about the C(2)–C(8) bond) which is forced by steric interaction with the bulky tosyl group. The salt **11** was conveniently reduced ($NaBH_4$) to a mixture of diastereomeric imidazolidines **2**, as a colourless oil.

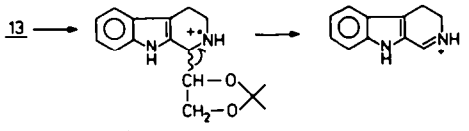
The crucial step in the synthesis of pyridindolol via the folate model (**2**) is the transfer of C(2) with the attached functionalized two carbon-fragment to a molecule of tryptophan. The feasibility of this transfer was examined by studying the reaction **2** with tryptamine **12**. A mixture of

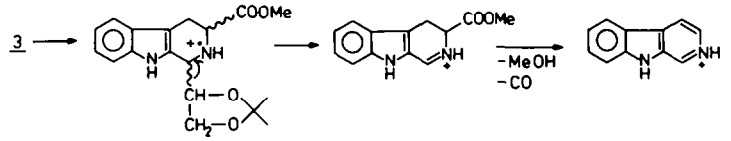


Scheme C.




Scheme D.




Scheme E.

the two synthons **2** and **12** in acetonitrile was refluxed in the presence of acetic acid for 3 hr (Scheme D), whereupon the β-carboline derivative **13** was obtained, as a diastereomeric mixture, in good yield (79%). The structure of **13** was attested by its NMR spectrum and, in particular, by the characteristic electron-impact induced fragmentation pattern in the mass spectrum (Scheme E). Particularly informative is the peak at *m/e* 171 (100%), which is associated with fragment **a**, formed upon loss of the acetonide chain.

The reaction of **2** with ethyl tryptophanate hydrochloride proceded in a manner analogous to that with **12**, and the corresponding β-carboline derivative **3** was formed as a diastereomeric mixture (72%). While the NMR spectrum of **3** was consistent with the assigned structure, its mass spectrum provided additional supporting evidence. The main fragmentation pathway, analogous to that of **13**, showed the facile loss of the acetonide side chain. The resulting ion **b** (*m/e* 229, 100%) underwent an expected decomposition involving the $COOC_2H_5$ moiety and an overall loss of the elements of MeOH + CO resulted in a prominent peak corresponding to fragment *c* (*m/e* 169, 55%).

Since the conversion of **3** into d,l-pyridindolol has been described in the literature,[4] the preparation of **3** via the aforementioned route constitutes a formal synthesis of the racemic alkaloid. Attempts to prepare pyridindolol with the natural configuration, starting from optically active glyceric acid[7a,b] have, owing to racemization of the intermediates in the synthesis of **2** (Scheme C) proved unsuccessful.

## EXPERIMENTAL

IR spectra were recorded on Unicam SP 200 or a Perkin–Elmer 257 spectrometers. The absorptions are given in $cm^{-1}$. PMR spectra were run on Varian Associates Model A-60, A-60 D and HA-100 instruments. The chemical shifts (δ) are given in ppm, using TMS as an internal standard. For the resonance signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Spin–spin coupling constants (J) are given in Hertz. Mass spectra were obtained with a Varian Mat-711 spectrometer.

*Ethyl 2,3-dihydroxypropionate* (**7b**)

2,3-Dihydroxypropionic acid (**7a**; Aldrich, aqueous solution 65%) was made anhydrous by azeotropic evaporation with ethanol, at 40° and drying for 2.5 days in vacuum over $CaCl_2$. The acid (25 g) was dissolved in 600 ml of ethanolic hydrogen chloride (1.6%) and the resulting soln was refluxed overnight and the solvent evaporated under reduced pressure. In contrast to the procedure described in the lit,[7a,b] the residue was distilled repeatedly. The distillate b.p. 83°/0.01 mm represented the pure product (checked by GLC, SE-30, 150°). Yield 10 g (32%) IR ($CHCl_3$): 3500, 1735 (C=O); PMR ($D_2O$): 1.32 (t, 3H, $COOCH_2CH_3$), 3.92 (d, 2H, J = 4, $-CH_2O$), 4.10–4.60 (m, 3H, HC–O and $COOCH_2CH_3$).

*Acetonide* (**8**)

To a soln of **7b** (2 g) and 2,2-dimethoxypropane (2 g) in toluene (10 ml), toluene-p-sulphonic acid (50 mg) was added and the mixture placed in an oil bath heated to 130°. After 45 min, the toluene was removed by evaporation and the residue was chromatographed on a small $Al_2O_3$ column. Elution with EtOAc gave pure **8** in 96% yield. IR ($CHCl_3$): 1750 (C=O), 1388, 1375 (acetonide); PMR ($CCl_4$): 1.10–1.50 (m, 9H, $-COOCH_2CH_3$ and 2 × acetonide Me), 3.90–4.70 (m, 5H, $COOCH_2$, HC–O– and $H_2C$–O–). MS: *m/e* 159 ($M^+-CH_3$), *m/e* 101 ($M^+-COOCH_2CH_3$).

*4,4-Dimethyl - 2 - [4'-(2',2' - dimethyl - 1',3' - dioxolanyl)] - 2 - imidazoline* (**9**)

A mixture of ester **8** (4.8 g) and 2,2-dimethyl-1,2-diamino-ethane (2.5 g) was dissolved in 10 ml of toluene and the soln refluxed overnight in a two-necked flask connected to a condenser and a $N_2$ line. Subsequently, a dropping funnel with a sidearm was placed between the flask and the condensor and the mixture heated at 240° (bath temp) to remove the toluene and the ethanol formed in the reaction. After cooling, the residue was distilled at 100° (water pump pressure), whereupon the imidazoline **9** came over as an oil. Yield 2.9 g (52%). IR ($CHCl_3$): 3450, 3200 (NH), 1638 (C=N), 1385, 1375 (acetonide); PMR ($CDCl_3$): 1.21, 1.25, 1.35, 1.38 (4 × s, 4 × Me), 3.31 (s, 2H, ring $-CH_2-$), 3.80–4.90 (m, 4H, HC–O, $H_2C$–O, and NH exchangeable with $D_2O$).

1 - *Tosyl*-4, 4-*dimethyl* - 2 - [4' - (2',2' - *dimethyl* 1', 3' - *dioxolanyl*)]-2-*imidazoline* (**10a**)

Imidazoline **9** (281 mg) and $Et_3N$ (140 mg) were dissolved in 4 ml of $CH_2Cl_2$ and to this solution, cooled in an ice-bath, were added 280 mg of tosyl chloride. The mixture was stirred at room temp for 3 hr and thereafter filtered and washed twice with water containing dil. $NaHCO_3$. Finally, the organic layer was washed with sat. NaCl and dried over anhyd $Na_2SO_4$. Evaporation of the solvent gave the tosyl derivative which was further purified by thick layer chromatography ($Al_2O_3$, eluent $CH_2Cl_2$) to give 221 mg (45%) of **10a**. IR ($CHCl_3$): 1642 (C=N), 1385, 1372 (acetonide), 1360 (tosyl), 1160 (tosyl); PMR ($CDCl_3$): 1.00, 1.18 (2 × s, 2 × Me), 1.38 (s, 2 × Me, acetonide), 2.42 (s, 3H, Me tosyl), 3.28, 3.63 (AB spin system, 2H, J = 10, ring $CH_2$), 4.35 (d, 2H, J = 7, acetonide $CH_2$), 5.31 (t, 1H, J = 7, acetonide CH), 7.40 (d, 2H, J = 8, 2 × tosyl H), 740 (d, 2H, J = 8, 2 × tosyl H).

1-*Acetyl* - 4,4 - *dimethyl* - 2 - [4' - (2,2' - *dimethyl* - 1',3' - *a* - *dioxolanyl*)] - 2 - *imidazoline* (**10b**)

Imidazoline **9** (800 mg) and $Et_3N$ (400 mg) were dissolved in 3 ml of $CH_2Cl_2$ and to this soln, cooled in an ice-bath, were added, dropwise, 400 mg of acetic anhydride in 2 ml of $CH_2Cl_2$. The mixture was stirred at room temp for 1 hr, and thereafter washed twice with water containing dil $NaHCO_3$. Finally, the organic layer was washed with sat NaCl and dried over anhyd $Na_2SO_4$. The product was further purified by dissolving it in $CH_2Cl_2$ and filtering the soln through $Al_2O_3$. Evaporation of the solvent yielded pure **10b** [840 mg (88%)]. IR ($CHCl_3$): 1678 (C=O), 1648 (C=N), 1395, 1382 (acetonide); PMR ($CDCl_3$): 1.28, 1.32, 1.42, 1.52 (4 × s, 4 × Me), 2.14 (s, 3H, $COCH_3$), 3.61 (s, 2H, ring $CH_2$), 3.82–4.60 (octet, 2H, AB part of an ABX spin system), 5.29–5.58 (q, 1H, X part of an ABX spin system).

1 - *Acetyl* - 3,4,4 - *trimethyl* - 2 - [4' - (2',2' - *dimethyl* - 1',3' - *dioxolanyl*)] - 2 - *imidazolinium iodide* (**11**)

The acetyl derivative **10b** was dissolved in 5 ml of $CH_2Cl_2$ and after addition of 2 g of methyl iodide, the mixture was maintained at reflux temp overnight. The residue was filtered off and washed thoroughly with ether. After drying, the salt (**11**) was obtained as a yellow foam. Yield 3.5 g (73%). IR ($CHCl_3$): 1740 (C=O), 1625 (C=N), 1390, 1382 (acetonide); PMR ($CDCl_3$): 1.38, 1.57, 1.67, 1.70 (4 × s, 4 × Me), 2.45 (s, 3H, $COCH_3$), 2.89, 3.40 (2 × d, J = 4.5, 2H, $CH_2$ imidazoline ring), 3.52 (s, 3H, $N^+$–$CH_3$), 4.35–4.70 (m, 2H, $H_2CO$), 5.85–6.10 (m, 1H, HC–O).

*Reduction of* **11**

The salt **11** (3.5 g) was dissolved in 5 ml of ethanol and to this soln 150 mg of $NaBH_4$ was added while the mixture was maintained at 0°. After allowing the mixture to stand at room temp for 2 hr a second portion of $NaBH_4$ (50 mg) was added. The mixture was allowed to stand for a further period of 45 min and 1 ml of a soln of sat $NH_4Cl$ was added and the mixture stirred. This was followed by 5 ml of $CHCl_3$ and the organic layer decanted. The organic layer was evaporated, the residue dissolved in $CHCl_3$ and the resulting soln washed successively with water and and sat. NaCl soln. Evaporation of the solvent resulted in an oily residue which was chromatographed on a small silicagel column (eluent EtOAc), whereupon 1.3 g (56%), of **2** was obtained as a colourless oil. IR ($CHCl_3$): 1648 (C=O), 1386, 1374 (acetonide); PMR ($CDCl_3$): 0.92, 1.18 (2 × s, 2 × Me), 1.28–1.60 (m, 6H, 2 × Me), 2.00–2.50 (m, 6H, N–$CH_3$ + $COCH_3$), 2.60–4.90 (m, 5H); MS: 256 ($M^+$-(acetonide group + acetyl group), 80%].

*Reaction of* **2** *with tryptamine*

To a soln of **2** (1 mmol) and tryptamine (1 mmol) in dry acetonitrile (3 ml), 1 ml of acetic acid was added and the mixture refluxed for 3 hr. After removal of MeCN and acetic acid under reduced pressure, the residue was made basic with $NaHCO_3$ soln and extracted with $CHCl_3$. The organic soln was dried, evaporated and the crude product chromatographed on a silicagel thick layer plate (eluent EtOAc) to yield 215 mg (79%) of **13** (diastereomeric mixture) as an oily residue. IR ($CHCl_3$): 3480, 3300 (NH), 1390, 1380 (acetonide); PMR ($CDCl_3$): 1.38, 1.52 (2 × s, 2 × Me), 1.75, (s, 1H, NH, exchangeable by $D_2O$), 2.50–2.95 (m, 2H, $CH_2$), 2.95–3.36 (m, 2H, $CH_2$), 3.82–4.45 (m, 4H, acetonide + 1 ring proton), 7.00–7.70 (m, 4H, aromatic protons), 8.60 (m, 1H, NH, exchangeable by $D_2O$).

*Reaction of* **2** *with methyl tryptophanate hydrochloride.*

A mixture of **2** (1 mmol), the hydrochloride of methyl tryptophanate (1 mmol) in 3 ml of MeCN and 1 ml of acetic acid was heated to reflux for 45 min. After evaporation of the solvent, the residue was made basic with $NaHCO_3$ solution. This was extracted with $CHCl_3$, the organic soln dried and the solvent removed under reduced pressure. The resulting material was chromatographed (thick layer, silicagel, eluent $CH_2Cl_2$–EtOAc 1:1) to give 240 mg (72%) of **3** as a mixture of diastereomers. IR ($CHCl_3$): 3460, 3350 (NH), 1725 (C=O), 1380, 1370 (acetonide); PMR ($CDCl_3$): 1.35 (s, 6H, acetonide methyls), 1.41, 1.52 (2 × s, 2 × Me), 2.39 (s, 1H, NH exchangeable by $D_2O$), 1.65–3.40 (m, 2H, imidazoline ring protons), 3.40–4.40 (a series of peaks in which singlets at 3.71, 3.80 and 4.13 can be recognized, 8H, $OCH_3$, $H_2C$–O, HC–O, H–C=O, ring-H), 6.90–7.60 (m, 4H, aromatic protons), 8.20–8.85 (m, 1H, NH).

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