Synthesis of the Antibiotic, (±)-Pyridindolol

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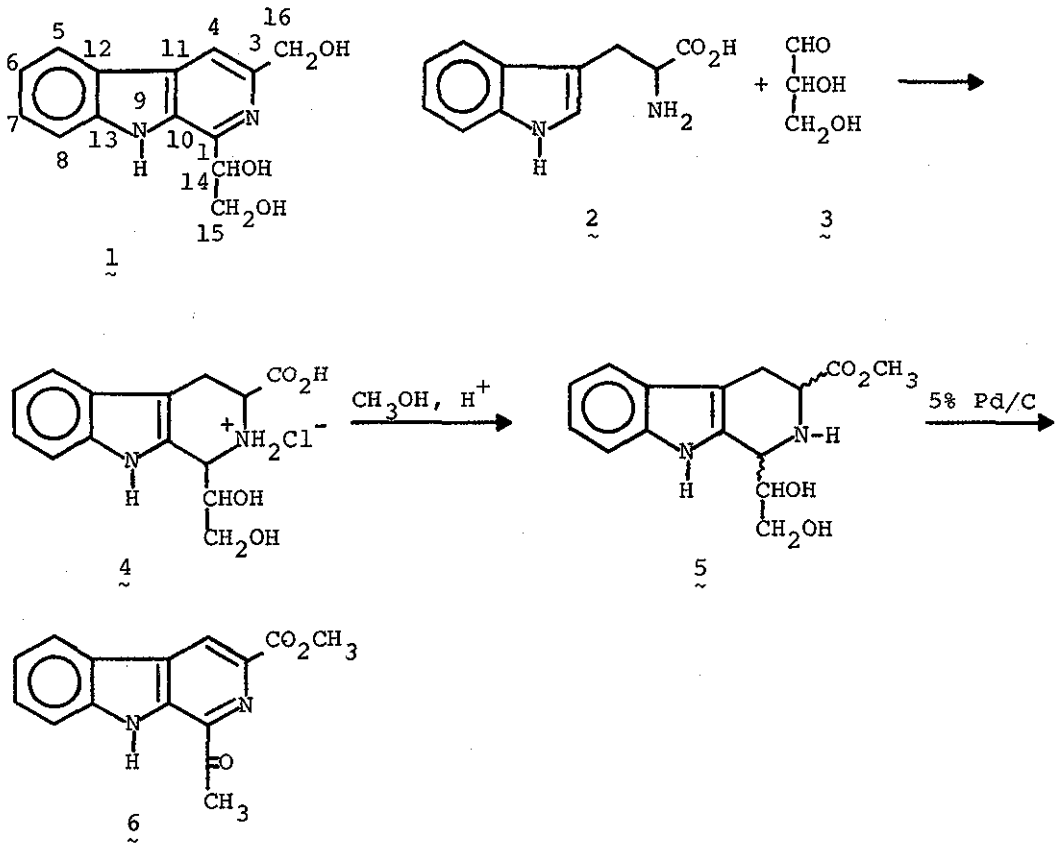
Pictet-Spengler condensation of tryptophan methyl ester 7 with glyceraldehyde acetonide 8 in refluxing benzene provided the 1,2,3,4-tetrahydro β-carboline 9 in good yield. The β-carboline was then converted in three steps to the β-galactosidase inhibitor, pyridindolol 1.

Pyridindolol (1), a β-galactosidase inhibitor produced by Streptomyces alboverticillatus, was first isolated and identified by Umezawa and coworkers.[1,2] We now wish to report the total synthesis of (±)-pyridindolol (1).

The first attempts to synthesize 1 in our laboratories were based on a biogenetic approach. Pictet-Spengler reaction of dl-tryptophan (2) with dl-glyceraldehyde (3) in an acidic media[3] provided the diol 4 in moderate yield (Scheme I). This diol was then esterified to provide the methyl ester 5, which was subsequently treated with 5% Pd/C to generate the fully aromatic β-carboline system. However, instead of the desired methoxycarbonyl derivative of 1 the product of this reaction was the methyl ketone 6 [mp 219-220°; IR ($CHCl_3$) 3420, 1720, 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.90 (s, 3H), 4.05 (s, 3H), 7.20-7.70 (m, 3H), 8.10 (d, J = 8 Hz, 1H), 8.90 (s, 1H), 10.40 (s, 1H); MS: m/e 268 (M^+)]. The

SCHEME I

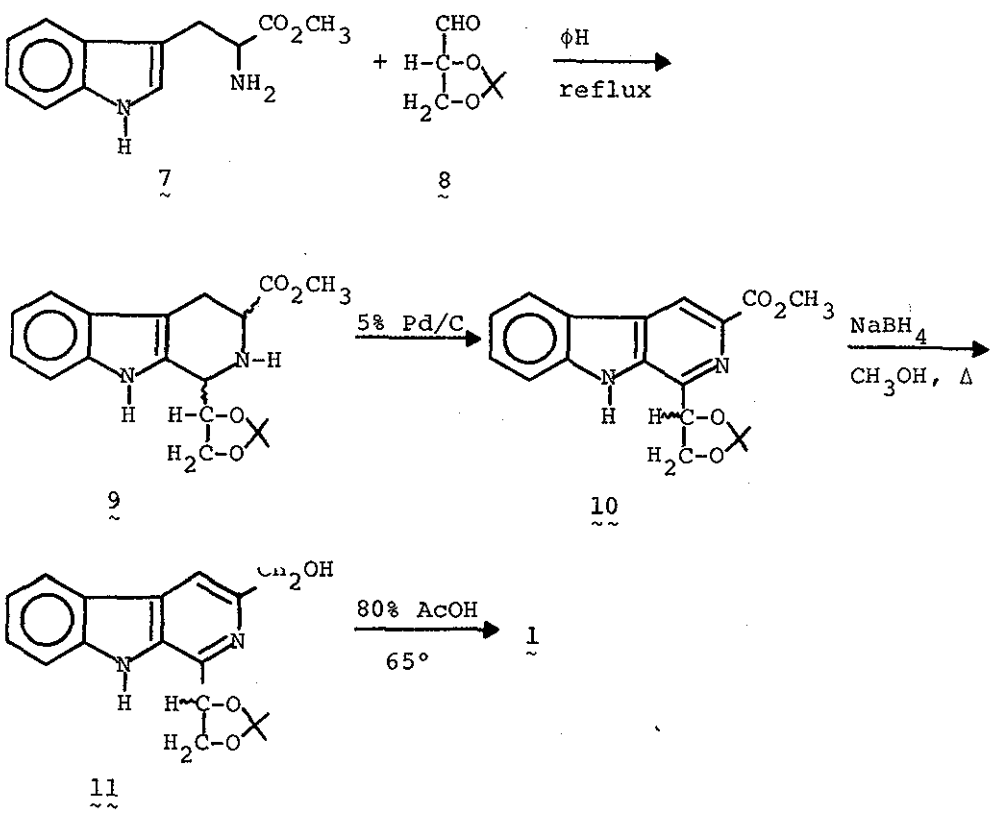


ketone 6 gave a positive test with 2,4-dinitrophenylhydrazine and a negative test with Tollen's reagent, in complete agreement with the assigned structure.

It was felt that some difficulty might be encountered in converting 5 to the 3-methoxycarbonyl derivative of 1, since 1,2,3,4-tetrahydro-β-carbolines with hydroxymethyl substituents attached to position 1 are rather labile;[3-5] therefore, the

need for protecting the hydroxyl functions to prevent loss of water was addressed. During work on the synthesis of other 1,2,3,4-tetrahydro-β-carbolines, it had been found that Pictet-Spengler reactions of tryptophan methyl ester with acid labile aldehydes could be carried out in high yield in non-acidic aprotic media.[6] These conditions would permit the use of a protected glyceraldehyde molecule which would otherwise be labile in acidic media. Many simple attempts to prepare a functionalized glyceraldehyde species were unsuccessful; however, the acetonide of D-glyceraldehyde was obtained relatively easily from D-mannitol by the combined methods of Vargha[7] and Fischer.[8] Pictet-Spengler condensation of tryptophan methyl ester with the aldehyde 8 in refluxing benzene provided a 90% yield of a mixture of diastereomers represented by structure 9: [IR (film) 3435, 3400, 3000, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.50 (s, 3H), 2,22 (s, 1H), 2.90 (m, 2H), 2.50-4.50 (m with 3 sharp singlets, 8H), 6.90-7.60 (m, 4H), 8.40 (s, 1H); MS: m/e 330 (M^+)]. Since the chirality at positions 1 and 3 of ring C would be destroyed on conversion to the β carboline 10 (Scheme II), no attempt was made to separate this mixture. The mixture of diastereomers 9 showed an overall rotation in the levorotary direction, which indicated that complete racemization had not occurred during reaction in refluxing benzene: heating 7 with 8 in an aqueous acidic medium would have led to a racemic mixture of 9. Aromatization of 9 with 5% Pd/C in refluxing cumene gave the β-carboline 10; however, this base was optically inactive. Not only had the chirality at positions 1 and 3 been

SCHEME II

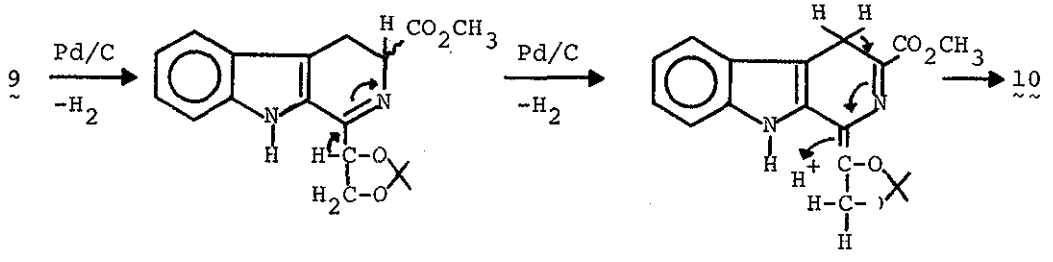


destroyed under these conditions, but racemization of the D-acetonide had also occurred. The structure of the β-carboline 10 was confirmed by IR, NMR, and mass spectroscopy [mp 220-222°, IR (film) 3430, 3000, 1720, 1620, 1250 cm^{-1}; NMR ($CDCl_3$) δ 1.55 and 1.60 (2s, 6H), 4.05 (s, 3H), 4.50 (m, 2H), 5.65 (t, 3H), 7.15-7.65 (m, 3H), 8.10 (d, J = 7.5 Hz, 1H), 8.70 (s, 1H), 9.60 (s, 1H); MS: m/e 326 (M^+)]. The methyl ester 10 was reduced to

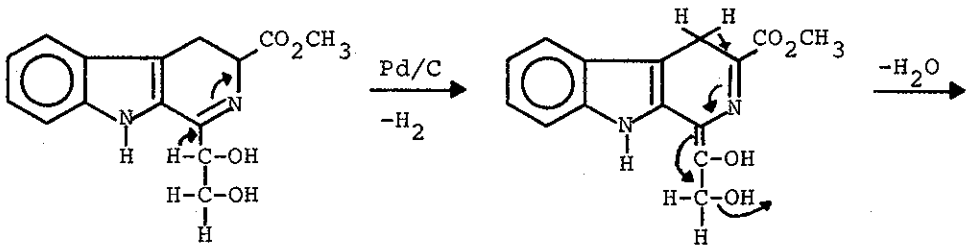
the alcohol 11 by stirring with $NaBH_4$ in refluxing methanol[9] or reaction with lithium borohydride [mp 124-125°, IR (film) 3435, 3420-3100, 3000, 1630; NMR ($CDCl_3$) δ 1.57 (s, 6H), 4.40 (m, 2H), 4.80 (s, 2H), 5.52 (t, 1H), 7.00-7.56 (m, 3H), 7.78 (s, 1H), 8.00 (d, J = 8 Hz, 1H), 9.15 (s, 1H); MS: m/e 298 (M^+)]. Removal of the acetonide group was carried out in 70% yield by warming 11 in 80% acetic acid for 25 hrs.[10] The spectral data for the triol 1 (mp 169-170°, lit.[1] mp 167-168°) obtained by this procedure were identical in all respects to the published data for pyridindolol (1), except for the optical rotation which in our case was zero.

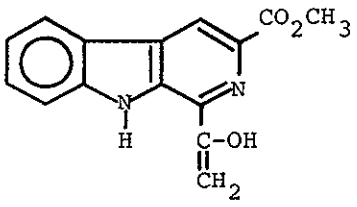
A possible mechanism for the racemization of the chiral center of the acetonide during the aromatization process, which is also consistent with the formation of the methyl ketone 6 generated from 5, is outlined in Scheme III. The common feature of both reactions is the introduction of the 1,2-double bond in ring C of the tetrahydro-β-carboline as shown in Scheme III. The other steps are proposed to follow as illustrated.

SCHEME III



SCHEME III (contd)





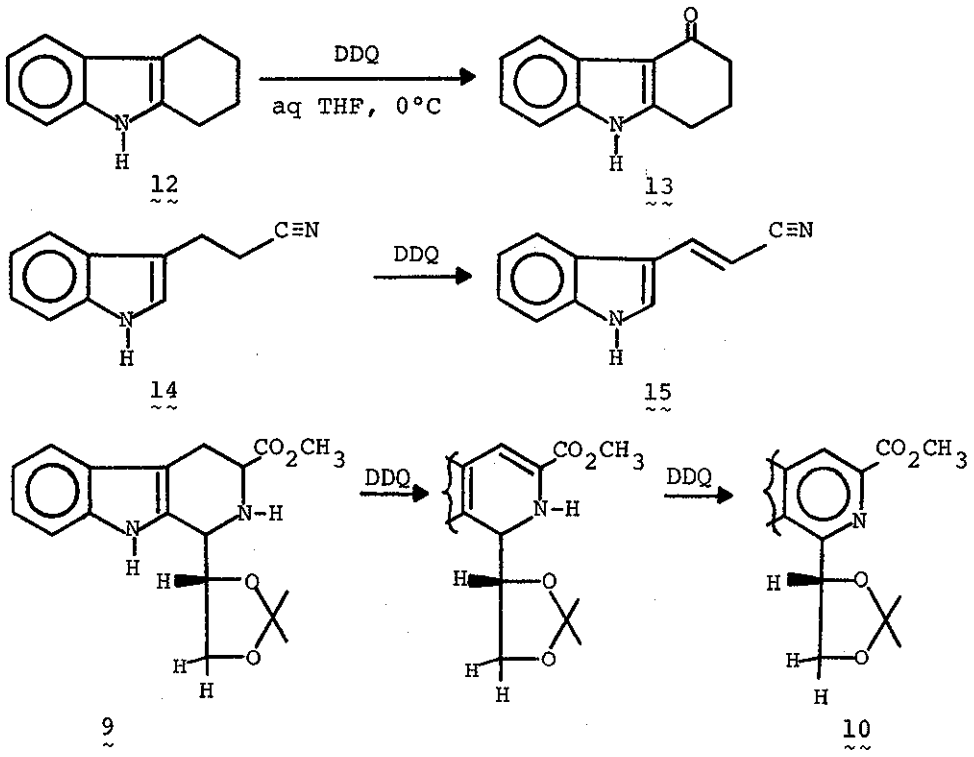
6 (enol form)

To test this hypothesis, other methods to convert 9 to 10 were considered. The introduction of unsaturation at the 3,4-position of ring C, followed by removal of hydrogens across the C(1)-N(2) bond to furnish the fully aromatic β-carboline 10, seemed particularly attractive.

Oikawa and Yonemitsu have recently reported that the four position of tetrahydrocarbazole 12 is selectively attacked by DDQ in aqueous solution[11] to provide an 83% yield of the 4-oxo derivative 13. Similarly, LeQuesne and coworkers have observed that the cyanoindole (14) on treatment with DDQ was dehydrogenated in high yield to provide the α-β unsaturated nitrile 15.[12] Therefore, the tetrahydro β-carboline 9, slightly enriched in the S isomer, was stirred in benzene with DDQ. The

yield of this reaction was only 45%; however, the β-carboline 10 obtained was optically active with a rotation ($\alpha_D^{23°}$ = 5.5°) in the dextrorotary direction (see Scheme IV). Reduction of the

SCHEME IV



methyl ester and cleavage of the acetonide (see above) provided pyridindolol ($\alpha_D^{23°}$ = 7.7°). Clearly the retention of some optical activity supports the mechanisms outlined in Scheme III (Pd/C) and Scheme IV (DDQ), for introduction of the 3-4 double bond followed by aromatization of ring C precludes racemization *via* the enamine, illustrated in Scheme III for the Pd/C oxidation.

Pyridindolol enriched in either the (+) isomer (D-acetonide) or the natural isomer (L-acetonide) can be prepared by this method from D-mannitol and L-mannitol, respectively. However, the optically active glyceraldehyde-acetonides will racemize overnight even on standing at low temperature.[13] The acetonide must be used immediately and we were never able to isolate 8 optically pure. The Pictet-Spengler product 9 was obtained on a 10 gram scale ($\alpha_D^{23°} = -11°$), and was converted to pyridindolol ($\alpha_D^{23°} = 7.7°$). With smaller amounts of material the tetrahydro β-carboline 9 could be formed in higher optical purity ($\alpha_D^{23°} = -25°$) but significant amounts are not yet available to convert 9 to the natural product.

In conclusion, it appears that preparation of β-carboline alkaloids in optically active form can be accomplished via Pictet-Spengler condensations in aprotic solvents. In the glyceraldehyde-D-acetonide case it does not seem possible to obtain pyridindolol ($\alpha_D^{23°} = -49°$),[1] optically pure, on a practical basis; however, the reaction in aprotic media does perhaps provide a means to achieve this objective with aldehydes less prone to racemization.

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References and Notes

[1]M. Kumagai, H. Naganawa, T. Aoyagi, H. Umezawa, H. Nakamura, and Y. Iitaka, J. Antibiot., 1975, 28, 876.

[2]T. Aoyagi, M. Kumagai, T. Hazato, M. Hamada, T. Takeuchi, and H. Umezawa, J. Antibiot., 1975, 28, 555.

[3]I. D. Spenser, Can. J. Chem., 1959, 37, 1851.

[4]R. A. Abramovich and I. D. Spenser, Advan. Hetero. Chem., 1964, 3, 83.

[5]H. O. House, "Modern Synthetic Reactions," 2nd Ed., W. A. Benjamin Inc., Reading, Mass., 1972, p. 36.

[6]J. Sandrin, D. Soerens, L. Hutchins, E. Richfield, F. Ungemach, and J. M. Cook, Heterocycles, 1976, 4, 1101.

[7]L. V. Vargha, Ber., 1933, 66, 1394.

[8]H. O. L. Fischer and E. Baer, Helv. Chim. Acta, 1934, 17, 622.

[9]M. S. Brown and H. Rapport, J. Org. Chem., 1963, 28, 3261.

[10]M. L. Lewbart, J. Org. Chem., 1968, 33, 1695.

[11]Y. Oikawa and Osamu Yonemitsu, J. Org. Chem., 1977, 42, 1213.

[12]R. Garnick and P. W. LeQuesne, Tetrahedron Lett., 1976, 3249.

[13]This phenomenon has also been observed in other laboratories, D. Seebach, private communication.

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