STEREOSPECIFIC SYNTHESIS OF TRANS, CIS-1,3,4-TRISUBSTITUTED 1,2,3,4-TETRAHYDRO-ß-CARBOLINES[1]

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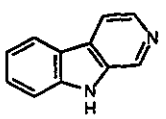
Abstract - Pictet-Spengler condensation of N_b-benzyl-ß-methyltryptophan methyl ester (2RS,3SR;**4**) with aldehydes followed by debenzylation afforded trans, cis-1,3,4-trisubstituted 1,2,3,4-tetrahydro-ß-carbolines in complete stereospecific fashion. Tetrahydro-ß-carbolines (**6a**) and (**6b**) were prepared by the direct condensation of ß-methyltryptophan methyl ester (**4**) with the corresponding aldehydes. The stereochemistry of the products was confirmed by an X-ray analysis of **6a**.

The Chemistry of ß-carbolines (ßC's;**1**) and tetrahydro-ß-carbolines (THßC's;**2**) has long been of interest because of their occurrence in a large number of alkaloids.[3,4] The pharmacological and neurochemical activities of ß-carbolines[4,5] and tetrahydro-ß-carbolines[4,6] have been extensively studied and reported.



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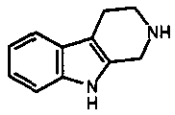

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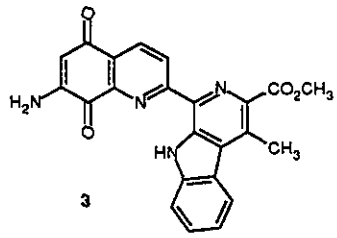

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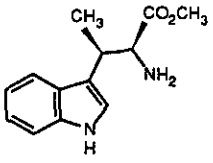
Although the synthesis of a large number of 1,2,3,4-THßC's with substituents at 1-3 positions has been previously reported,[4,5k,7] only few 4-substituted derivatives have been prepared.[4] Cook and his co-workers have achieved the stereospecific synthesis of a number of trans-1,3-disubstituted 1,2,3,4-THßC's by the Pictet-Spengler (P-S) condensation of N_b-benzyltryptophan methyl ester with aldehydes followed by debenzylation.[7b,n] These workers have successfully used the P-S condensation of N_a-methyl-N_b-benzyltryptophan methyl ester in the stereospecific synthesis of alkaloids (±)- suaveoline[7c] and (-)- alstonerine.[7f] Several groups have used the P-S condensation of N_b-substituted tryptophan esters toward the total synthesis of a number of other alkaloids all involving tetrahydro-ß-carboline nucleus.[4,7d,e,h,j,k,l] Nearly all of these condensations have been nonstereospecific and diastereomeric mixtures of THßC's have been obtained.

In our research toward the total synthesis of the antitumor antibiotic lavendamycin methyl ester[8] (3) the P-S condensation of ß-methyltryptophan or its methyl ester[9] (4) with an appropriately substituted quinolinedione aldehyde was studied. Concurrently, the P-S reaction of ß-methyltryptophan with a variety of aldehydes to produce ßC's (5) and THßC's (6) was also undertaken.



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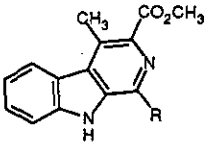

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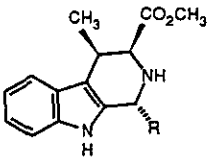

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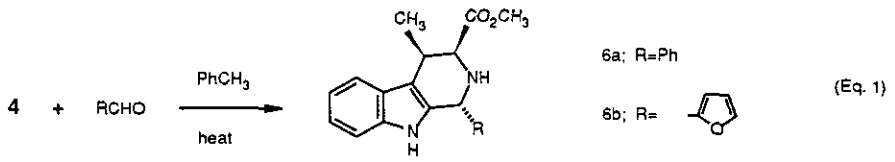
ß-Carbolines and tetrahydro-ß-carbolines are known to be ligands to the benzodiazepine receptors.[4,5c,k,h] Because of the presence of substitution at C-4, compounds (5) and (6) may show stronger binding activity to the benzodizepine receptors compared to the derivatives of tryptophan.[10] We previously reported the synthesis of a number of ß-carbolines of structure 5.[9]

We have now found that the P-S condensation of the methyl ester of isomer A of ß-methyltryptophan(2RS,3SR;4)[9] or its N_b-benzyl derivative with various aldehydes is stereospecific and exclusively produces the trans,cis-1,3,4-trisubstituted 1,2,3,4-THßC's. Thus direct condensation of 4 with benzaldehyede and furfural (Method I) in boiling toluene gave 81 and 97% yield of 6a and 6b respectively (Eq.I).[11]

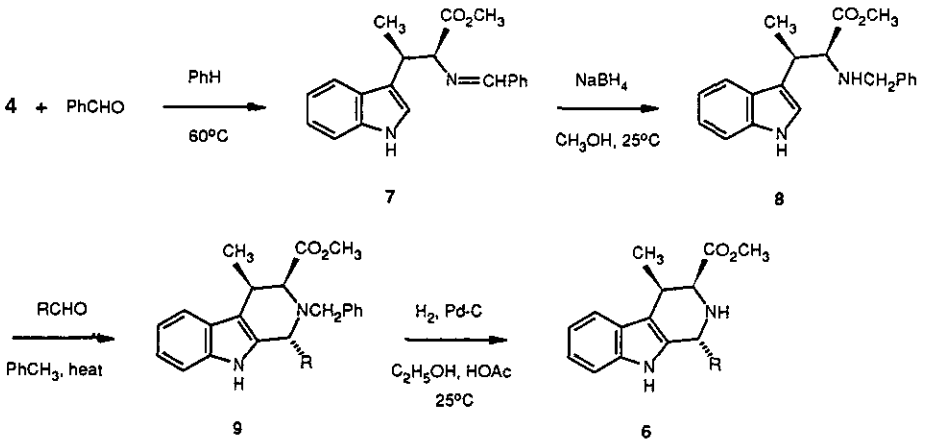
Method I



(Eq. 1)

In contrast to the previously reported P-S reaction of tryptophan methyl ester which produced a mixture of cis and trans isomers,[12] this condensation was stereospecific. Since the direct condensation of 4 with some aldehydes produced a mixture of ßC's and THßC's, a number of THßC's were synthesized by the P-S reaction of N_b-benzyl derivative of 4 (8) followed by debenzylation (Scheme I, Method II).[7n]

Scheme I (Method II)[a]



R = methyl (9c, 6c), ethyl (9d, 6d), isobutyl (9e, 6e), cyclohexyl (9f, 6f), benzyl (9g, 6g), 2-hydroxypenyl (9h, 6h), 2-pyridyl (9i, 6i), 2-quinolinyl (9j).

[a] for convenience only one enantiomer of the racemate mixtures of 4, 6, 7, 8 and 9 is shown.

ß-Methyltryptophan methyl ester (2RS,3SR; 4) was prepared via an efficient stereoselective method developed by us.[9] Treatment of 4 with benzaldehyde in dry benzene at 60° for 4 h produced 7 in 95% yield. Aldimine (7) was reduced to the $\underline{N_b}$-benzyl derivative (8) in 94% yield by sodium borohydride in dry methanol at 25° C. Condensation of 8 with a variety of alkyl, cycloalkyl, aryl and heteroaryl aldehydes in refluxing toluene stereospecifically gave N-benzyl derivatives (9) in excellent yields of 72-88%. Debenzylation of 9 by molecular hydrogen in the presence of palladium on charcoal afforded the THßC,s (6) in 53-85%. Hydrogenolysis of 9j always produced the ß-carboline (5; R = 2-quinolinyl) and not the desired THßC (6). The reaction conditions, yields and mps and elemental analyses for compounds (9) and (6) are shown in Tables I and III. Tables II and IV present the nmr, ir, and ms data for 9 and 6. The stereochemistry of the products was established by X-ray analysis of 6b[13] and determined to be <u>trans</u>, <u>cis</u>. The C(1) furyl group is <u>trans</u> to $C(3)CO_2CH_3$ and $C(4)CH_3$ (Figure 1).

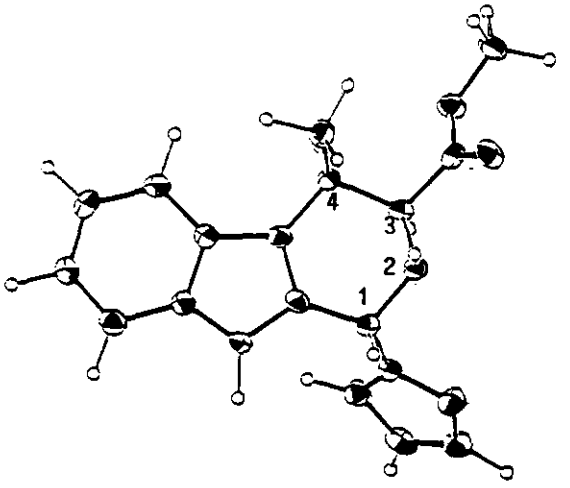
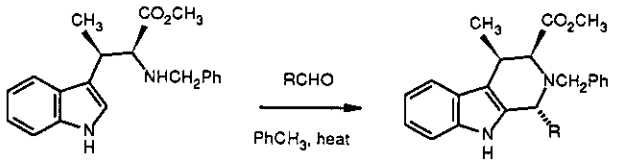


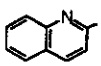
Figure 1: ORTEP Drawing

Table I

N_b-Benzyl Derivatives of THβC's



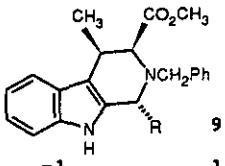
8 **9**

R	Reaction Time/h	Yield %	mp[a] °C	Elemental Analysis Calcd / Found C	H	N
CH_3	14	88	186-187	75.83 75.62	6.94 7.03	8.04 8.02
CH_3CH_2	12	86	164-165	76.21 75.79	7.23 7.15	7.73 7.67
$(CH_3)_2CHCH_2$	4.5	80	181	76.89 76.64	7.74 7.74	7.17 6.96
	20	83	220.5	77.85 77.53	7.74 7.83	6.72 6.61
$PhCH_2$	5	82	178	79.22 79.12	6.65 6.67	6.60 6.53
	24	84	252-254	76.03 76.38	6.14 6.01	6.57 6.61
	20	85	218	75.89 75.82	6.12 6.07	10.21 10.12
	12	72	199-200	78.07 77.89	5.90 5.96	9.10 9.06

[a]The samples were recrystallized from 95% ethanol.

Table II

Spectral Data of N_b-Benzyl Derivatives of THβC's



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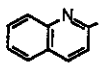
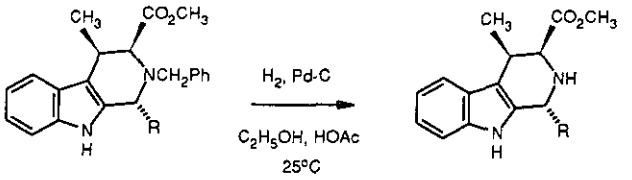
R	EIms(m/z)	ir(KBr, ν, cm^{-1})	^{1}H-nmr($CDCl_3$, δ, ppm)
CH_3	348(M^+),257,183 171(100),169, 156	3400,2970,1710 1460,1200,1150 750,725,700	1.43(d,J=7Hz,3H),1.46(d,J=14Hz,3H),3.52 (quint,J=7Hz,1H),3.66(s,3H),3.85 (d,J=7Hz,1H),3.86(d,J=7Hz,1H),4.00(d,J= 14Hz,1H),4.28(q,J=7Hz,1H),7.00-7.20(m, 2H),7.20-7.50(m,6H),7.60(d,J=7Hz,1H), 7.70(br s,1H).
CH_3CH_2	362,(M^+),333,185 170,91(100)	3375,2985,1720 1460,1270,1250 1025,745	0.70-0.90(m,3H),1.30-1.55(m,4H),3.56(s, 3H),3.67(s,2H),3.90(s,2H),4.10(s,1H), 4.50(s,1H),7.00-7.20(m,2H),7.20-7.50 (m,6H),7.55-7.75(m,2H)
$(CH_3)_2CHCH_2$	390(M^+),299 170,91(100)	3360,2940,2875 1725,1460,1280 1225,1025,745	0.43(d,J=7Hz,3H),0.76(d,J=7Hz,3H),1.25- 1.32(m,1H),1.49(d,J=7Hz,3H),1.55-1.70 (m,2H),3.50-3.65(m,1H),3.67(d,J=14Hz,1H), 3.80(s,3H),3.80-4.00(m,1H),4.13(d,J=5Hz, 1H),4.21(d,J=14Hz,1H),7.00-7.20(m,2H), 7.20-7.35(m,4H),7.45(m,2H),7.60(d,J=9Hz, 1H),7.65(br s,1H)
	416(M^+),183 144,91(100)	3390,2940,2850 1720,1450,1270 1235,1025,750	0.60-0.95(m,2H),1.00-1.35(m,3H),1.48(d,J= 7Hz,3H),1.55-1.85(m,5H),2.00(m,1H),3.45- 3.70(m,3H),3.75(s,3H),4.05-4.20(m,2H), 7.00-7.20(m,2H),7.20-7.45(m,6H),7.65(d, J=9Hz,1H),7.71(br s,1H).
$PhCH_2$	333(M^+-91,100) 183,91	3430,2950,1730 1460,1140,745	1.48(d,J=7Hz,3H),2.80-2.95(m,1H),3.20- 3.35(m,1H),3.50-3.65(m,1H),3.71(s,3H), 3.90-4.10(m,3H),4.20-4.35(m,1H),6.90-7.15 (m,6H),7.20-7.40(m,8H),7.55-7.70(m,1H).
	335(M^+-91,100) 275,249,234,91	3370,3050,2970 2855,1730,1455 1250,1200,740	1.50(d,J=7Hz,3H),3.45-3.65(m,2H),3.70(s, 3H),3.86(d,J=5Hz,1H),4.10(d,J=7Hz,1H), 5.60(s,1H),6.85(d,J=7Hz,1H),6.90-7.50 (m,12H),7.60(d,J=7Hz,1H),10.03(s,1H)
	411(M^+),320,273 233,183,91(100)	3190,3050,2900 1730,1460,1320 1150,780	1.54(d,J=7Hz,3H),3.60-3.80(m,2H),3.63 (s,3H),3.80-4.00(m,2H),5.61(s,1H),6.90- 7.40(m,9H),7.60-7.80(m,3H),8.50(br s,1H), 8.60(d,J=5Hz,1H)
	461(M^+),370,354 318,283,273,269 (100),91	3400,3170,3060 2975,2950,2850 1725,1600,1460 1300,1200,1150	1.53(d,J=7Hz,3H),3.50(s,3H),3.60(d,J=10Hz, 1H),3.75-3.95(m,3H),5.80(s,1H),6.95-7.10 (m,2H),7.10-7.30(m,6H),7.30-7.50(m,2H), 7.60-7.75(m,3H),7.80(d,J=9Hz,1H),8.10(d, J=9Hz,1H),9.65(br s,1H)

Table III
Tetrahydro-ß-Carbolines



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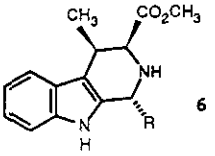
R	Reaction Time/h	Yield %	mp[a] °C	Elemental Analysis Calcd / Found C	H	N
	14	81[b]	206-206.5	74.98 74.88	6.29 6.28	8.74 8.62
	1.5	97[b]	160-161	69.66 69.42	5.84 5.87	9.03 9.00
CH_3	4	70	194-196	69.75 69.56	7.02 7.01	10.84 10.78
CH_3CH_2	4	74	185-186	70.56 70.51	7.40 7.44	10.29 10.14
$(CH_3)_2CHCH_2$	4	79	156-157	71.97 71.89	8.05 7.99	9.33 9.29
	4	53	156-157	73.59 73.79	8.03 8.08	8.58 8.51
$PHCH_2$	4	85	204-205	75.42 75.40	6.63 6.68	8.38 8.26
	4	74	185-185.5	71.41 71.89	5.99 6.14	8.33 8.38
	4	73	177-178	71.01 70.71	5.96 6.08	13.07 12.87

[a]The samples were recrystallized from 95% ethanol.

[b]Obtained by Method I. Compound **(6b)** was prepared in refluxing xylene.

Table IV

Spectral data of THß-C's



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R	EIms(m/z)	ir(KBr, ν, cm^{-1})	^{1}H-nmr($CDCl_3$, δ, ppm)
	CIms;321(MH^+) 284,269,257, 243,229	3400,3025,2970 1750,1470,1210, 1150,740	1.23(d,J=7Hz,3H),3.50(m,1H),3.74(s,3H), 3.95(d,J=5Hz,1H),5.30(s,1H),7.10-7.30 (m,9H),7.60(d,J=9Hz,1H),7.70(br s,1H)
	310(M^+,100), 251,235,194 180,167	($CHCl_3$) 3460 2950,1730,1430	1.20(d,J=7Hz,3H),2.40(br s,1H),3.00-3.60(m,1H),3.74(s,3H),4.00(d,J=4Hz,1H), 5.16(s,1H),5.80-6.10(m,1H),6.10(m,1H), 7.00-7.60(m,5H),7.64(br s,1H)
CH_3	258(M^+,100), 199,183,171, 169,156	3320,3050,2960 1740,1435,1325 1255,1165,1000 750,735	1.16(d,J=7Hz,3H),1.48(d,J=7Hz,3H),2.40 (br s,1H),3.30-3.50(m,1H),3.80(s,3H), 4.07(d,J=5Hz,1H),4.20-4.40(m,1H),7.00-7.20(m,2H),7.20-7.35(m,1H),7.50(d,J=9Hz, 1H),7.70(br s,1H)
CH_3CH_2	272(M^+),243(100) 183,170	3400,3150,2960 2920,1740,1450 1220,1150,750 725	1.00-1.20(m,6H),1.60-1.85(m,2H),2.15 (br s,1H),3.30-3.50(m,1H),3.80(s,3H), 3.90-4.10(m,2H),7.00-7.20(m,2H),7.30(d, J=7Hz,1H),7.50(d,J=7Hz,1H),7.75(br s,1H)
$(CH_3)_2CHCH_2$	300(M^+),243(100) 183,170	3390,3150,2955 1740,1465,1310 1215,750	0.96(d,J=7Hz,3H),1.00(d,J=7Hz,3H),1.14 (d,J=7Hz,3H),1.20-1.45(m,2H),1.60-1.80 (m,1H),1.90(br s,1H),3.30-3.45(m,1H), 3.80(s,3H),4.01(d,J=5Hz,1H),4.15(dd,J=10 and 5Hz,1H),7.00-7.20(m,2H),7.22-7.35 (m,1H),7.50(d,J=9Hz,1H),7.65(br s,1H)
	326,243,241(100) 183,181,167	3400,2925,2850 1730,1450,1320 1270,1200,1135 735	1.10(d,J=7Hz,3H),1.10-1.45(m,3H),1.50-1.90(m,8H),3.30-3.50(m,1H),3.78(d,J=5Hz, 1H),3.80(s,3H),4.05(d,J=5Hz,1H),7.00-7.20(m,3H),7.30(d,9Hz,1H),7.50(d,J=9Hz, 1H),7.70(br s,1H)
$PHCH_2$	243(M^+-91,100) 183,168	3315,3080,2980 2940,1745,1450 1220,1160,760, 710	1.14(d,J=7Hz,3H),1.22(s,1H),2.90-3.05 (m,1H),3.10-3.25(m,1H),3.43(m,1H),3.82 (s,3H),4.12(d,J=4Hz,1H)4.41(t,J=7Hz,1H), 7.00-7.50(m,10H)
	326(M^+),249 234(100)	3400,3050,2955 1735,1460,1245 750	1.20(d,J=7Hz,3H),3.50(m,1H),3.78(s,3H), 3.90(d,J=5Hz,1H),5.43(s,1H),6.70-6.85 (m,2H),6.91(d,J=9Hz,1H),7.10-7.35(m,3H), 7.45(d,J=9Hz,1H),7.60(d,J=9Hz,1H),8.10 (br s,1H),11.70(br s,1H)
	321(M^+),243, 233,219(100), 183,169	3410,2935,2880 1740,1450,1220, 745	1.21(d,J=7Hz,3H),3.42(m,1H),3.83(s,3H), 4.03(d,J=4Hz,1H),5.39(s,1H),7.00-7.20(m, 3H),7.30-7.45(m,3H),7.46-7.58(m,2H),7.60 7.71(m,1H),8.60(d,J=5Hz,1H),8.90(br s,1H)

EXPERIMENTAL

General: Melting points were measured with a Thomas Hoover capillary apparatus. Infrared spectra were recorded on a Nicolet 5ZDXFTIR spectrophotomer. Nuclear magnetic resonance spectra were obtained with a Gemini 200 spectrometer in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Hewlett Packard 5980A mass spectrometer. Elemental analyses were performed by Midwest Microlabs, Ltd.

Method I

3-Carbomethoxy-4-methyl-1-phenyl-1,2,3,4-tetrahydro-ß-carboline (6a).

To a stirred solution of **4** (300 mg, 1.3 mmol) in 15 ml of dry toluene under N_2, 438 mg (0.42 ml, 4.13 mmol) of freshly distilled benzaldehyde was added and refluxed for 14 h. The solvent was evaporated, and the sample was dried on a vacuum pump overnight and recrystallized from 95% ethanol to give 341 mg (81%) of a white solid. Tables III and IV show the mp, elemental analysis and spectral data. In the preparation of **6b** an excess (1.15 equiv.) of furfural was used.

Method II

N-Benzylidene-ß-methyltryptophan methyl ester (7).

ß-Methyltryptophan methyl ester (**4**, 10.78 g, 0.0465 mol) was dissolved in benzene (50 ml) and to this freshly distilled benzaldehyde (5 ml, 5.22 g, 0.0492 mol) was added. The reaction mixture was stirred and heated at 60° under N_2 for 4 h. Evaporation of the solvent gave 14.58 g (98%) of a solid which was recrystallized from 95% ethanol, to give colorless crystals, mp 118-118.5° C.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29, N, 8.74. Found: C, 74.74; H, 6.35; N, 8.93; ms (m/z): 320 (M^+), 261, 117, 145, 144 (100), 143; ^{1}H-nmr($CDCl_3$): δ 1.42 (d, J = 7Hz, 3H), 3.63 (s, 3H), 4.00 (quint, J = 7Hz, 1H), 4.23 (d, J = 7Hz, 1H), 6.95 (s, 1H), 7.10 - 7.25 (m, 2H), 7.30 - 7.50 (m, 4H), 7.65 - 7.80 (m, 3H), 7.90 (s, 1H), 8.00 (br s, 1H), ir (KBr, ν, cm^{-1}): 3480, 3000, 2890, 1740, 1660 (C = N).

N_b-Benzyl-ß-methyltryptophan methyl ester (8).

To a solution of 14.1 g (0.044 mol) of 7 in 200 ml of methanol, 1.96 g (0.0519 mol) of sodium borohydride was slowly added and the mixture was stirred at room temperature for 4 h. Methanol was evaporated and to the solid, 150 ml of ether and 150 ml of water were added. The ether layer was separated and the aqueous layer was extracted with 3 x 100 ml of ether. The combined ether extracts were washed with 100 ml of 7% Na_2CO_3, dried over magnesium sulfate and evaporated to give 13.6 g (96%) of a white solid which was recrystallized from methanol, mp 102-103° C. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69. Found: C, 75.02; H, 7.01; N, 8.73; ms (m/z): 322 (M^+), 263, 144(100) 117, 115, 91; ^{1}H-nmr($CDCl_3$): δ 1.39 (d, J = 7Hz, 3H), 1.81 (s, 1H), 3.30 - 3.60 (m, 1H), 3.50 (s, 3H), 3.56 (s, 2H), 3.76 (d, J = 13Hz, 1H), 6.85 - 7.25 (m, 4H), 7.03 (s, 5H), 7.35 - 7.75 (m, 1H), 8.00 (br s, 1H); ir (KBr, ν, cm^{-1}): 3480, 3000, 2875, 1740.

1,2-Dibenzyl-3-carbomethoxy-4-methyl-1,2,3,4-tetrahydro-ß-carboline (9g).

To a stirred solution of 8 (250 mg, 0.776 mmol) in 5 ml of dry toluene under Ar, phenylacetaldehyde (185 mg, 0.18 ml, 1.54 mmol) was added and refluxed for 4.5 h. Evaporation of the solvent gave a yellowish solid which was recrystallized (95% ethanol, 270 mg, 82%). The elemental analysis, mp and spectral data are given in Tables I and II. For **9c**, **9d**, **9e**, **9f**, **9h** and **9j** one equivalent of 8 was respectively treated with 5, 4, 4, 1, 1.5, 2 and 1.2 equivalents of aldehydes. The completion of the reactions was determined by tlc.

1-Benzyl-3-Carbomethoxy-1,2,3,4-tetrahydro-ß-carboline (6g).

To a stirred solution of 250 mg (0.59 mmol) of **9g** in 3 ml of acetic acid and 10 ml of 95% ethanol, 0.4 g of 10% Pd-C was added. To the reaction flask a balloon full of hydrogen was attached and the contents were stirred at room temperature for 4 h. The mixture was filtered through a layer of celite, and the celite was washed with ethanol and the solution was evaporated. To the resulting yellowish paste a 5% solution of $NaHCO_3$ (pH 7.5) was added and the mixture was extracted with ether (4 x 50 ml). The ether extract was dried ($MgSO_4$) and evaporated to give a fluffy yellow solid (168 mg, 85%). The product was recrystallized from 95% ethanol, mp 204-205° C. Tables III and IV show the elemental analysis and spectral data for **6g**.

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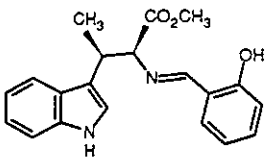
11. Condensation of 4 with salicylaldehyde even under refluxing xylene gave aldimine



(97%, mp 138-140° C)

and not the THßC (**6h**). The structure of this aldimine was confirmed by elemental analysis and spectroscopic methods (nmr, ir, ms).

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13. The crystal structure was determined by J. C. Huffman, Indiana University, and a manuscript on the X-ray data is in preparation.

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