REDUCTION OF OXINDOLES WITH SODIUM BIS(2-METHOXYETHOXY)ALUMINUM HYDRIDE, A NOVEL REDUCING AGENT[1)]

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Abstract- 1,3-Dimethyl-3-(2'-dimethylaminoethyl)-5-tetrahydropyranyloxy-oxindole (**5**), obtained on C3-alkylation of oxindole (**4**), was reduced stereoselectively with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) to carbinolamine (**6**). Oxindoles (**7**, **8**, **9**, **10** and **11**) similarly were reduced and cyclized to (±)-*N*[1]-noresermethole (**13**), (±)-*O*-tetrahydropyranyl-*N*[1]-noreseroline (**14**), (±)-physovenol methyl ether (**15**), (±)-esermethole (**16**), and (±)-*N*[1]-benzylnoresermethole (**17**), respectively.

Physostigmine, a major alkaloid from *Calabar* beans,[1] and its carbamate analogues, are being evaluated in Alzheimer's diseases and their total synthesis, therefore, receives attention. Improvements in the synthesis of physostigmine from oxindoles prepared by the Julian route [2-4] were recently reported. In these syntheses, the oxindoles were reduced with lithium aluminum hydride (LAH) which is sensitive toward air and is hazardous in large scale preparation because highly flammable, peroxide-forming ethers are required. In our total synthesis of compounds related to *Calabar* alkaloids from 1, 3-dimethyl-5-methoxy-2-hydroxyindoline (**3**),[5] we reduced the oxindole (**2**) stereoselectively to carbinolamine (**3**) with sodium bis(2-methoxyethoxy)aluminum hydride in toluene, known commerically as Vitride. Vitride is chemically equivalent to LAH but more selective than LAH and is stable to oxygen, highly soluable in a variety of solvents and easy to work up. It is a mild and safe novel reducing agent, especially for large scale reduction. Here we report several other applications of Vitride in the reduction of oxindoles.

Oxindole (**5**), obtained from tetrahydropyranyl ether oxindole (**4**) [6] on alkylation with 2-dimethylaminolethyl chloride hydrochloride, was reduced stereoselectively with Vitride to give carbinolamine (**6**). The *cis*-arrangement of 2-OH and 3-(2'-dimethylaminoethyl) in **6** was determined by comparsion of its ^{1}H-nmr spectrum with that of **3** whose configuration was confirmed by X-ray analysis. [5] Nitriles (**7**) and (**8**) [6], when treated with Vitride, cyclized to (±)-*N*[1]-noresermethole (**13**) and

1) This paper is dedicated to Dr. Arnold Brossi, at the occasion of his 70th birthday.

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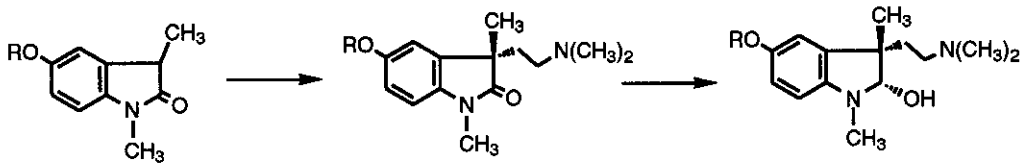
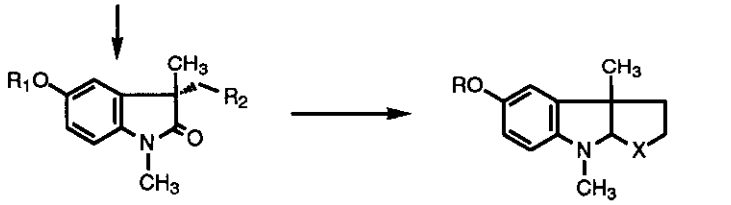
(±)-*O*-tetrahydropypranyl-*N*^{1}-noreseroline (**14**) respectively. Ester (**9**) [7] was similarly reduced to give (±)-physovenol methyl ether (**15**). Other examples are amides (**10**) and (**11**), which were made from acid (**12**) with methyl isocyanate and benzyl isocyanate as reported [4] and prepared here by treating ester (**9**) with methylamine and benzylamine. They were reduced with Vitride to (±)-esermethole (**16**) and (±)-*N*^{1}-benzylnoresermethole (**17**), respectively.



1: R=CH_3
4: R=tetrahydropyranyl

2: R=CH_3
5: R=tetrahydropyranyl

3: R=CH_3
6: R=tetrahydropyranyl



7: R_1=CH_3; R_2=CN
8: R_1=tetrahydropyranyl; R_2=CN
9: R_1=CH_3; R_2=$COOCH_3$
10: R_1=CH_3; R_2=$CONHCH_3$
11: R_1=CH_3; R_2=$CONHCH_2Ph$
12: R_1=CH_3; R_2=COOH

13: R=CH_3; X=NH
14: R=tetrahydropyranyl; X=NH
15: R=CH_3; X=O
16: R=CH_3; X=NCH_3
17: R=CH_3; X=NCH_2Ph

Compounds (**13-17**) are important intermediates in the synthesis of *Calabar* alkaloids and their congeners. The simple and efficient reduction of oxindoles with Vitride makes oxindole route attractive to prepare these compounds on large scale.

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EXPERIMENTAL

Melting points (uncorrected): Fisher-Johns apparatus; ir spectra (cm^{-1}): MIDIC FTIR instrument; ^{1}H-nmr (in $CDCl_3$ with Me_4Si as internal reference, δ ppm, J Hz): Varian XL-300 MHz spectrometer; ms (m/z) for electron impact (EI-ms): V.G. Micromass 7070 mass spectrometer; thin layer chromatography (silica gel GHLF, 250 μm): Analtech Inc.; Column chromatography (silica gel GHLF, 250 μm): Merck 60 (230-400 mesh).

*(±)-1,3-Dimethyl-3-(2'-dimethylaminoethyl)-5-tetrahydropyranyloxyoxindole (**5**)*

The oxindole (**4**) (261 mg, 1 mmol) was dissolved in 10 ml of toluene and 195 mg (4 mmol) of sodium amide was added. The mixture was stirred at room temperature under N_2 for 1 min, then 2-dimethylaminoethyl chloride hydrochloride (289 mg, 2 mmol) was added. The mixture was refluxed under N_2 with stirring for 2 h. After cooled to room temperature, 10 ml of H_2O was added, the toluene layer was separated out and the water layer was extracted with ether (2X10 ml). The combined organic layers were washed with brine (15 ml), dried over Na_2SO_4, evaporated in vacuo to give 248 mg of brown syrup. The syrup was chromatographed (CH_2Cl_2 : MeOH = 20 : 1) to give 165 mg (0.50 mmol, 50 %) of a light yellow oil.

5: Ir (film): 1711, 1601, 1495 cm^{-1}; ms (EI): 332 (M^+); ^{1}H-nmr: 7.00 (dd, 1H, J =2.5, 8.3, C6-H), 6.96 (d, 1H, J = 2.5, C4-H), 6.72 (d, 1H, J = 8.3, C7-H), 5.30 (m, 1H, C2'-H), 3.95 (m, 2H, C6'-H_2), 3.20 (s, 3H, N1-CH_3), 2.20 (s, 6H, N(CH_3)$_2$), 2.20-1.00 (m, 10 H, -(CH_2)-), 1.40 (s, 3H, C3-CH_3).

*(±)-1,3-Dimethyl-3-(2'-dimethylaminoethyl)-5-tetrahydropyranyloxy-2-hydroxyindoline (**6**)*

The oxindole (**5**) (155 mg, 0.49 mmol) was dissolved in 4 ml of toluene, and 0.14 ml (0.5 mmol) of Vitride was added. The mixture was stirred at room temperature under N_2 for 4 h, then quenched with 8 ml of 5 % NaOH solution. The toluene layer was separated out and the water layer was extracted with ether (2X10 ml). The combined organic layers were washed with brine (15 ml), dried over Na_2SO_4, evaporated in vacuo to give 135 mg (0.4 mmol, 82.4 %) of a light yellow oil.

6: Ir (film): 3399, 1595, 1267 cm^{-1}; ms (EI): 334 (M^+); ^{1}H-nmr: 6.87 (dd, 1H, J = 2.5, 8.2, C6-H); 6.69, (d, 1H, J = 2.5, C4-H), 6.36 (d, 1H, J = 8.3, C7-H), 5.12 (m, 1H, C2'-H), 4.42 (s, 1H, C2-H), 4.00 (m, 2H, C6'-H_2), 3.60(br s, 1H, OH), 2.72 (s, 3H, N1-CH_3), 2.20 (s, 6H, N(CH_3)$_2$), 2.50-1.30 (m, 10H, -(CH_2)-), 1.31 (s, 3H, C3-CH_3).

*(±)-1,3-Dimethyl-5-methoxyoxindole-3-acetic acid methylamide (**10**)*

The ester (**9**) (132 mg, 0.5 mmol) was heated with 2 ml of 40 % methylamine aqueous solution in a sealed tube (oil bath 100 °C) for 24 h. After cooled to room temperature, 20 ml of 2N HCl was added and the mixture was extracted with ether (3X20 ml). The extracts were washed with brine (30 ml), dried over Na_2SO_4, evaporated in vacuo. The residue was chromatographed to give 110 mg (0.42 mmol, 84 %) of an oil. Its spectra were identical with those of the (-)-isomer.[4]

*(±)-1,3-Dimethyl-5-methoxyoxindole-3-acetic acid benzylamide (**11**)*

The ester (**9**) (132 mg, 0.5 mmol) was dissolved in 1 ml of MeOH and 2 ml of benzylamine was added. The mixture was refluxed under N_2 for 24 h. After cooled to room temperature, 20 ml of 2N HCl was added and the mixture was extracted with ether (3X20 ml). The combined ether extracts were washed with brine (30 ml), dried over Na_2SO_4, evaporated in vacuo. The residue was chromatographed to give 150 mg (0.44 mmol, 89 %) of a colorless oil. Its spectra were identical with those of the (-)-isomer.[4]

*(±)-N^1-Noresermethole (**13**)*

The oxindole (**7**) (160 mg, 0.69 mmol) was dissolved in 5 ml of toluene and 0.4 ml (1.4 mmol) of Vitride was added. The mixture was stirred at room temperature under N_2 for 3 h, then quenched with 8 ml of 5 % NaOH. The toluene layer was separated out and the aqueous layer was extracted

with ether (2X10 ml). The combined organic layers were dried over Na_2SO_4, concentrated to about 5 ml, then a saturated ethanolic fumaric acid (94 mg, 0.81 mmol) was added to give 138 mg (0.41 mmol, 59 %) of white fumarate, mp 198-199 °C. ((-)-isomer [8]: mp 199-200 °C). The spectra are identical with those of the (-)-isomer.[8]

*(±)-O-Tetrahydropyranyl-N^1-noreseroline (**14**):*

Prepared in the same way as **13**, yield 92.5 %. Its spectra were identical with those of a standard sample. [6]

*(±)-Physovenol methyl ether (**15**)*

Prepared in the same way as **13**, yield 62 %. Its spectra were identical with those of its (-)-isomer.[9]

*(±)-Esermethole (**16**)*

Prepared in the same way as **13**, yield 56 %. Its spectra were identical with those of its (-)-isomer.[5]

*(±)-N^1-Benzylnoresermethole (**17**)*

Prepared in the same way as **13**, yield 56 %. Its spectra were identical with those of its (-)-isomer.[8]

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