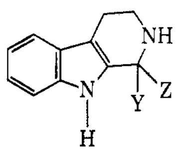
1,2,3,4-tetrahydro-β-carbolines, respectively, is a well-documented reaction.[1] 6-Hydroxy- and alkoxytryptamine derivatives also react quite readily with acetone in aqueous solution, affording the expected 1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline derivatives.[2] Tryptamine and 5-methoxytryptamine, on the other hand, do not react with simple ketones to any appreciable extent under the same conditions, and the corresponding carbolines have been prepared by cyclization of the Schiff bases using dilute sulfuric acid[3] or phosphorus oxychloride[2] as catalysts. A previous report of the cyclodehydration of tryptamine and acetone under rather unusual circumstances lacks adequate proof of the structure of the product.[4]

Using acetone as solvent, and with ethyl polyphosphate[5] as catalyst, we were able to prepare 1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (I) in one step in 66% yield. The melting point of our product (140–141°) is practically the same as that reported by Vanderwerff,[3] and quite different from that of Hester's compound (111.5–115.5°).[2] The uv spectra, however, are similar, and our structural assignment is supported by ir and nmr spectral evidence. Also, the $N(2)$-benzoyl derivative, judging from its melting point, is the same as that described by Manske over 40 years ago.[4]



I, Y = Z = Me
II, Y, Z = $(CH_2)_4$
III, Y, Z = $(CH_2)_5$

1-Spirocyclopentano- (II) and 1-spirocyclohexano-1,2,3,4-tetrahydro-β-carboline (III) were obtained similarly by cyclodehydration of tryptamine and cyclopentanone or cyclohexanone, respectively. The low solubilities of the hydrochlorides in dilute acid made their isolation and purification as such particularly easy. The uv spectra of all three compounds show that the indole chromophore is intact. The absence of ir absorption around 1665 cm^{-1} excludes the possibility of their being Schiff bases, and the absence of C(2)-H signals in the aromatic region of the nmr spectra shows that cyclization did indeed take place.

Experimental Section

Ir spectra were recorded with Perkin-Elmer 337 and 621 spectrophotometers, uv spectra with a Zeiss DMR-21, and nmr spectra with a Varian A-60 spectrometer using TMS as internal reference. Elementary analyses were performed by F. and E. Pascher, Bonn. Tlc was carried out on Merck silica gel chromatofoils, using cyclohexane–$CHCl_3$–Et_2NH (5:4:1). Melting points were determined in open capillaries, and are uncorrected.

1,1-Dimethyl-1,2,3,4-tetrahydro-β-carboline (I).—A solution of tryptamine (0.66 g) and ethyl polyphosphate (3.0 g) in acetone (80 ml) was refluxed during 36 hr. The solvent was then removed under vacuum, and the residue was diluted with water and neutralized with 4 N NaOH to yield a precipitate (0.54 g) which, recrystallized from cyclohexane, melted at 140–141°. The R_f values of tryptamine and of the product were 0.11 and 0.24, respectively: λ_{max}^{EtOH} (log ϵ) 225 (4.55), 274 (3.78), 279 (3.80), 289 nm (3.71); $\bar{\nu}_{max}^{KBr}$ 1145 (C–N), 1450 cm^{-1}(*gem*-dimethyl); δ^{CDCl_3} 1.46 (s, 6 H, *gem*-dimethyl), 2.15 (s, 1 H, 2-H), 2.71 and 3.21 (2 t, J = 5.8 Hz, 4 H, CH_2CH_2), 7.0–7.5 (m, 4 H, 5-, 6-, 7-, and 8-H), 8.0 (br s, 1 H, 9-H); the signals at δ 2.15 and 8.0 disappear upon exchange with D_2O. *Anal.* Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.80; H, 8.25; N, 13.70.

Benzoylation of I yielded a compound which after recrystallization from acetone melted at 280–282°: λ_{max}^{EtOH} (log ϵ) 225 (4.60), 273 (3.72), 279 (3.69), 289 nm (3.61); $\bar{\nu}_{max}^{KBr}$ 1630 cm^{-1} ($PhCONR_2$). *Anal.* Calcd for $C_{20}H_{20}N_2O \cdot {}^1/_4H_2O$: C, 77.74; H, 6.70; N, 9.07. Found: C, 77.64; H, 6.61; N, 9.13.

I, heated with an excess of methyl iodide in acetone, afforded the methiodide, which decomposed without melting at 200°: λ_{max}^{EtOH} (log ϵ) 225 (4.81), 272 (3.88), 278 (3.84), 288 nm (3.76). *Anal.* Calcd for $C_{15}H_{21}N_2I$: C, 50.57; H, 5.94; N, 7.86; I, 53.62. Found: C, 50.77; H, 5.89; N, 7.77; I, 35.71.

1-Spirocyclopentano-1,2,3,4-tetrahydro-β-carboline (II) **Hydrochloride.**—A solution of tryptamine (0.70 g) in cyclopentanone (9.0 ml), to which ethyl polyphosphate (0.45 ml) was added, was kept at 100° during 12 hr. The reaction mixture was diluted with H_2O (40 ml) and acidified with concentrated HCl (4 ml), whereupon a crystalline precipitate (0.60 g) appeared which, recrystallized from H_2O, melted at 263–264°: λ_{max}^{EtOH} (log ϵ) 222 (4.68), 272 (3.94), 279 (3.92), 289 nm (3.76). *Anal.* Calcd for $C_{15}H_{19}N_2Cl$: C, 68.55; H, 7.30; N, 10.66; Cl, 13.49. Found: C, 68.59; H, 7.33; N, 10.78; Cl, 13.54.

The free base, recrystallized from cyclohexane, melted at 139–140°; δ^{CDCl_3} 1.43 (s, 1 H, 2-H), 1.88 (s, 8 H, 4 CH_2), 2.71 and 3.17 (2 t, J = 5.5 Hz, 4 H, CH_2CH_2), 7.0–7.6 (m, 4 H, 5-, 6-, 7-, and 8-H), 7.73 (br s, 1 H, 9-H); the signals at δ 1.43 and 7.73 disappear upon exchange with D_2O.

1-Spirocyclohexano-1,2,3,4-tetrahydro-β-carboline (III) **Hydrochloride.**—A solution of tryptamine (0.70 g) in cyclohexanone (9.0 ml), to which ethyl polyphosphate (0.45 ml) was added, was kept at 100° during 12 hr. The reaction mixture was diluted with H_2O (40 ml) and acidified with concentrated HCl (4 ml), whereupon the product (0.62 g) crystallized: recrystallized from H_2O, mp 279–280°; λ_{max}^{EtOH} (log ϵ) 222 (4.62), 272 (3.92), 279 (3.91), 289 nm (3.79). *Anal.* Calcd for $C_{16}H_{21}N_2Cl \cdot {}^1/_2H_2O$: C, 67.21; H, 7.74; N, 9.78; Cl, 12.40. Found: C, 66.83; H, 7.91; N, 9.89; Cl, 12.56.

The free base, recrystallized from cyclohexane, melted at 133.5–135°: δ^{CDCl_3} 1.64 (s, 11 H, 5 CH_2 and 2-H), 2.65 and 3.09 (2 t, J = 5.5 Hz, 4 H, CH_2CH_2), 6.95–7.55 (m, 4 H, 5-, 6-, 7-, and 8-H), 7.69 (br s, 1 H, 9-H); upon exchange with D_2O, the signal at δ 1.64 decreased to 10 H, and the signal at δ 7.69 disappeared.

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Registry No.—I, 6678-85-9; I benzoyl derivative, 42282-64-4; I MeI, 42282-65-5; II, 42282-67-7; II HCl, 42282-68-8; III, 6716-66-1; III HCl, 6716-70-7; tryptamine, 61-54-1; acetone, 67-64-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1.

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Stereochemistry of Reduction of Substituted Cyclohexanones with Lithium Triisobutyl-*n*-butylaluminate[1]

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We have recently reported the results of an investigation concerned in part with evaluation of triisobutyl-

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aluminum (TIBA) as a stereoselective agent for the reduction of ketones.[2] We found that the stereochemical outcome of the reduction reaction was nominally dependent on reactant ratio, and more specifically was influenced by the ability of the aluminum alkyl to act as a Lewis acid in forming associated species and/or complexes with unreacted ketone or with reduction products. The present work is concerned with a similar evaluation of the "ate complex," lithium triisobutyl-*n*-butylaluminate (LTA). It was hoped that incorporation of tetravalent aluminum in the reducing agent would circumvent the complications arising from the complexing nature of the trivalent aluminum compound, triisobutylaluminum. Additionally, the greater steric requirement of the tetravalent "ate complex" as well as its possibly different mechanistic pathway of reduction was considered an exciting possibility for effecting stereoselective reductions. The mechanism of reaction between ketones and tetraalkylaluminum species has not been discussed in the literature.

Lithium triisobutyl-*n*-butylaluminate was prepared by mixing solutions containing equimolar quantities of triisobutylaluminum and *n*-butyllithium. The reagent was either used directly or isolated by precipitation with hexane. The results obtained for reduction of 3,3,5-trimethylcyclohexanone (1) and 4-*tert*-butylcyclohexanone (2) are presented in Table I.

Table I

Run	Ketone	Solvent	Ketone/ LTA	% alcohols[b]	% axial alcohol
1	1	Benzene	1.0	95	97
2	1	Benzene	0.5	94	97
3	1	Benzene	2.0	83	96
4[a]	1	Benzene	1.0	89	98
5	2	Ether	1.0	100	47
6	2	Ether	0.5	73	46
7	2	Ether	2.0	86	49
8	2	Benzene	1.0	102	47
9	2	Benzene	0.5	104	47
10	2	Benzene	2.0	86	44

[a] LTA added to solution of ketone. [b] Based on millimoles of ketone converted.

Reduction was accompanied by a small amount (*ca.* 0–3%) of alkylation. Because of the minute quantities of alkylated products, no attempt was made to determine their nature or stereoisomeric composition. Clearly, the stereochemistry of reduction is independent of the nature of the solvent and of the order in which reagents are added. Quantitative conversion to alcohols was observed in several cases, indicating that formation of an aluminum enolate does not occur. In this respect, the present method is superior to reduction with TIBA, which is accompanied by 2–12% enolization.

The stereochemistry of ketone reduction with TIBA is dependent on the ratio of reactants. For example, reduction of 3,3,5-trimethylcyclohexanone with TIBA affords 63% of the axial alcohol when the TIBA to ketone ratio is 0.5, but 93% axial alcohol when the ratio is 5.0. Similarly, reduction of 4-*tert*-butylcyclohexanone with TIBA affords 14–44% axial alcohol when the ratio of TIBA to ketone is varied from 0.5 to 5.0. Reduction with lithium triisobutyl-*n*-butylaluminate is more selective, leading to isolation of 97% of the least stable (axial) alcohol in the former case and 47% in the latter. Furthermore, the isomeric composition of the product mixture is not dependent on reactant ratio, so that maximal selectivity can be attained by employing a stoichiometric quantity of reducing agent rather than (at least) a fivefold excess as in the case of TIBA. The economic consequences of this observation are obvious. Moreover, it seems that LTA might be advantageously employed in obtaining maximal selectivity in reduction of substrates with several reducible sites where use of excess reducing agent is precluded.

Experimental Section

Reagent grade ether and benzene were refluxed for 24 hr over $LiAlH_4$ and $NaAlH_4$, respectively, distilled through a 3-ft Vigreux column, and stored over sodium–lead alloy (dri-Na, J. T. Baker Chemical Co.) in a nitrogen atmosphere. Triisobutylaluminum (Ethyl Corp.) was assayed by EDTA titration and found to be satisfactory as received. Analysis of the gases evolved upon hydrolysis indicated the presence of 2.7% active hydride in the triisobutylaluminum. *n*-Butyllithium (Foote Mineral Co.) was used as received. 3,3,5-Trimethylcyclohexanone (Chemical Samples Co.) was distilled through a 2-ft glass helix packed column and the middle fraction was employed in this study. 4-*tert*-Butylcyclohexanone (Frinton Laboratories) was sublimed (10 mm) before use. Manipulation of air-sensitive compounds were performed either in a Kewaunee inert atmosphere box equipped with recirculating system[3,4] or by employing special bench top techniques.[4] Lithium was assayed with a Coleman Instruments Co. Model 21 flame photometer and aluminum by titration with EDTA. Products were analyzed by gas–liquid partition chromatography utilizing a 20-ft column packed with 5% 20M Carbowax on Chromosorb G and a Hewlett-Packard Model 700 chromatograph. Ethyl benzoate was employed as an internal standard in reductions of 3,3,5-trimethylcyclohexanone and analyses conducted at 135°. 3,3,5-Trimethylcyclohexanone was employed as an internal standard in reduction of 4-*tert*-butylcyclohexanone and analyses performed at 150°.

Lithium Triisobutyl-*n*-butylaluminate.—*n*-Butyllithium (23.6 mmol, 14.7 ml of 1.6 *M* solution in hexane) was added to a flame-dried 100-ml flask containing 30 ml of hexane. With vigorous stirring triisobutylaluminum (23.6 mmol, 21.25 ml of 1.11 *M* solution in benzene) was added affording a copious precipitate. After filtration the solid was washed with three 20-ml portions of hexane and dried (0.07 mm, 12 hr), affording white product (16.8 mmol, 71%). Analyses gave a lithium to aluminum ratio of 1.03.

General Procedure for Reduction.—A 50-ml erlenmeyer flask containing a magnetic stirring bar was flamed and allowed to cool in the entry port of an inert atmosphere box. After transfer into the box, the flask was sealed with a rubber septum, secured with an elastic band, and then connected by means of a needle to a nitrogen-filled manifold. A solution of lithium triisobutyl-*n*-butylaluminate (*ca.* 0.3 *M*) was introduced followed by sufficient solvent to bring the final volume to 10.0 ml. Stirring was initiated and the flask was immersed in a 22° water bath and allowed to come to temperature. A solution (*ca.* 1.0 *M*) of the appropriate ketone was added and allowed to react for 2.0 hr, and the reaction was quenched with 5% HCl. Internal standard was added, and the product mixture was analyzed by glc.

Registry No.—1, 873-94-9; 2, 98-53-3; LTA, 14239-17-9; TIBA, 100-99-2.

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