Communications to the Editor

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A NEW METHOD FOR THE PREPARATION OF 3,4-DIHYDRO AND 1,2,3,4-TETRAHYDRO-β-CARBOLINES

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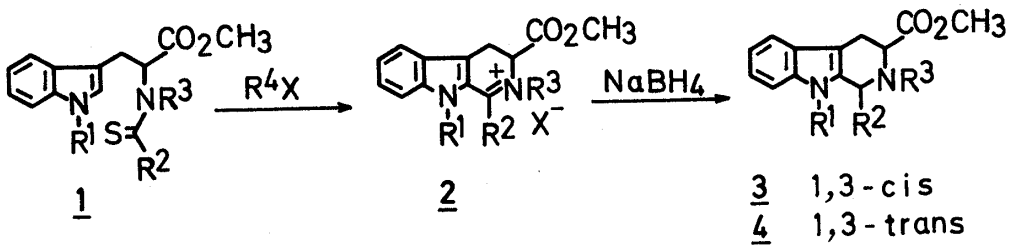
The $NaBH_4$ reduction of 1,3-disubstituted 3,4-dihydro-β-carbolines (2) gave cis (3)- or trans -1,2,3,4-tetrahydro-β-carbolines (4) with satisfactory stereoselectivity. The synthesis of optically active 2 and 3 is also described.

KEYWORDS ——— N_b-thioacyl tryptophan ; 3,4-dihydro-β-carboline-3-carboxylate 1-substituted ; 1,2,3,4-tetrahydro-β-carboline-3-carboxylate 1-substituted ; Bischler-Napieralsky reaction ; Pictet-Spengler reaction

Recently[1] we found that treatment of N_b-thioacyl tryptophan derivatives (1) with an alkylating or acylating reagent in an aprotic solvent gave rise to the cyclization reaction to result in the formation of a variety of 3, 4-dihydro-β-carbolines (2) which are hardly accessible by the classical Bischler- Napieralsky reaction.[2]

In continuation of the above study, this paper describes the reduction of 2 with $NaBH_4$ to yield 1,2,3,4-tetrahydro-β-carbolines (3 and/or 4), and also the application of this cyclization-reduction method to the synthesis of optically active 1,2,3,4-tetrahydro-β-carbolines (D- and L-3) from D- and L-N_b-thioacyl tryptophans. The results are summerized in Table I and II.

The reduction of 2 with $NaBH_4$ proceeded almost stereoselectively to give the 1,3-cis isomer (3) as a major product. Only N_b-benzyl derivative (2h) afforded the 1,3-trans isomer (4h) predominantly. The stereochemistry of the reduction products[3-6] was deduced from the spectral (^1H and ^{13}C NMR) and physical (mp and Rf values) properties, and also from chemical correlation with known compounds. Particularly informative was a characteristic ABX pattern for C-3 methine and C-4 methylene protons in the ^1H NMR spectra (J_{AB}=14-16 Hz, J_{AX}=10-12 Hz, J_{BX}=3-5 Hz) which was observed with all the 1,3-cis isomers (3a-g) in agreement with the results reported by several authors.[3a,b]



1 2 3 1,3-cis 4 1,3-trans

a) $R^1=R^3=H$, $R^2=CH_3$
b) $R^1=R^3=H$, $R^2=C_6H_5$
c) $R^1=R^3=H$, $R^2=C_6H_{11}$
d) $R^1=R^3=H$, $R^2=(CH_3)_3C$
e) $R^1=CH_3$, $R^2=C_2H_5$, $R^3=H$
f) $R^1=CH_3$, $R^2=C_6H_5$, $R^3=H$
g) $R^1=CH_3$, $R^2=C_6H_{11}$, $R^3=H$
h) $R^1=H$, $R^2=CH_3$, $R^3=C_6H_5CH_2$

Chart 1

Comparison of the diastereoisomeric ratios with those of the Pictet-Spengler (P.S.) reaction products is of interest. A great difference is observed with N_a-methyl derivatives on entries 5, 6, and 7; in contrast to 1,3-trans predominance in the P.S. reaction, mainly the 1,3-cis isomers (3e, f, g) were obtained by our method. On the other hand, the result with N_b-benzyl derivative (entry 8), is parallel with those of the P.S. reaction of various N_b-benzyl tryptophan derivatives with an aldehyde or its congeners.[7)]

Table I. The Reduction of DL-2 with $NaBH_4$[a)]

Entry	DL-2	Yields (%) of reduction products				P.S. reaction
		3	(mp , °C)	4	(mp , °C)	Ratio (3 : 4)[e)]
1	a	93	(130-131)	-[c)]		91 : 9[f)]
2	b	95	(209-210)	-[c)]		40 : 60
3	c	85[d)]	(150-152)	10[d)]	(144-147)	40 : 60
4	d	95	(116-117)	-		
5	e[b)]	94[d)]	(70- 73)	-		0 : 100
6	f[b)]	85	(130-132)	3		0 : 100
7	g[b)]	61	(128-129)	6	(148-150)	0 : 100
8	h	10	(Foam)	85	(144-145)	3 ≪ 4[g)]

a) Carried out at -20∿-70°C in MeOH.
b) Prepared from 1e, f, g by treatment with CH_3I in CH_3CN at 50°C in 88% (2e), 79% 2f), and 33% (2g) yield, respectively.
c) A trace of 4 was detected in the reaction mixture by TLC.
d) $NaBH_3CN$ was used. $NaBH_4$ was less effective in stereoselectivity (3c/4c=4:1).
e) Ratios reported in Lit. 3e), unless otherwise stated.
f) The P.S. reaction of H-Trp-OH and acetaldehyde. Lit. 9a).
g) N_b-Benzyl H-Trp-OCH_3 and acetaldehyde gave 48% of 4h and 9% of 3h in our hands.

The cyclizations of D- and L-N_b-methylthiocarbonyl tryptophan methyl esters (D- and L-1a) (entries 9 - 16) were examined with several different reagents as shown in Table II. All the reagents employed were found to be effective for our purpose, and the corresponding salts (X=I, Br, or Cl) of the optically active 1-methyl-3,4-dihydro-β-carboline derivatives (D- and L-2a)[8] were obtained in good yields. Each salt was stereoselectively converted into the 1,3-cis isomer (D- or L-3a) with $NaBH_4$. Specific rotation values of the products (entries 9, 10, 11, 12, 15, and 16) coincided with one another and also with that of the authentic sample.[9] This indicates that the reduction, and thus the cyclization proceeded without racemization. As for D- and L-phenylthiocarbonyl derivatives (1b) on entries 17 and 18, the cyclization products (D- and L-2b) could not be obtained in crystalline form, so we converted the crude products into the tetrahydro-β-carbolines (D- and L-3b) without purification. Although not determined precisely, optical purity[10] of the products (D- and L-3b) thus obtained is presumed to be considerably high, since the reaction conditions were also as mild as those used for the preparation of optically active 1-methyl derivatives (2a and 3a).

Table II. The Cyclization and the Reduction of the Optically Active Isomers

Entry	1	R^4X	Cyclization (1 → 2)			Reduction	
			Conditions[a]	2(%)[b]	$[\alpha]_D^{20}$[c]	3(%)[d]	$[\alpha]_D^{20}$[d]
9	L-a	CH_3I	CH_3COCH_3, RT, 24h	90	+221°	90	-83.2°
10	D-a	CH_3I	CH_3COCH_3, RT, 24h	87	-222°	90	+82.4°
11	L-a	$C_6H_5CH_2Br$	CH_2Cl_2, Refl, 24h	74	+263°	91	-81.6°
12	D-a	$C_6H_5CH_2Br$	CH_2Cl_2, Refl, 24h	75	-264°	91	+81.0°
13	L-a	$CH_2=CHCH_2Br$	CH_2Cl_2, Refl, 48h	84	+260°		
14	L-a	CH_3COCl	CH_2Cl_2, Refl, 24h	72	+299°		
15	L-a	C_6H_5COCl	CH_2Cl_2, Refl, 24h	83	+305°	90	-80.6°
16	D-a	C_6H_5COCl	CH_2Cl_2, Refl, 24h	82	-308°	92	+80.2°
17	L-b	CH_3I	CH_2Cl_2, Refl, 24h	Not purified		78[e]	-91.8°[f]
18	D-b	CH_3I	CH_2Cl_2, Refl, 24h	Not purified		63[e]	+89.8°[f]

a) Solvent, temp, time. b) Yields of isolated products as HX salts corresponding to R^4X used. c) $[\alpha]_D^{20}$ (c=1.0, MeOH). d) Yields and $[\alpha]_D^{20}$ (c=1.0, MeOH) of isolated products as HCl salts. The authentic L-isomer[9] ; $[\alpha]_D^{20}$ -82.4° (c=1.0, MeOH). e) Yields from 1. f) Measured in 1N-HCl.

Cyclization (L-1a → L-2a) (entry 11).[11] ------- A solution of L-1a (2.76g, 10 mmol) and benzyl bromide (1.71 g, 10 mmol) in CH_2Cl_2 (40 ml) was refluxed for 24 h under an argon atmosphere without light, and then concentrated in vacuo. The resulting crystals were collected, rinsed with CH_2Cl_2, and dried to give 2.40 g (74%) of L-2a (X=Br) as pale yellow needles; mp 196-198°C (dec.), $[\alpha]_D^{20}$ +263° (c=1.0, MeOH).

Reduction (L-2a → L-3a). ------- $NaBH_4$ (271 mg, 7.1 mmol) was added to a cooled (-70°C) solution of L-2a (2.1 g, 6.5 mmol) in MeOH (150 ml). The solution was stirred for 1 h at the same temperature, and the reaction was quenched by addition of acetone (1 ml). After concentration, the resulting oil was dissolved in CH_2Cl_2, washed with water, and dried over $MgSO_4$. Removal of the solvent and treatment of the residue with HCl-Et_2O gave 1.81 g of L-3a (HCl salt): mp 245-248°C (dec.), $[\alpha]_D^{20}$ -79.6° (c=1.0, MeOH). Recrystalization from MeOH gave 1.66 g (91%) of pure L-3a (HCl salt) as colorless prisms; mp 252-254°C (dec.), $[\alpha]_D^{20}$ -81.6° (c=1.0, MeOH).

REFERENCES AND NOTES

1) A. Ishida, T. Nakamura, K. Irie, and T. Oh-ishi, Chem. Pharm. Bull., 30, 4226 (1982). There are some ERRATA in Chart on p. 4227: g) R^1=Y=H, R^2=CH_3 ; h) R^1=Y=H, R^2=C_6H_5 ; i) R^1=Y=H, R^2=C_6H_{11} should be corrected to g) R^1=CH_3, R^2=Y=H ; h) R^1=C_6H_5, R^2=Y=H ; i) R^1=C_6H_{11}, R^2=Y=H.
2) a) D. G. Harvey, E. J. Miller, and W. Robson, J. Chem. Soc., 1941, 153. b) I. Murakoshi, Yakugaku Zasshi, 77, 550 (1957). c) H. R. Snyder and F. X. Werber, J. Am. Chem. Soc., 72, 2962 (1950).
3) 3a,b,c : Known compounds; a) K. T. D. De Silva, D. King, and G. N. Smith, Chem. Commmun., 1971, 908; b) F. Hamaguchi, T. Nagasaka, and S. Ohki, Yakugaku Zasshi, 94, 351 (1974); c) J. Sandrin, D. Soerens, and J. M. Cook, Heterocycles 4, 1249 (1976); d) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, and J. M. Cook, J. Org. Chem., 44, 535 (1979); e) F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, J. Am. Chem. Soc., 102, 6976 (1980).
4) 3e,f,g : The ^{13}C NMR signals for C-1 and C-3 appeared at lower-field (52.8 and 56.0 ppm in 3e; 57.8 and 56.4 ppm in 3f; 56.5 and 55.9 ppm in 3g) than those reported for the corresponding trans isomers (Lit. 3c, e).
5) 3h and 4h: Debenzylation by hydrogenolysis with Pd-C gave 3a (85%) and 4a (91%), respectively.
6) 3d: The cis-relationship is deduced only from analogy with other 1,3-cis homologues; ^{13}C NMR ($CDCl_3$) signals for C-1 and C-3 appeared at 62.2 and 56.2 ppm, in the range predictable from the spectra of the analogous cis isomers. In the ^1H NMR ($CDCl_3$) spectrum, an ABX pattern for C-3 and C-4 protons with a long-range coupling with a C-1 proton was observed at 3.65 ppm (1H, dd, J=3.7 and 11.0 Hz), 3.13 ppm (1H, ddd, J=14.5, 3.7, and 1.7 Hz), and 2.75 ppm (1H, ddd, J=14.5, 11.0, and 1.7 Hz).
7) a) F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, J. Org, Chem., 46, 164 (1981); b) R. T. Brown and C. L. Chapple, Chem. Commun., 1973, 886; c) G. Massiot and T. Mulamba, Chem. Commun., 1983, 1147.
8) T. Kametani, N. Takagi, N. Kanaya, and T. Honda, Heterocycles, 19, 535 (1982).
9) Esterification of L-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[9a] with $SOCl_2$-MeOH gave authentic L-3a. Yamada et al. similarly prepared the optically active Et-ester[9b]: a) A. Brossi, A. Focella, and S. Teitel, J. Med. Chem., 16, 418 (1973); b) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, Chem. Pharm. Bull., 22, 2614 (1974).
10) Optically active 1-phenyl derivatives (D,L-2b and 3b) are unknown in literature.
11) CH_3I in acetone at room temperature (entry 9) gave a better result (see Lit. 1).

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