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General Method for the Assignment of Stereochemistry of 1,3-Disubstituted 1,2,3,4-Tetrahydro-β-carbolines by Carbon-13 Spectroscopy

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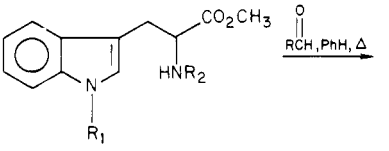
Abstract: The compression effect observed in carbon-13 magnetic resonance spectroscopy, when combined with conformational analysis in terms of $A^{(1,2)}$ strain, and 1,4-gauche interactions have been employed to provide a general method for stereochemical assignments in the 1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline area. Diastereomeric bases were separated, and the stereochemistry of each isomer was assigned on the basis of the carbon spectrum. The signals for C-1 and C-3 in the trans diastereomers were clearly upfield from those of the corresponding cis isomers (see Table I). The validity of the ^{13}C NMR technique was confirmed by chemical as well as physical (X-ray analysis) means. For the case of bases substituted with aryl groups at position 1 the (*o*-nitrophenyl)-β-carboline **7a** (cis by ^{13}C NMR) was cyclized (H_2, PtO_2) to lactam **10** while trans isomer **9b** provided only amine **8b**, as expected, on the basis of strain arguments. Moreover, the stereochemistry of **12a** (trans by ^{13}C NMR) was corroborated by single-crystal X-ray analysis which permitted extension of the technique from 1-aryl- to 1-alkyl-substituted 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines. In addition, a study was undertaken to examine the effect of $A^{1,2}$ strain on configurational preference of the Pictet–Spengler reaction in formation of tetrahydro-β-carbolines. In cases where C-1 was substituted with a group which occupied a molecular volume equal to or greater than ethyl, a preponderance of the trans diastereomer was formed and, furthermore, the same phenomenon was observed when the indole nitrogen was substituted with a methyl function. The potential of the ^{13}C NMR method for determination of the relative and absolute stereochemistry in 1,3-disubstituted tetrahydro-β-carbolines and 1-substituted tetrahydro-β-carbolines is also discussed.

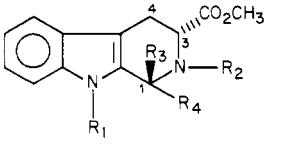
Recent interest in the pharmacological properties of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines,[1a-d] the potential implication of β-carbolines in mechanisms which operate in alcoholism and mental illness,[2] and the discovery of alkaloids such as 5α-carboxystrictosidine[3] prompted a study[4a,b] designed to provide a general method for stereochemical assignments in the 1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline area. Investigation of such a technique has also been stimulated by the recent controversy regarding interaction of β-carbolines (the so-called γ-substance) with the benzodiazepine receptor.[5] Several methods for this purpose are available; most of these, however, suffer from serious drawbacks. For instance, ORD/CD has been employed successfully by Brossi[6] in the 1-methyl-3-carboxy series, but pure samples of the tetrahydro-β-carbolines are necessary for accurate assignments and such diastereomers are often difficult to separate.[4b] In a different vein, chemical correlation (preferential cyclization only of the cis isomer) of stereochemistry, carred out by Smith,[3] required synthesis of specific compounds with the proper functionality at carbon atoms 1 and 3 to permit cyclization. This noninstrumental approach is too laborious to be employed in a general sense. Proton NMR also has not provided consistent results since the signals for the protons located at C-1 often overlap and, furthermore, NMR analysis of the rotamers (N_b-acetyl) of **2a** and **2b** has resulted in conflicting assignments in the 1-phenyl-3-methoxycarbonyl series **2a** and **2b**.[7,8] Consequently, proton NMR must also be considered ineffective, in a general sense, for stereochemical assignments in this field.

In 1976, however, it was reported in preliminary fashion[4a] that carbon-13 magnetic resonance spectroscopy was indeed the method of choice for assignments in the 1-phenyl-3-methoxycarbonyl bases **2a** and **2b**. Moreover, in that same year Wenkert[9] published definitive studies on the application of ^{13}C NMR for structure proof and stereochemical assignments of a number of yohimbinoid and ajmalicinoid alkaloid systems. In a similar study, Gribble and Levy[10] employed deuterium labeling and relaxation times to assign the carbon signals in a quinolizine alkaloid isolated from *Dracontomelum mangiferum*. It became clear that carbon spectroscopy would be devoid of the complications observed in proton NMR and, therefore, additional studies were initiated in

Scheme I



1, $R_1 = R_2 = H$
11a, $R_1 = R_2 = H$, HCl salt
b, $R_1 = H$, $R_2 = CH_2Ph$
c, $R_1 = CH_3$, $R_2 = H$



2a, $R_1 = R_2 = R_3 = H$, $R_4 = Ph$, cis
b, $R_1 = R_2 = R_4 = H$, $R_3 = Ph$, trans
c, $R_1 = R_2 = R_3 = H$, $R_4 = C_6H_{11}$, cis
d, $R_1 = R_2 = R_4 = H$, $R_3 = C_6H_{11}$, trans
12a, $R_1 = R_2 = R_4 = H$, $R_3 = CH_2CH_3$, trans
b, $R_1 = R_4 = H$, $R_2 = CH_2Ph$, $R_3 = CH_2CH_3$
c, $R_1 = R_2 = R_3 = H$, $R_4 = CH_2CH_3$, cis
d, $R_1 = CH_3$, $R_2 = R_4 = H$, $R_3 = CH_2CH_3$, trans

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(1) (a) Grabowska, M.; Antkiewica, L.; Michaluk, J. *Diss. Pharm. Pharmacol.* **1972**, *24*, 423. (b) Rahwan, R. G. *Toxicol. Appl. Pharmacol.* **1975**, *34*, 3–27. (c) Messiha, F. S.; Geller, I. *Proc. West. Pharmacol. Soc.* **1976**, *19*, 336. (d) Ho, B. T.; Taylor, D.; McIsaac, W. M. *Adv. Behav. Biol.* **1971**, *1*, 97.

(2) Cohen, G.; Collins, M. *Science (Washington D.C.)* **1970**, *167*, 1749. David, U. E.; Walsh, M. J. *Ibid.* **1970**, *167*, 1005. Bamgbose, S. O. A.; Dramane, K. L.; Okogun, J. I. *Planta Med.* **1977**, *31*, 193.

(3) DeSilva, K. T. D.; King, D.; Smith, G. N. *Chem. Commun.* **1971**, 908.

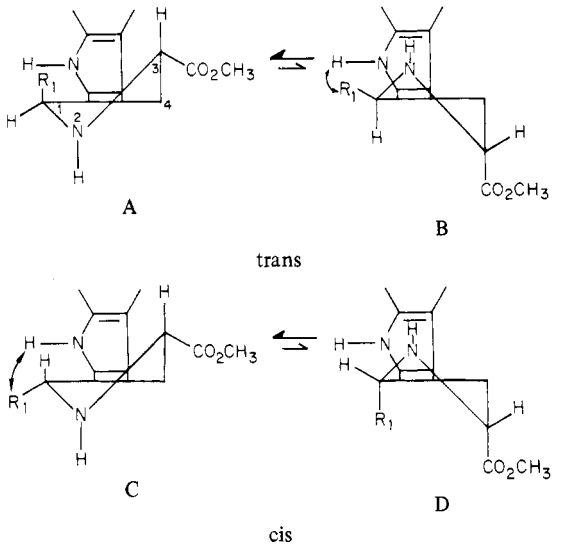
(4) (a) Sandrin, J.; Soerens, D.; Cook, J. M. *Heterocycles* **1976**, *4*, 1249. (b) Ungemach, F. M.S. Thesis, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin, 1978.

(5) Fox, J. L. *Chem. Eng. News* **1980**, 24 and work described therein.

(6) Brossi, A.; Focella, A.; Teitel, S. *J. Med. Chem.* **1973**, *16*, 418.

0002-7863/80/1502-6976$01.00/0

Scheme II



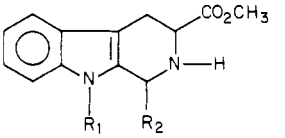
our laboratories to determine the limits of the method described earlier[4a] over an entire series of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines. In addition, it was hoped the method could be extended from 1-aryl- to 1-alkyl-substituted tetrahydro-β-carbolines and could be employed for assignments in the 3-hydroxymethyl cases, as well as the 3-methoxycarbonyl compounds originally reported on.[4a]

The carbon NMR method rests on the well-documented compression effect[11] observed in C-13 spectroscopy and can be illustrated very briefly for *cis*- and *trans*-1-phenyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (**2a** and **2b**), the syntheses of which are outlined in Scheme I. Tetrahydro-β-carbolines **2a** and **2b** were prepared by a Pictet–Spengler condensation between tryptophan methyl ester **1** and benzaldehyde in aprotic, nonacidic media[12] or in an aqueous acidic environment. The cis and trans diastereomers were isolated and separated (see Experimental Section), and the carbon-13 spectrum of each was determined. The signal assignments were based on nuclear Overhauser effects, correlations with known compounds, and off-resonance decoupled spectra (see Chart I for details). Clearly, the carbon signals for C-1 and C-3 assigned to cis isomer **2a** [C-1 (58.7 ppm), C-3 (56.9 ppm)] were downfield relative to those of **2b** [C-1 (54.9 ppm), C-3 (52.3 ppm)] which was then assigned as the trans diastereomer. Examination of molecular models and conformational analysis indicated that of the two possible twist chair conformations (Scheme II) for trans compound **2b** (A or B), conformer A should represent the structure of the more stable species for a 1,4-gauche interaction between the hydrogen at C-1 and the substituent located on C-3 as present in B. Furthermore, this conformer experienced still an additional unfavorable interaction between the indole N_a-H and the equatorial phenyl group located at C-1 ($A^{(1,2)}$ strain).[13] The more stable conformer A carries the methoxycarbonyl group at C-3 in the equatorial position, while the substituent at C-1, although now in an axial position, is devoid of the interaction due to $A^{(1,2)}$ strain between position 1 and the N_a-indole hydrogen atom. A similar analysis in the cis case **2a** led to the conclusion that conformer C (no ^{13}C-γ effect between atoms attached to carbons 1 and 3) is much more stable than conformer D; consequently, it would be expected that the signals for carbon atoms 1 and 3 in trans isomer **2b** (^{13}C-γ effect) would appear at higher field in the carbon spectrum than those of the corresponding cis isomer, in which the more stable conformer (C) experienced no ^{13}C-γ effect. This was found to be the case in 1-cyclohexyl-3-methoxycarbonyl bases **2c** (cis) and **2d** (trans), as well as the 1-phenyl compounds discussed above (see Table I). Assignment of the signals for most of the compounds in Figure I was straightforward; in contrast other data were required for specific assignment of signals to C-1 and C-3, respectively, since both of these lines appeared as doublets in the off-resonance decoupled spectrum. Additional data, moreover, were required to support the assumption that the assignments of cis and trans to indoles **2a–2d** were correct and that the tetrahydro-β-carbolines were not subject to other subtle conformational influences which might lead to erroneous conclusions. In this

Table I. Carbon-13 NMR Signals for C-1 and C-3

compd		C-1	C-3
2a	cis	58.7	56.9
2b	trans	54.9	52.3
2c	cis	57.7	56.6
2d	trans	55.4	53.4
3a	trans	54.8	51.1
3b	trans	54.5	52.8
4	cis-1_d		57.0
5a	cis	58.8	56.4
5b	cis	57.9	55.8
6	trans	55.9	51.3
7a	cis	53.1	56.5
8a	trans	52.8	52.7
9a	trans	49.9	52.9
12a	trans	51.7	52.8
12c	cis	53.8	56.5
12d	trans	51.1	52.2
13a	cis	58.9	56.6
13b	trans	54.1	53.2
14a	cis	56.9	56.3
14b	trans	52.9	52.6
15a	cis	56.2	55.4
15b	trans	53.4	52.0
16a	cis	47.8	56.2
16b	trans	45.5	51.0

Table II. Ratio of the Cis/Trans Diastereomers



compd	R_1	R_2	ratio (cis/trans)	ref
2a,b	H	C_6H_5	40/60	12
2c,d	H	C_6H_{11}	40/60	12
3a	CH_3	C_6H_5	0/100[a]	12
3b	CH_3	C_6H_{11}	0/100[a]	12
7a,9a	H	2-$NO_2C_6H_4$	25/75	1
12c,a	H	CH_2CH_3	43/57	
12d	CH_3	CH_2CH_3	0/100[a]	
13a,b	H	2-OHC_6H_4	33/66	
16a,b	CH_3	CH_3	30/70[b]	
17a,b	H	CH_3	91/9	6
18, $N_bC(=O)CH_3$	H	$CH_2CH_2CH_3$	2/98	3
19, $N_bC(=O)CH_3$	H	$CH_2CH_2CH_2CH_3$	30/70	3
20, $N_bC(=O)CH_3$	5-α-(methoxycarbonyl)-strictosidine penta-acetate		32/68	3

[a] None of the cis isomer was observed in the reaction product either by TLC or ^{13}C magnetic resonance spectroscopy. [b] Ratio determined from ^{13}C NMR spectrum of the mixture.

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(8) Saxena, A. K.; Jain, P. C.; Anand, N.; Dua, P. R. *Indian J. Chem.* **1973**, *11*, 417.
(9) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645 and references cited therein.
(10) Gribble, G. W.; Nelson, R. B.; Johnson, J. L.; Levy, G. C. *J. Org. Chem.* **1975**, *40*, 3720. Gribble, G. W.; Nelson, R. B.; Levy, G. C.; Nelson, G. L. *Chem. Commun.* **1972**, 703 and references cited therein.
(11) Levy, G. C.; Nelson, G. S. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972; pp 43–44. Eliel, E.; Allinger, N. L. *Top. Stereochem.* **1974** *8*, 26–28.
(12) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; Di Pierro, M.; Cook, J. M. J. *Org. Chem.* **1979**, *44*, 535.
(13) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

Chart I. Carbon-13 NMR Shifts of 1,3-Disubstituted 1,2,3,4-Tetrahydro-β-carbolines

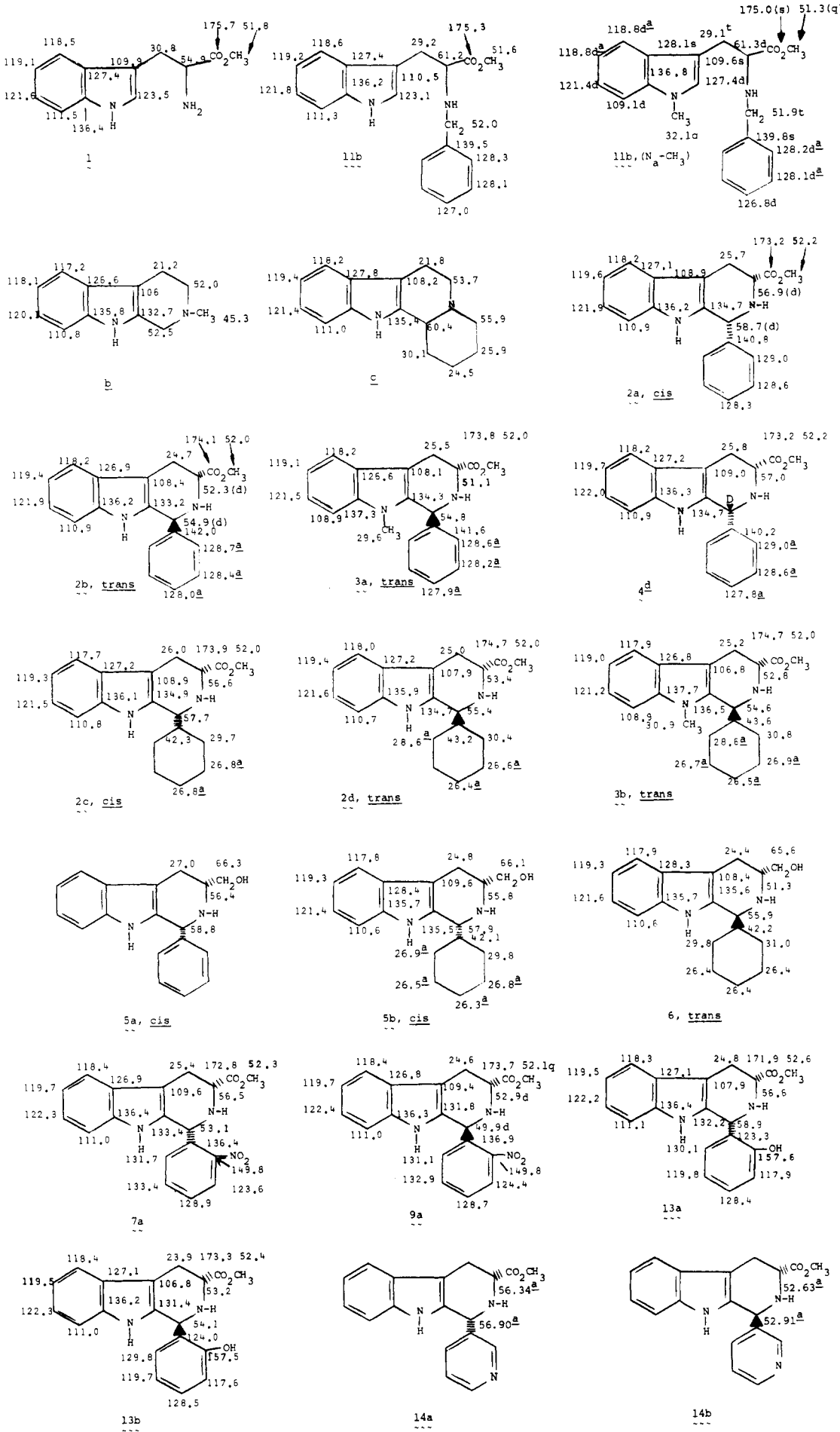
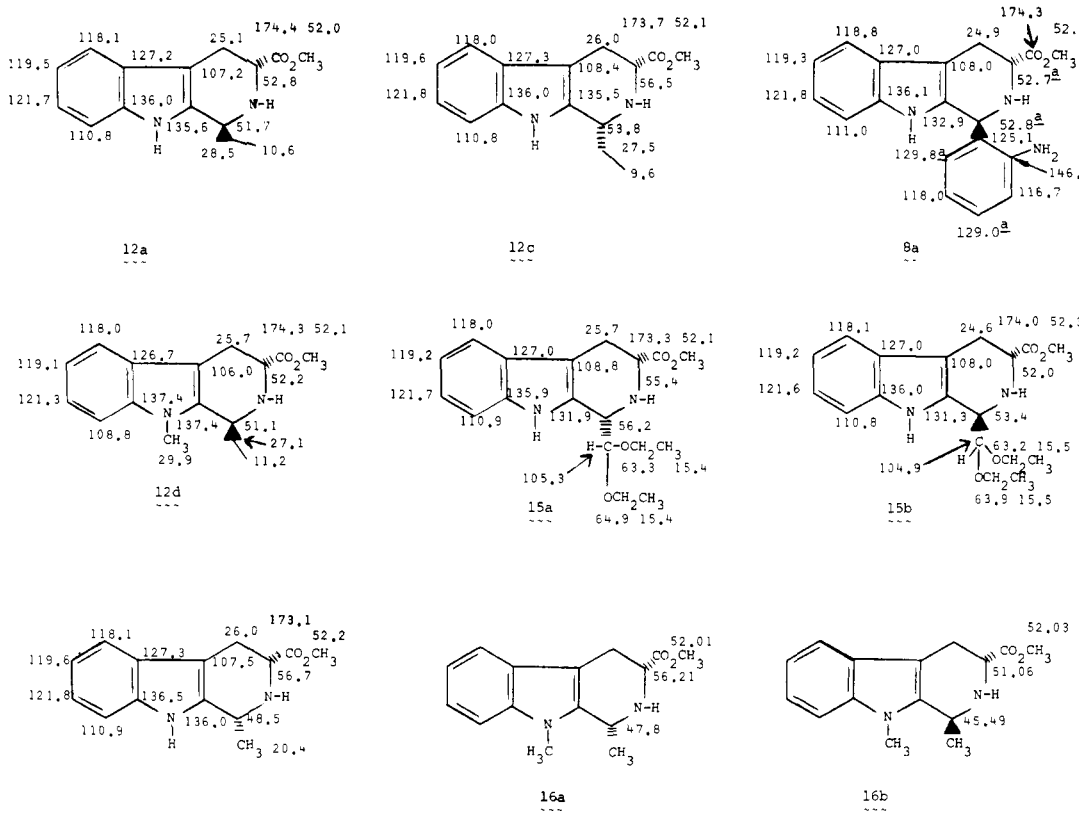


Chart I (*Continued*)



[a]The signals for carbon atoms designated a are interchangeable.
[b]C. Poupat, A. Ahond and T. Sevenet, Phytochem, 15, 2019 (1979).
[c]See reference 10.
[d]The signal for C-1 was absent in the normal ^{13}C fourier transform spectrum obtained with rapid pulsing (see reference 10). This is due to a longer T_1 for the fully deuterated carbon and a resulting relative saturation for the signal. Furthermore, a decrease in signal intensity for C-1 can be expected from ^{13}C-D splitting, quadruple broadening and a decreased NOE (H. Spiesecke and W. G. Schneider, J. Chem. Phys., 1961, 35, 722).
[e]The chemical shifts are reported with tetramethylsilane as the internal standard, furthermore, a (-) value indicates an upfield shift toward TMS. The following compounds were used as model compounds for the signal assignments illustrated in Figure I: toluene, aniline, O-toluidine, p-toluidine, nitrobenzene, O-nitrotoluene, O-creosol, p-creosol, benzyl alcohol, 3-methylpyridine and n-butylcyclohexane (see reference 15); p-toluidine, p-creosol, p-nitrobenzene and p-xylene (G. A. Olah and D. A. Forsyth, J. Am. Chem. Soc., 1975, 97, 3137). For convenience only, one antipode of the tetrahydro β-carboline is represented in Figure I; however, these materials are racemic for (dl)-tryptophan was the starting amine for this work.

regard, N_a-methyl tryptophan methyl ester was heated with either benzaldehyde or cyclohexylcarboxaldehyde which provided the corresponding 1-substituted derivatives **3a** and **3b**, respectively, in excellent yield. Examination of molecular models had indicated that the $A^{(1,2)}$ strain between the substituent at C-1 and the N_a-methyl group would be so pronounced that only the trans isomer should be formed. In agreement with this, only one diastereomer was isolated from each synthesis (>85% yield, see Table II); furthermore, the carbon signals for **3a** [C-1 (54.8 ppm), C-3 (51.1 ppm)] were virtually identical with those of trans **2b** [C-1 (54.9 ppm), C-3 (52.3 ppm)]. This same phenomenon was observed in the case of **3b** (see Table I).

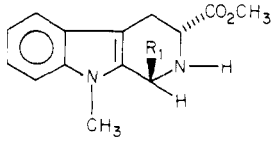
While the latter two experiments demonstrated, indirectly, the validity of the approach, additional experiments were necessary to accurately access which signal in Table I was due to the resonance line for C-1. For this purpose, tryptophan methyl ester **1** was condensed with deuteriobenzaldehyde (PhC=OD, prepared by the method of Hill)[14] in the presence of *p*-toluenesulfonic acid to provide a mixture of two components, the R_fs of which were identical with those of **2a** and **2b**. These diastereomers were separated by chromatography and the NMR mass spectrum and melting point of the more accessible cis compound **4** were found to be in complete agreement with a structure such as **4** (**2a**, 1-*d*). The carbon spectrum of **4** was devoid[10] of the signal at 58.7 ppm due to C-1 in **2a**; therefore, it was clear that the signal at 58.7 ppm in **2a** was due to the carbon at position 1 while the absorbtion at 56.9 ppm must correspond to that of C-3. To further corroborate this assignment and to extend this to the 1-cyclohexyl bases (**2c** and **2d**), we treated the cis-1-phenyl- (**2a**), *cis*-1-cyclohexyl- (**2c**), and *trans*-1-cyclohexyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (**2d**), respectively, with lithium aluminum hydride in tetrahydrofuran. The 3-hydroxymethyl-substituted bases were isolated and subjected to carbon NMR spectroscopy. In all cases [**2a** → **5a** (Δ, −0.5 ppm), **2c** → **5b** (Δ, −0.8 ppm), and **2d** → **6** (Δ, −2.1 ppm)] the signal for the carbon atom at C-3 was shifted upfield by 0.5 ppm or more; the same phenomonon was observed on going from methyl acetate to ethanol (Δ, −1.7 ppm).[15]

Having now determined the chemical shifts for carbon atoms 1 and 3 contained in the 1-phenyl and 1-cyclohexyl series, direct chemical proof was required to establish that the C-13 method was correct in the most unequivocal sense of the word. Smith and co-workers[3] have shown that *cis*-1-(hydroxymethyl)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (as the N_b-amide) would cyclize to a lactone while the trans isomer would not. Spenser[16] had, however, demonstrated that these 1-hydroxymethyl derivatives were quite labile and, consequently,

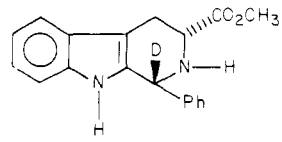
(14) Hill, E. A.; Milosevich, S. A. *Tetrahedron Lett.* **1976**, 3013.

(15) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; pp 140 (alcohols) and 150 (esters).
(16) Spenser, I. D. *Can. J. Chem.* **1959**, *37*, 1851.

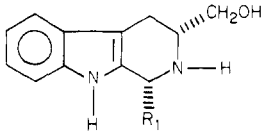
Chart II



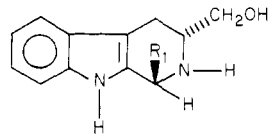
3a, R_1 = Ph, trans
b, $R_1 = C_6H_{11}$, trans



4, cis

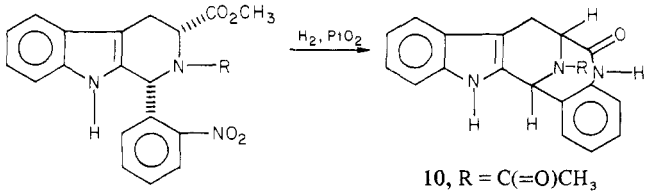


5a, R_1 = Ph
b, $R_1 = C_6H_{11}$



6, $R_1 = C_6H_{11}$

Scheme III



7a, R = H
b, R = C(=O)CH_3

10, R = C(=O)CH_3

the cis (**7a**) and trans (**9a**) 1-(*o*-nitrophenyl) bases depicted in Scheme III were chosen for our study. A mixture of the cis (**7a**) and trans (**9a**) diastereomers was obtained from the PS cyclization of **1** with *o*-nitrobenzaldehyde, and the two components were separated by careful chromatography. The assignment of stereochemistry was initially based on the carbon spectrum of these two molecules (see Table I). When trans isomer **9a** was subjected to catalytic hydrogenation, only 2-amino derivative **8a** was isolated; however, cis diastereomer **7a**, under analogous conditions, gave only a complex mixture of products. Hobson[17] had pointed out earlier that formation of an amide (N_b) would flatten the twist-chair conformation of ring C of a tetrahydro-β-carboline and would bring the two groups cis 1,3-disposed into closer poximity to permit more facile cyclization. In view of this, both ortho nitro bases **7a** (cis) and **9a** (trans) were converted to corresponding acetamide derivatives **7b** and **9b**, respectively, on treatment with acetic anhydride and pyridine. The trans amide (**9b**) gave only amide **8b** when treated with hydrogen (PtO_2) while the cis isomer, under the same treatment, was converted to pentacyclic lactam **10** in 30% yield. Clearly, this latter transformation represents chemical proof of the validity of the C-13 method for assignments when position 1 is substituted with an aryl group. Furthermore, the data obtained from carbon spectra fully supported the earlier assignments of Hamaguchi et al.[7] In addition, *o*-hydroxyphenyl compounds **13a** (cis) and **13b** (trans) were prepared; the assignment of stereochemistry via carbon-13 spectroscopy fully supported those reported in the literature.[7]

In view of the marked pharmacological activity of 1-pyrido-substituted 1,2,3,4-tetrahydro-β-carbolines documented in reference **1a** the 1-(3-pyrido)-3-methoxycarbonyl compounds **14a** (cis) and **14b** (trans) were prepared from **1** and 3-pyridinecarboxaldehyde.[4b] Examination of the data in Table I now permitted the assignment of cis stereochemistry to **14a** (56.9, 56.3 ppm) for the signals occurred downfield with respect to **14b** [52.9, 52.6 ppm (trans)]; moreover the chemical shifts for trans 2-anilino base **8a** (52.8, 52.7) were nearly identical with those of **14b**. This example illustrates that the signal assignments are internally consistent especially when comparison of similar 1-substituents such as anilines and pyridines are made.

Attention was now turned from molecules which contain a large group at C-1 to those which bear smaller substituents. It has been

(17) Hobson, J. D.; Raines, J.; Whiteoak, R. J. *J. Chem. Soc.* **1963**, 3495.

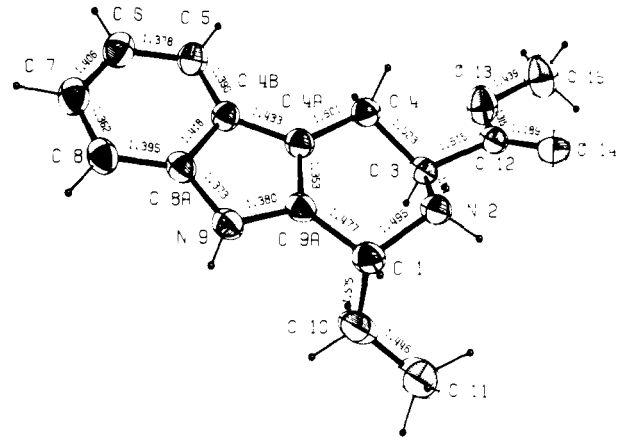
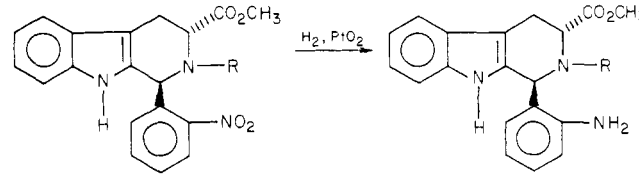


Figure 1. Crystal conformation and bond lengths for **12a**. ORTEP* drawing shows bond lengths and crystal conformation of **12a**. Heavy atoms are drawn with 40% probability ellipsoids but H atoms are arbitrary. Esd's of bond lengths are less than 0.004 Å in the ring system and less than 0.006 Å in the side chains. The complete details of the X-ray structure are available in the supplementary material (Johnson, C. K. ORTEP*, Oak Ridge, National Laboratory Report ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, Tenn. 1965).

Scheme IV



9a, R = H
b, R = C(=O)CH_3

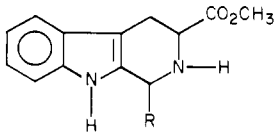
8a, R = H
b, R = C(=O)CH_3

known for some time that 1,3-disubstituted tetrahydro-β-carbolines which have a methyl group at C-1 are obtained predominantly as the cis diastereomer,[6] as shown in Table II; however, extrapolation to larger groups should be avoided, since it can lead to erroneous conclusions.[8] In view of this, it was decided to prepare the 1-ethyl-substituted tetrahydro-β-carboline from **11a** and propionaldehyde, as illustrated in Scheme I. When **11a** was heated with propionaldehyde in acidic solution, a good yield of the trans (**12a**) and cis (**12c**) bases was realized and in fact, the isomer distribution, illustrated in Table II, indicated that the $A^{(1,2)}$ strain was significant enough in the 1-ethyl bases to favor trans 1-ethyl diastereomer **12a**, which predominated in the product mixture. The two diastereomers were separated from each other by LC (Waters-500, SiO_2),[18] and the carbon spectra recorded. After initial assignment of stereochemistry (via ^{13}C NMR), attempts were made to corroborate the findings by another method. Certainly, chemical correlation of the cis isomer (via cyclization) was out of the question. It had, however, been reported earlier that N_b-benzyltryptophan methyl ester **11b** reacted with either salicyaldehyde,[4b] glyoxal diethyl acetal, or propionaldehyde in stereospecific fashion[19] to provide only the trans 1,3-disubstituted β-carboline (e.g., **12b**). When **12b** was subjected to catalytic debenzylation, the only material isolated corresponded to **12a** previously assigned the trans configuration. Moreover, excellent agreement was observed between the chemical shifts for carbon atoms 1 and 3 in the spectrum of **12a** (51.7, 52.8 ppm) and the signals in the spectrum of **12d** [51.8, 52.2 ppm (N_a-CH_3)] as compared to the values for the cis diastereomer **12c** (53.8, 56.5 ppm). Apparently, the $A^{(1,2)}$ strain which operated in **3a** and **3b** to favor the trans base was also present in **12d** (N_a-CH_3). In support of this only a single isomer, **12d**, was obtained when **11c** was heated with propionaldehyde in an aqueous acidic medium.

(18) We thank Dr. Amos Heckendorf, Waters Associates, for performing this separation.

(19) Ungemach, F.; Di Pierro, M.; Weber, R.; Cook, J. M. *Tetrahedron Lett.* **1979**, 3225.

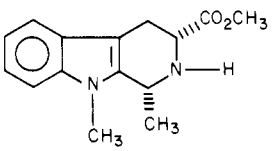
Table III. Physical Data of cis and trans 1,3-Disubstituted 1,2,3,4-Tetrahydro-β-Carbolines



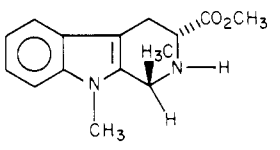
compd	diastereomer	R	R_f	mp, °C	ref
2a	cis	Ph		220-222	7
2b	trans	Ph		176-177	7
2a	cis	Ph	0.56	201-203	12
2b	trans	Ph	0.43	175-177	12
2c	cis	C_6H_{11}	0.70	153-155	12
2d	trans	C_6H_{11}	0.59	147-149	12
3a N_a-methyl	trans	C_6H_5		196-198	
3b N_a-methyl	trans	C_6H_{11}		151-152	
7a	cis	2-$NO_2C_6H_4$		193-195	7
7a	cis	2-$NO_2C_6H_4$	0.64	198-200	5
9a	trans	2-$NO_2C_6H_4$		175-179	7
9a	trans	2-$NO_2C_6H_4$	0.54	183-185	5
12a	trans	CH_2CH_3	0.65	150-152	
12c	cis	CH_2CH_3	0.75	112-114	
12d N_a-methyl	trans	CH_2CH_3		77-78	
13a	cis	2-HOC_6H_4		183-186	7
13a	cis	2-HOC_6H_4	0.75	189-192	12
13b	trans	2-HOC_6H_4		142-146	7
13b	trans	2-HOC_6H_4	0.60	168-169	12
14a	cis	3-C_5H_4N	0.70	234-236	5
14b	trans	3-C_5H_4N	0.66	213-215	5
15a	cis	$HC(OEt)_2$	0.75	98	12
15b	trans	$HC(OEt)_2$	0.69	124-125	12
17a 3-acid	cis	CH_3		293	6
17b 3-acid	trans	CH_3		242-244	6

In order to avoid simple extrapolation of the shifts observed in the 1-aryl cases to those of the 1-alkyl derivatives, we crystallized a sample of *trans*-1-ethyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline **12a** and it was subjected to single-crystal X-ray analysis.[20] The crystallographic results (see Figure 1) completely confirm the identification of **12a** as the trans isomer and now permit use of this approach for other 1-alkyl bases in this series. Along these lines, cis and trans 1-diethylacetal derivatives **15a** and **15b** were prepared[12] and their structures assigned by ^{13}C NMR. Interestingly, in all of the tetrahydro-β-carbolines listed in Table III, the cis diastereomer consistently had a higher melting point that that of the trans compound with the exception of the 1-ethyl- and 1-diethylacetal-substituted bases in which the sequence of melting points was reversed. This demonstrates the superiority of the carbon NMR technique for assignments in this series over the comparison of such physical data as melting point.

In agreement with the tendency of small groups (CH_3) to occupy equitorial positions at C-1 of 1-alkyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines, Brossi reported that N_a-hydro-1-methyl-3-carboxyl derivatives **17a** and **17b** were present in the reaction mixture in a ratio of cis to trans (91/9) which correlates with the smaller amount of $A^{(1,2)}$ strain in such molecules. It has been shown earlier (see above), however, that this repulsion drastically increased the amount of trans diastereomer in the mixture when the indole nitrogen was present as N_a-methyl. Nowhere is the utility of the ^{13}C NMR method more obvious than in the case of *cis*- and *trans*-N_a-methyl-1-methyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines **16a** and **16b**. In this case, the products of the Pictet–Spengler reaction of **11c** and acetaldehyde were isolated as a mixture of epimers. Not only was it clear from the ^{13}C NMR spectrum of the mixture that **16a** was the cis diastereomer (47.8, 56.2 ppm; see Table I) and that **16b** (45.5, 51.0 ppm) could be assigned trans stereochemistry but also the isomers were present in a ratio of cis to trans of 30/70 (see Table II). This indicated that $A^{(1,2)}$ strain had now become



16a



16b

the dominant force in determining the diastereomeric preference in this reaction (see also examples **18**, **19**, and **20** listed in Table II). For this study materials **16a** and **16b** were not separated from each other, which again attests to the strength of the ^{13}C NMR method. In all of the examples examined here, the signals for C-1 and C-3 of the cis isomers are clearly distinct from the analogous resonance lines for the trans diastereomers and, consequently, an approximate cis/trans ratio can be determined from examination of the carbon spectrum of the mixture if the NOE effects are suppressed. This technique provides, for the first time, a facile method for studying the effect of $A^{(1,2)}$ strain in determining configurational preference in 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines which could be extended to other molecules that contain twist chair conformations of substituted cyclohexenes.

Conclusion

With the advent of the ^{13}C NMR method for stereochemical assignments and the Pictet–Spengler reaction in aprotic media,[4,12,21] optically active 1,3-disubstituted tetrahydro-β-carbolines of known configuration are easily accessible. For example, if L-tryptophan methyl ester (free base) is heated with aldehydes in nonacidic, aprotic media,[4,12,21,22] 1,3-disubstituted tetrahydro-β-carbolines could be prepared with configurations *S*(C-3), *S*(C-1) or *S*(C-3), *R*(C-1). The assignment of stereochemistry for each diastereomer *via* the carbon spectrum would automatically establish the relative and absolute configurations in both of the stereoisomers. Furthermore, discovery of a stereospecific reaction sequence (N_a-H, N_b-CH_2Ph) which provides only the trans stereoisomer,[4b,19,22] when combined with the ^{13}C NMR technique, furnishes a route to one diastereomer of known absoute stereochemistry in an extremely facile manner. In addition, the 3-methoxycarbonyl group could then be removed by Yamada's method[23] to yield 1-substituted 1,2,3,4-tetrahydro-β-carbolines of known absolute configuration.

Examination of the data depicted in Table II is quite informative, for the effect of molecular size on the degree of $A^{(1,2)}$ strain between the N_a-R and C-1 substituents is well illustrated. Clearly, any group at C-1 which occupies a molecular volume similar to or greater than an ethyl function will favor a preponderance of the trans diastereomer in the PS reaction, while the incorporation of an indole N_a-methyl function will also lead to a preponderance of the trans isomer even when position 1 is substituted with a methyl group.

There is a correlation between the melting point and R_f value on TLC with the stereochemistry of the tetrahydro-β-carbolines (see Table III). The melting points for each of the cis bases are generally higher than those for the corresponding trans diastereomers. This difference arises from the diequatorial nature of the cis compounds which decreases the steric bulk prependicular to the indole plane permitting tighter packing in the crystal, in contrast to the trans isomers which have the axial group perpendicular to the plane of the indole ring. There are, however, exceptions to this trend, as mentioned above (see structures **12a**, **12c**, **15a**, and **15b**), which further demonstrate the utility of the ^{13}C NMR method for these assignments. In all of the 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines examined in this work (see Table III) the cis diastereomers had the R_f of greater value. The higher mobility of the cis isomer is due to the lower sorptivity

(20) We thank the National Institutes of Health for generous use of their X-ray facilities.

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(23) Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, *61*. Akimoto, H. et al. *Chem. Pharm. Bull.* **1974**, *22*, 2614. Yamada, S.; Akimoto, H. *Tetrahedron Lett.* **1969**, 3105.

on the resin, and this is a consequence of the steric accessibility of the polar groups involved.[24,25] The phenomenon (R_f) observed provides some idea of which isomer is present but is in no way quantitative since examples exist in the literature where the relationship does not hold.[3,26]

Finally, recent studies by pharmacologists have indicated that dual effects initiated by drugs such as propranolol[27] are often due to the mixture of enantiomers with a specific effect mediated by a specific enantiomer. Because the same phenomenon may occur with 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines[1,2,5] the need for a fast, accurate method for assignment of relative and absolute stereochemistry is required. The carbon-13 NMR technique fulfills this need for it appears to be general and is much superior to other methods for this purpose because of the consistency and the ease of data collection.

Experimental Section

Microanalyses were performed on a F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60 MHz spectrometer and a Varian CFT-20 ^{13}C NMR spectrometer. Infrared spectra were taken on a Beckman Acculab-1 instrument, and mass spectra were recorded on Hitachi RMU-6, Finnigan GC/MS and AEI MS-902 mass spectrometers.

Analytical TLC plates used were E. Merck Brinkman UV active silica gel or alumina on plastic. The TLC plates were developed with the spray reagent, ceric ammonium sulfate in 50% sulfuric acid. DL-Tryptophan, tryptamine–hydrochloride, salicylaldehyde, cyclohexanecarboxaldehyde, 3-pyridinecarboxaldehyde, *o*-nitrobenzaldehyde, and benzaldehyde were purchased from Aldrich Chemical Co.

The synthesis of *cis*- and *trans*-(3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)benzene (**2a** and **2b**), *cis*- and *trans*-(3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)-cyclohexane (**2c** and **2d**), *cis*- and *trans*-(3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)formyl diethyl acetal (**15a** and **15b**), and *cis*- and *trans*-(3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(2-hydroxybenzene) (**13a** and **13b**), respectively, have been described elsewhere (see ref 12).

(3-(Methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)benzene (3a). N_a-Methyl tryptophan methyl ester (**1**, 8.7 g, 0.037 mol) prepared by the method of Yoneda[26] was dissolved in dry benzene (100 mL), and benzaldehyde (5.0 g, 0.047 mol) was added. The solution was refluxed for 24 h until TLC indicated the absence of starting material. The solvent was evaporated under reduced pressure to provide a yellow oil which was crystallized from benzene to yield **3a** (7.5 g). An additional amount of **3a** (3.6 g) was obtained on chromatography of the mother liquors on silica gel, combined yield 94%; mp 196–198 °C (benzene). IR (KBr): 1735 cm^{-1} (ester). NMR ($CDCl_3$): δ 2.42 (1 H, s, NH), 2.80–3.40 (2 H, m), 3.25 (3 H, s, NCH_3), 3.70 (3 H, s, OCH_3), 3.70–4.00 (1 H, m), 5.30 (1 H, s, C-1 proton), 7.00–7.70 (9 H, m, aromatic protons). Mass spectrum: m/e 320 (M^+).

(3-(Methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)cyclohexane (3b). The β-carboline (**3b**) was prepared by refluxing equimolar amounts of N_a-methyltryptophan methyl ester (2.32 g, 0.01 mol) and cyclohexylcarboxaldehyde (1.12 g) in dry benzene (40 mL), as described in the preceding experiment. The product was recrystallized from benzene to provide an 85% yield (2.7 g) of **3b**; mp 151–152 °C (benzene). IR (KBr): 3380 and 1735 cm^{-1} (ester). NMR ($CDCl_3$): δ 1.00–2.00 (11 H, m), 2.20 (1 H, s, NH), 3.00–3.20 (2 H, m), 3.60 (3 H, s, NCH_3), 3.70 (3 H, s, OCH_3), 4.15 (2 H, m), 7.10–7.70 (4 H, m). Mass spectrum: m/e 326 (M^+).

Lithium Aluminum Hydride Reduction of *cis*-(3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)cyclohexane (2c) To Provide *cis*-(3-(Hydroxymethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)cyclohexane (5b). The cis 1-cyclohexyl-3-methoxycarbonyl derivative (**2c**, 1.0 g, 0.0032 mol, R_f = 0.70[4,12]) was dissolved in dry tetrahydrofuran (40 mL), and lithium aluminum hydride (1.0 g) was added in one portion. The mixture was refluxed for 4 h and then cooled in an ice bath, at which time methylene chloride (200 mL) was added to the reaction, followed by careful addition of ice water. When the exothermic reaction had ceased, sodium hydroxide (100 mL of 25%) solution was added to dissolve the inorganic hydroxides. The layers were separated, and the aqueous layer was shaken with methylene chloride (3 × 100 mL). The organic layers were combined, washed with brine, and dried (K_2CO_3). Removal of solvent under reduced pressure furnished an oil which was crystallized from methanol to provide a 70% yield of **5b** (0.64 g); mp 178–180 °C. IR (KBr): 3340 cm^{-1} (NH), also braod OH, ester C=O no longer present. NMR (Me_2SO-d_6): δ 1.00–2.00 (10 H, m), 2.15 (1 H, m), 2.80 (2 H, m), 3.60 (2 H, m), 4.05 (1 H, m), 4.80 (1 H, m), 6.80–7.60 (5 H, m). Mass spectrum: m/e 284 (M^+).

***trans*-(3-(Hydroxymethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)cyclohexane (6).** The trans isomer (**6**, 1.11 g, R_f = 0.59)[4,12] was reduced with lithium aluminum hydride (2.0 g) in tetrahydrofuran (100 mL) in a manner analogous to that described above; however, 24 h were required to obtain complete reduction of the ester carbonyl. The yield of **6** was 0.70 g (70%); mp 163–165 °C (CH_3OH). IR (KBr): 3440 (NH, OH), 3300 (NH), 1450 cm^{-1}, no ester C=O. NMR ($CDCl_3$): δ 1.00–2.40 (12 H, m), 3.20–4.00 (5 H, several overlapping multiplets), 7.00–7.60 (4 H, m), 7.80 (1 H, br s, NH). Mass spectrum: m/e 284 (M^+).

Lithium Aluminum Hydride Reduction of *cis*-(3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)benzene (2a) To Furnish *cis*-(3-(Hydroxymethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)benzene (5a). The cis 1-phenyl-3-methoxycarbonyl derivative (**2a**, 0.75 g, 0.0024 mol, R_f = 0.56)[12] was dissolved in tetrahydrofuran (100 mL), and lithium aluminum hydride (1.0 g) was added. The mixture was refluxed for 15 h, at which time an additional gram of $LiAlH_4$ was added and the reflux continued for an additional 8 h. The workup was identical with that discussed above. The yellow oil was crystallized from benzene to provide **5a** (0.40 g, 60% yield) as a white solid, mp 186–189 °C (benzene). IR (KBr): 3450–3100 cm^{-1} (NH, OH), no ester C=O. NMR (Me_2SO-d_6): δ 2.80–3.40 (3 h, two overlapping multiplets), 3.60 (3 H, m), 4.70 (1 H, s), 5.10 (1 H, s), 6.80–7.50 (10 H, m). Mass spectrum: m/e 278 (M^+).

The trans compound was prepared in 70% yield under analogous conditions to that described above; mp 175–178 °C (CH_3OH). IR (KBr): 3420 (NH), 3300–3100 cm^{-1} (OH, NH), no ester C=O; NMR (Me_2SO-d_6): δ 2.60 (2 H, m), 2.95 (1 H, m), 3.45 (2 H, t, J = 5 Hz), 4.65 (1 H, broad singlet), 5.25 (1 H, s), 6.80–7.60 (10 H, m). Mass spectrum m/e 278 (M^+).

Preparation of *cis*-(1-(Deuterio)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)benzene (4). Tryptophan methyl ester (**1**, 8 g, 0.036 mol) and deuteriobenzaldehyde (PhC=OD)[14] (3.6 g, 0.034 mol) were dissolved in dry benzene (250 mL), and the solution was refluxed for 12 h. Water (0.3 mL) was removed by means of a Dean–Stark trap. The volume of solution was decreased under reduced pressure to 7.5 mL and the mixture placed in the refrigerator. White crystals (3.2 g) of the imine precipitated from the solution; mp 118–120 °C. IR (KBr): 3150 (NH), 1740 (ester C=O), 1615 cm^{-1} (C=N). NMR ($CDCl_3$): δ 3.35 (1 H, d, J = 8 Hz), 3.50 (1 H, d J = 5 Hz), 3.72 (3 H, s, OCH_3), 4.30 (1 H, d of d, J_1 = 8 Hz, J_2 = 5 Hz), 6.80–7.80 (9 H, m), 8.10 (1 H, br s). The signal for the vinyl proton (δ 7.90) in the protioimine[12] was not present in the spectrum of the deuterio derivative.[28] Mass spectrum: m/e 307 (M^+).

The imine-*d* (3.5 g) was placed in the original reaction mixture and the solution refluxed for an additional 12 h. Only imine-*d* and the higher melting diketopiperazide (mp 260 °C)[29] were produced.

p-Toluenesulfonic acid (0.6 g) and benzene (60 mL) were refluxed for 3 h, and water was removed *via* a Dean–Stark trap. To this mixture of dry benzene and *p*-TsOH was added the deuterioimine (1.0 g) and the mixture refluxed for $^1/_2$ h, at which time TLC indicated the absence of starting material. Two new spots appeared on TLC with R_f values identical with the cis and trans isomers of 1-phenyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**2a** and **2b**). The mixture was separated on silica to provide *cis*-1-phenyl-1-deuterio-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**4**), mp 203–205 °C (lit. value[4] 201–203 °C). IR (KBr): 1735 cm^{-1} (ester C=O). NMR ($CDCl_3$): δ 2.80–3.20 (2 H, m), 3.75 (3 H, s, OCH_3), 3.80–4.10 (1 H, m), 6.90–7.60 (10 H, m). Mass spectrum: m/e 307 (M^+).

(24) Preobrazhenskaya, M. N.; Mikhailova, L. N.; Chemerisskaya, A. A. *J. Chromatogr.* **1971**, *61*, 269.

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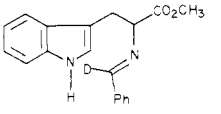
(27) Regoli, D.; Regoli, U.; Gysling, E. *Can. J. Physiol. Pharmacol.* **1972**, *50*, 214.

(28) The structure of the deuterioimine i is as shown.



i

(29) Kametani, T.; Ihara, M.; Suzuki, T.; Shima, K. *J. Heterocyclic Chem.* **1968**, *5*, 799.

The proton at carbon 1 present at δ 5.25 in the protio derivative (**2a**)[12] was absent in the spectrum of the 1-deuterio derivative **4**, as expected.

Unfortunately the trans isomer could not be obtained in pure enough form for characterization, although the components contained in a mixed sample of trans 1-protio (**2b**) and trans 1-deuterio (**2b**) had the same R_f on TLC in several solvent systems.

Preparation of *cis*- (7a) and *trans*-(3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(2-nitrobenzene) (19a). DL-Tryptophan methyl ester hydrochloride (15.3 g, 0.060 mol) and *o*-nitrobenzaldehyde (10.0 g, 0.066 mol) were refluxed for 2 days with stirring in a 1:3 water/methanol solution. The solvent was evaporated in vacuo; the residue was basified with ammonium hydroxide (14%) and extracted with toluene. The toluene layer was dried with sodium sulfate and refluxed for 2 days in the presence of a Dean–Stark trap until no starting material (tryptophan methyl ester) remained. The presence of two compounds was observed by TLC (silica gel; 1:2% methanol/chloroform; R_f = 0.64 and 0.54). The toluene was removed under reduced pressure, and the residue was chromatographed on silica gel. The cis nitrocarboline (**7a**) was eluted from the column (1.2 g); mp 198–200 °C ($CHCl_3$) [lit.[7] mp 193–195 °C (MeOH)]. IR (KBr): 3430, 3380, 3320 (s, NH), 3020–3070 (w, aromatic CH), 2960, 2900, 2850, 2810 (w, aliphatic CH), 1730, 1715 (C=O ester), 1515, 1335 cm^{-1} (s, N⁻⁻O). NMR ($CDCl_3$): δ 3.20 (2 H, C-4 methylene), 3.80 (3 H, s), 4.00 (1 H, t, J = 5 Hz, C-3 hydrogen), 5.70 (1 H, s, C-1 hydrogen), 7.00–8.00 (9 H, m).

A mixture of both diastereomers followed (4.7 g). Mass spectrum of the mixture: m/e (electron impact) 351 (5, M^+), 349 (4), 348 (7), 335 (13), 334 (21), 333 (15), 319 (16), 318 (25), 317 (37), 260 (29), 259 (35), 258 (62), 257 (57), 218 (25), 166 (100), 135 (37).

The trans nitrocarboline (**9a**) was the last material to be eluted from the column, obtained as a yellow solid (**9a**, 7.6 g); mp 183–185 °C ($CHCl_3$) [lit.[7] mp 175–179 °C (MeOH)]. IR (KBr): 3390 (indole NH), 3310 (NH), 3070 (w, aromatic CH), 2980, 2910 (w, aliphatic CH), 1740, 1710 (C=O ester), 1515, 1340 cm^{-1} (s, N⁻⁻O). NMR ($CDCl_3$): δ 3.20 (2 H, d, J = 9 Hz), 3.60 (3 H, br s), 3.90 (1 H, t, J = 9 Hz, C_3H), 5.90 (1 H, s, C_1H), 6.90–7.50 (8 H, m), 7.90 (1 H, s, indole NH).

The overall yield was 64% although at times yields of >80% were observed.

Preparation of *cis*-(3-(Methoxycarbonyl)-2-acetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(2-nitrobenzene) (7b) and *trans*-(3-(Methoxycarbonyl)-2-acetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(2-nitrobenzene) (9b). The nitroamine (7a) was dissolved in dry, distilled pyridine, and excess acetic anhydride was added. After the solution stood for 2 days, the solvent was removed in vacuo. The residue was made basic with ammonium hydroxide (14%) and subsequently extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The cis amide (7b) was recrystallized from chloroform; mp 228–230 °C ($CHCl_3$) [lit.[7] mp 243 °C (MeOH)]. IR (KBr): 3210 (br, indole NH), 3010–3050 (aromatic CH), 2940, 2900 (w, aliphatic CH), 1735 (s, C=O ester), 1625 (s, C=O amide), 1520, 1345 cm^{-1} (s, N⁻⁻O). NMR ($CDCl_3$): δ 2.10 (3 H, s), 3.30–3.70 (6 H, m, OCH_3, C_3H, C_4H), 4.80 (1 H, s, C_1H), 6.90–7.80 (9 H, m).

The trans amide (**9b**), prepared from **9a** under analogous conditions to those described above, was recrystallized from methanol; mp 210–215 °C (MeOH) [lit.[7] mp 207 °C (MeOH)]. IR (KBr): 3410, 3310 (NH), 3000–3040 (w, aromatic CH), 2950, 2920 (w, aliphatic CH), 1740, 1710 (C=O ester), 1615 (C=O amide), 1520, 1340 cm^{-1} (N⁻⁻O). The trans amide was too insoluble to obtain a good NMR spectrum.

15-Acetyl-7,8,13,14-tetrahydro-7,14-aminobenz[*b*]azamino-[5,6-*b*]indol-6[5*H*]-one (10). The cis nitroamide (**7b**, 1 g, 0.0025 mol) was hydrogenated (50 psi) in acetic acid (150 mL) over PtO_2 (50 mg) for 14 h at room temperature. The solvent was removed under reduced pressure. The residue was made basic with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The lactam (**10**) was chromatographed on silica gel to provide a white solid (250 mg, 30%); mp 300–310 °C [lit.[7] mp 295–300 °C (MeOH)]. IR (KBr): 3200–3300, 3120 (s, NH), 3070 (aromatic C–H), 2980, 2920, 2850 (aliphatic CH), 1640–1660 (s, C=O amide), 1585, 1500, 1485 cm^{-1} (C⁻⁻C). NMR (Me_2SO-d_6): δ 2.10 (3 H, two singlets, amide rotomers), 3.50 (Me_2SO), 3.30 (H_2O covered both C_7H and C_8H's), 5.80, 6.20 (1 H, $C_{14}H$), 6.90–7.60 (8 H, m), 10.00, 10.70 (2 H, indole NH and lactam NH). Mass spectrum: m/e (electron impact) 331 (M^+).

trans-(3-(Methoxycarbonyl)-2-acetyl-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indol-1-yl)(2-aminobenzene) (8b). The trans nitroamide (**9b**, 1.8 g, 0.0046 mol) was dissolved in acetic acid (200 mL) and was hydrogenated (50 psi) over PtO_2 (53 mg) for 33 h at room temperature. The solvent was removed in vacuo. The residue was basified with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue and an authentic sample of the pentacyclic lactam **10** were eluted together on a silica gel TLC plate; the parallel spot of the residue was purified by chromatography on silica gel and was found to be the trans amide (**8b**), for no cyclization had occurred; mp 217–219 °C (benzene) [lit.[7] 225 °C (MeOH)]. IR (KBr): 3340, 3200–3220 (s, NH), 3100, 3080 (aromatic CH), 2950, 2900, 2850 (aliphatic CH), 1740 (s, C=O ester), 1660 (s, C=O amide), 1610, 1585, 1525, 1470 cm^{-1} (C⁻⁻C). NMR (Me_2SO-d_6): δ 2.00 (3 H, s), 2.50 (Me_2SO), 3.10 (2 H, d, J = 5 Hz, C_4H), 3.40 (H_2O), 3.60–4.00 (4 H, OCH_3, C_3H), 5.50 (1 H, s, $C_{10}H$), 6.90–8.00 (9 H, m), 10.20, 10.50 (2 H, NH protons). Mass spectrum: m/e (electron impact) 363 (13, M^+), 346 (11), 345 (39), 344 (37), 343 (69), 287 (14), 286 (41), 285 (100), 284 (57), 283 (76), 271 (52).

trans-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(2-aminobenzene) (8a). The trans nitrocarboline (**9a**, 1.0 g, 0.002 mol) was dissolved in methanol (50 mL) and hydrogenated (50 psi) for 16 h at room temperature over PtO_2 (0.1 g). After removal of the catalyst by filtration, the solvent was evaporated in vacuo and the residue was crystallized from methanol to furnish **8a** (0.55 g, 60%); mp 148–150 °C (MeOH). IR (KBr): 3460, 3380, 3300 (s, NH), 3050, 3020 (w, aromatic CH), 2940, 2910, 2850 (w, aliphatic CH), 1700 (s, C=O ester), 1630, 1600, 1575, 1490 cm^{-1} (C⁻⁻C). NMR ($CDCl_3$): δ 2.80–3.20 (5 H, aromatic NH_2, NH), 3.50 (4 H, OCH_3, C_3H), 5.10 (1 H, s, C_1H), 6.30–7.40 (8 H, m), 8.00 (1 H, s, indole NH). Mass spectrum: m/e (electron impact) 322 (14, M^+ + 1), 321 (57, M^+), 320 (10), 317 (12), 305 (12), 305 (11), 304 (23), 272 (26), 260 (32), 245 (35), 235 (47), 234 (40), 233 (58).

Preparation of *cis*- (14a) and *trans*-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(3-pyridine) (14b). Tryptophan methyl ester (**1**, 11.8 g, 0.054 mol) and 3-pyridinecarboxaldehyde (6.5 g, 0.060 mol) were refluxed for 2 days in toluene (100 mL); a Dean–Stark trap was employed to remove the water which formed in the reaction mixture. The solvent was evaporated in vacuo and a precipitate (8.0 g) formed. The remainder of the material was isolated as an oil (7.2 g). Examination of the material by TLC (silica gel) with 10% methanol/ethyl acetate indicated two components were present in this mixture (R_f = 0.70 and 0.66). Both the oil and the solid were combined and were chromatographed on silica gel. The cis pyridyl indole (**14a**, R_f = 0.70) was eluted first (4.3 g); mp 234–236 °C (MeOH). IR (KBr): 3310 (NH), 3140, 3000–3100 (aromatic CH), 2930, 2880, 2860, 2830, 2800 (aliphatic CH), 1720 (s, C=O ester), 1585, 1570, 1485, 1460 cm^{-1} (C⁻⁻C). NMR (Me_2SO-d_6): δ 2.50 (Me_2SO), 3.00 (2 H, m), 3.30 (H_2O), 3.60–4.00 (4 H, OCH_3, C_3H), 5.20 (1 H, m, C_1H), 6.80–7.70, 8.20–8.50 (9 H, m). Mass spectrum: m/e (chemical ionization) 308 (26, M^+ + 1), 307 (100, M^+), 306 (16), 292 (11), 249 (11), 248 (52), 247 (25), 246 (38), 234 (22), 233 (18), 231 (17), 229 (19), 220 (30), 219 (82).

The next fraction contained a mixture of both diastereomers (3.3 g). Finally the trans pyridyl indole (**14b**, R_f = 0.66) was recovered (1.4 g); mp 213–215 °C (MeOH). IR (KBr): 3350 (NH), 3150, 3100, 3060 (aromatic CH), 2980, 2950, 2870, 2840 (aliphatic CH), 1735, 1710 (C=O ester), 1590, 1580, 1490 cm^{-1} (C⁻⁻C). NMR ($CDCl_3$): δ 2.40 (1 H, s), 3.20 (2 H, d, J = 6 Hz), 3.70 (3 H, s), 4.00 (1 H, t, J = 6 Hz, C_3H), 5.40 (1 H, s, C_1H), 7.00–7.70, 8.30–8.60 (9 H, m). Mass spectrum: m/e (chemical ionization) 308 (22, M^+ + 1), 307 (100, M^+), 306 (14), 292 (11), 249 (10), 248 (51), 247 (22), 246 (32), 234 (21), 233 (17), 220 (38), 219 (85), 169 (32), 144 (38).

The overall yield was 54%.

Preparation of *trans*-(12a) and *cis*-(3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(1-ethane) (12c). Tryptophan methyl ester hydrochloride (**11a**) (15.0 g, 0.059 mol) and propionaldehyde (4.0 g, 0.0687 mol, 11% molar excess) were dissolved in a methanol/water solution (250 mL, 75/25% v/v). The mixture was refluxed (cold-finger condensor, dry ice/chloroform bath) for 48 h at which time TLC indicated the presence of two new components [R_f = 0.75 and 0.65, silica gel, acetone/chloroform (50:50)] in the reaction medium. The solution was cooled and the sovlent removed under reduced pressure, after which, the oil which remained was brought to Ph 10 with aqueous ammonia (14%). The alkaline solution was extracted with chloroform (5 × 400 mL), and the chloroform layer was dried (Na_2SO_4). Removal of the solvent under reduced pressure gave an oil which was crystallized from benzene to provide *trans* isomer **12a** (R_f = 0.65). This material was recrystallized from methanol to furnish white crystals (8.0 g), mp 150.5–152.5 °C. Crystallization of the mother liquor (benzene) next provided cis isomer **12c** (6.5 g, mp 112–114 °C, R_f = 0.75). The overall yield in this sequence of **12c** and **12a** was 69% (29% cis, 40% trans; the ratio of cis to trans was, therefore, nearly 3:4).

Cis **12c**: mp 112–114 °C; R_f = 0.75; IR (KBr) 3350, 1715, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 7 Hz), 1.90 (2 H, octet, J = 7 Hz),

2.20 (1 H, s, NH), 3.10 (2 H, m), 3.85 (1 H, q, J = 5 Hz), 3.90 (3 H, s), 4.18 (1 H, broad singlet to triplet), 7.00-7.65 (4 H, m), 8.20 (1 H, s, NH). Mass spectrum: m/e (relative intensity) 258 (M^+, 72%), 257 (11), 254 (35), 243 (10), 199 (28), 197 (59), 182 (29), 169 (70).

Trans **12a**: mp 152.5-153.0 °C (CH_3OH): R_f = 0.65; IR (KBr) 3310, 3150, 2950, 1725, 1440, 1420, 1200, 730 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, t, J = 6.0 Hz), 1.68 (2 H, q, J = 6 Hz), 2.28 (1 H, s, NH), 3.07 (2 H, m, C_4H), 3.73 (3 H, s, OCH_3), 4.00-4.10 (2 H, m, C_1H, C_3H), 7.20-7.50 (4 H, m), 8.00 (1 H, s, indole NH). Mass spectrum: m/e (relative intensity) 258 (M^+, 80%), 257 (20), 254 (10), 243 (34), 243 (34), 229 (100), 199 (50), 197 (54), 182 (39), 170 (56), 169 (80).

Preparation of *trans*-(3-(Methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)(1-ethane) (12d). Propionaldehyde (1.25 g, 0.021 mol) and N_a-methyl tryptophan methyl ester **11c** (hydrochloride, 5.0 g, 0.019 mol) were heated to reflux in a methanol/water solution (150 mL, 75/25% v/v) in a manner analogous to the previous experiment. The solution was refluxed for 52 h and then worked up similarly to the procedure described immediately above to provide the *trans*-N_a-methyl-1-ethyl-tetrahydro-β-carboline (**12d**, 6 g). This material was purified by column chromatography (silica gel, benzene/methylene chloride, gradient elution) to give **12d** (4.40 g) in 87% yield; mp 77-78 °C (benzene). IR (KBr): 3360, 1745, 760 cm^{-1}. NMR ($CDCl_3$): δ 1.10 (3 H, t, J = 7 Hz), 1.70 (2 H, m), 2.20 (1 H, s), 2.95 (2 H, m), 3.50 (3 H, s), 3.85 (3 H, s), 3.60-3.80 (1 H, buried under singlets), 3.90 (1 H, s, braod singlet to triplet, C_1H), 6.80-7.50 (4 H, m). Mass spectrum: m/e (relative intensity) 272 (M^+).

***trans*-(3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)formyl Diethyl Acetal (15b).** 2-Benzyl-(3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl)formyl diethyl acetal (10 g, 0.024 mol) was dissolved in a solution of absolute ethanol (150 mL) and acetic acid (45 mL). The mixture was subjected to catalytic hydrogenation (52.3 psi) for 24 h over 10% Pd/C (2.0 g). The catalyst was filtered from the mixture, and the solvent was removed under reduced pressure. The residue was treated with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was dried with Na_2SO_4 and evaporated under reduced pressure to provide a crystalline solid (8.2 g, 0.024 mol), mp 124-125 °C (TLC on silica with benzene, R_f = 0.69). This material was shown to be *trans*-(3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indol-1-yl)formyl diethyl acetal (**15b**). All spectral data were identical with the spectra obtained for the trans isomer previously isolated from the Pictet-Spengler reaction of tryptophan methyl ester and glyoxal diethyl acetal (lit.[12] mp 125 °C). In ref 12, a typing error led to the reversal of the cis and trans assignments which was corrected in the Erata for *J. Org. Chem.*, 1979; however, we mention it here for the sake of completeness. The base of mp 98 °C (R_f = 0.75) was the cis diastereomer while the β-carboline of mp 125 °C (R_f = 0.69) was the trans isomer.

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Supplementary Material Available: Details of the X-ray crystal structure of *trans*-1-ethyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**12a**), tables of crystal and refinement data, atomic parameters, and structure factor amplitudes, and figures of the bond and torsion angles for **12a** and the crystal packing of the molecules of **12a** (20 pages). Ordering information is given on any current masthead page.

Natural-Abundance ^{15}N Nuclear Magnetic Resonance Spectroscopy of Coronands, Cryptands, and Some of Their Complexes with Diamagnetic Metal Ions[1]

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Abstract: Natural-abundance ^{15}N nuclear magnetic resonance spectra of nitrogen-containing crown ethers, cryptand ligands, and other ligands with pyridine-type nitrogens and their complexes with alkali, alkaline-earth, silver(I), and thallium(I) ions are reported. The complexation shifts tend to go downfield with increasing charge and increasing ionic character of the nitrogen-to-metal-ion bond but upfield with increasing polarizability of the ion. The downfield shifts are generally more pronounced if the ions fit tightly into the cyclic ligand. For those metal ions expected to form essentially covalent bonds to nitrogen, the complexation shifts are not easily predicted. Some of the thallium- and silver-cryptate complexes display sizable one-bond ^{15}N-metal couplings.

Introduction

Because complexation of metal ions with organic ligands is known to affect many of the NMR properties of the ligands such as chemical shifts, coupling constants, and relaxation times, many studies have been made of the thermodynamics, kinetics, and structural effects of complexation, using NMR techniques. The recent heightened interest in complexes of alkali and alkaline-earth metal ions with ethylenediaminetetracetic acid (EDTA) and its analogues,[3] naturally occurring complexones,[4] and especially crown ethers[5] and cryptands,[6] is the result of the demonstrated importance of alklai ion complexation in membrane-carrier processes.[4,6c] Proton and carbon-13 NMR studies have been made of complexing antibiotics,[4,7] chelate ligands,[8,9] crown ethers,[10] and

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