

Studies on the Syntheses of Heterocyclic Compounds. Part DVII (I).
A Synthesis of (\pm)-*N*-Norgalanthamine

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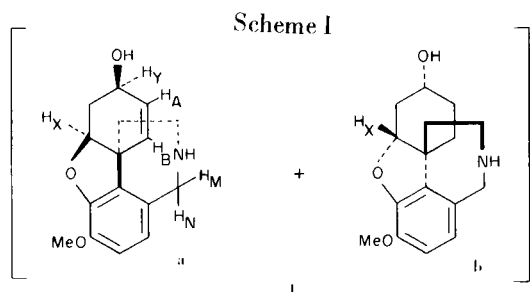
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(\pm)-*N*-Norgalanthamine (Ia) and (\pm)-*N*-norlycoramine (Ib) was synthesized through the phenolic oxidation of *N*-(4-hydroxyphenethyl)-2-bromo-5-hydroxy-4-methoxybenzamide (IIb).

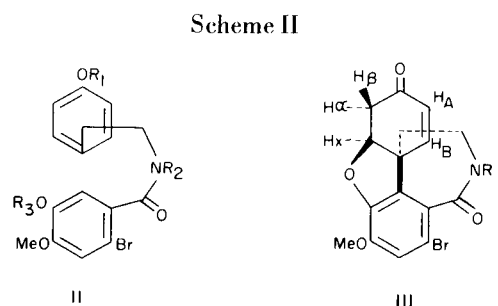
Narcissamine (I), one of the *Amaryllidaceae* alkaloids, was isolated by Boit and his co-workers (3a) and Fales and his associates (3b) from several of the garden varieties of daffodils, but the structure of the alkaloids was not elucidated at that time. Laiho and Fales (4) published the structure of narcissamine to be a *quasi*-racemic alkaloid consisting of an equimolar amount of (-)-demethylgalanthamine (Ia) and (+)-demethyldihydrogalanthamine (Ib) by means of the high resolution techniques of gas and thin layer chromatographies.

4-methoxybenzamide (IIb), which was obtained by the Schotten-Baumann reaction of 4-benzyloxyphenethylamine (5) and 5-benzyloxy-2-bromo-4-methoxybenzoyl chloride (5), followed by debenylation with hydrochloric acid in ethanol. The enone type compound IIIb was obtained successfully and the reaction of IIIb with lithium aluminum hydride in tetrahydrofuran gave the (\pm)-enol Ia after chromatographical separation, but the epimer Vb could not be isolated by activated alumina chromatography. The nmr spectrum of the compound Ia



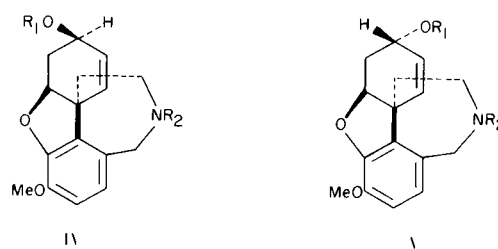
We have synthesized (\pm)-*N*-norgalanthamine [(\pm)-demethylgalanthamine] (Ia), which was converted into (\pm)-*N*-norlycoramine [(\pm)-demethyldihydrogalanthamine] (Ib) by catalytic hydrogenation. Since both compounds were synthesized as two components of I in order to examine the structure of narcissamine, we now wish to report these results.

Previously, one of the present authors (5) reported a total synthesis of (\pm)-galanthamine (IVa) and (\pm)-epigalanthamine (Va) in good yield from *N*-(4-hydroxyphenethyl)-*N*-methyl-2-bromo-5-hydroxy-4-methoxybenzamide (IIa) *via* the enone type compound IIIa by phenolic oxidation. This method was applied to a synthesis of the title compound; thus, we have examined the phenolic oxidation of *N*-(4-hydroxyphenethyl)-2-bromo-5-hydroxy-



a: R₁ R₃ H, R₂ Me
b: R₁ R₂ R₃ H

a: R Me
b: R H



a: R₁ H, R₂ Me
b: R₁ R₂ COCH₃

a: R₁ H, R₂ Me
b: R₁ R₂ H

showed the signals for olefinic protons at δ 5.95 and 6.07 as distorted AB type doublets ($J = 10.0$ Hz) [cf. (\pm)-galanthamine, δ 5.95 and 6.01 (distorted AB type doublets); (\pm)-epigalanthamine, δ 5.77 and 6.05 (a typical pair of doublets)], and the ir spectrum showed an alcoholic hydroxyl absorption at 3575 cm^{-1} [cf. (\pm)-galanthamine, 3575 cm^{-1}], a secondary amine at 3400 cm^{-1} , and an olefinic system at 1620 cm^{-1} . Treatment of the compound Ia with acetic anhydride in pyridine gave the *O,N*-diacetate IVb, the ir spectrum of which showed two carbonyl absorptions at 1718 (OAc) and 1645 cm^{-1} (NAc). The identification was supported by the conversion of the enol (Ia) into (\pm)-galanthamine through Eschweiler-Clarke reaction with formaldehyde in the presence of formic acid.

Finally, the compound Ib [(\pm)-*N*-norlycoramine] was obtained by catalytic hydrogenation of Ia on 5% palladium-carbon. In the ir and nmr spectra of Ib, an olefinic signal was not recognized. Spectral comparison of a mixture of the above samples with the natural product could not be carried out because of no available narcissamine.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were run by a Hitachi 215 infrared spectrophotometer. Nmr spectra were recorded on a Hitachi H-60 spectrometer using TMS as internal standard. Mass spectra were taken by a Hitachi RMU-7 mass spectrometer.

N-(4-Hydroxyphenethyl)-2-bromo-5-hydroxy-4-methoxybenzamide (IIb).

To a stirred suspension of 12.5 g. of 4-benzyloxyphenethylamine in 200 ml. of chloroform and 120 ml. of 3% sodium hydroxide solution was added dropwise a solution of the acid chloride [prepared from 18.2 g. of 5-benzyloxy-2-bromo-4-methoxybenzoic acid and 9.6 g. of thionyl chloride] in 100 ml. of chloroform. Stirring was continued for 0.5 hour at room temperature. After the reaction, the organic layer was separated, washed with water, 10% hydrochloric acid, and water, and dried over sodium sulfate. To the amide obtained by evaporation was added 300 ml. of ethanol and 200 ml. of concentrated hydrochloric acid, and the mixture was refluxed for 7.5 hours. Evaporation left a solid which was washed with saturated sodium bicarbonate and water. Recrystallization from ethanol gave 14.2 g. (72% yield) of IIb as colorless needles, m.p. 178° ; ν max (potassium bromide) cm^{-1} : 3420 (OH), 3300 (NH), 1653 (C=O).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{BrNO}_4$: C, 52.45; H, 4.40; N, 3.83. Found: C, 52.53; H, 4.28; N, 3.92.

Phenolic Oxidation of the Amide (IIb).

To a stirred solution of 27 g. of potassium ferricyanide, 68 g. of sodium bicarbonate, and 300 ml. of water was added a suspension of 5 g. of IIb in 600 ml. of chloroform and the stirring was continued for 1.5 hours at 50° . The chloroform layer was separated, washed with water, dried over sodium sulfate and evaporated to give 260 mg. of a brown gum, which was chromatographed on 20 g. of silica gel. Elution with chloroform-methanol (98:2) gave 38 mg. (0.7% yield) of IIIb as colorless prisms, m.p.

$167\text{-}168.5^\circ$ (benzene); ν max (chloroform) cm^{-1} : 3420 (NH), 1685-1640 (C=O), 1620-1610 (C=O and C=C); nmr (deuteriochloroform) δ : 3.89 (s, 3H, OCH_3), 2.73 (q, 1H, $J = 18.0$ and 3.5 Hz, H_β), 3.15 (q, 1H, $J = 18.0$ and 3.0 Hz, H_α), 4.84 (m, 1H, H_χ), 5.89 (d, 1H, $J = 10.0$ Hz, H_A), 6.53 (q, 1H, $J = 10.0$ and 2.0 Hz, H_B), and 7.10 ppm (s, 1H, aromatic proton).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{BrNO}_4$: C, 52.77; H, 3.87; N, 3.84. Found: C, 52.98; H, 4.02; N, 3.63.

(\pm)-*N*-Norgalanthamine (Ia).

To a stirred suspension of 550 mg. of lithium aluminum hydride in 40 ml. of tetrahydrofuran was added dropwise a solution of 240 mg. of the above enone IIIb in 30 ml. of tetrahydrofuran within 30 minutes at room temperature, and the mixture was refluxed on a water-bath for 10 hours with stirring. Ethyl acetate and water were added to decompose the excess of reagent, and the supernatant solvent was decanted. The remaining paste was extracted with chloroform, and the extract and supernatant solvent were combined. Evaporation of organic layer gave 135 mg. of a pale yellow syrup, which was chromatographed on activated alumina. Elution with chloroform gave 65 mg. (36.1% yield) of Ia as colorless needles, m.p. $149\text{-}152^\circ$ (from ether); ν max (chloroform) cm^{-1} : 3575 (OH), 3400 (NH), 1620 (C=C); nmr (deuteriochloroform) δ : 3.81 (s, 3H, OCH_3), 3.72 (d, 1H, $J = 15.5$ Hz, H_M or H_N), 4.10 (d, 1H, $J = 15.5$ Hz, H_M or H_N), 4.12 (m, 1H, H_Y), 4.59 (m, 1H, H_X), 5.95 (distorted d, 1H, $J = 10.5$ Hz, H_A), 6.07 (distorted d, 1H, $J = 10.5$ Hz, H_B), and 6.64 ppm (s, 2H, aromatic protons).

Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_3 \cdot 2\text{H}_2\text{O}$: N, 4.53. Found: N, 4.53.

O,N-Diacetate (IVb).

A mixture of 1.2 ml. of acetic anhydride, 0.4 ml. of pyridine and 9 mg. of Ia was heated at $85\text{-}90^\circ$ for 3 hours with stirring. To this mixture was added 25 ml. of chloroform, and the extract was washed with 5% sodium bicarbonate and water, dried over sodium sulfate, and evaporated to give 14 mg. of a yellow oil, which was chromatographed on 1.0 g. of silica gel. Elution with chloroform gave 8 mg. (67.8% yield) of IVb as a colorless oil; ν max (chloroform) cm^{-1} : 1718 (OCOCH_3), 1645 (NCOCH_3); nmr (deuteriochloroform) δ : 2.01 (s, 3H, NCOCH_3), 2.06 (s, 3H, OCOCH_3), 3.81 (s, 3H, OCH_3), and 6.62 ppm (s, 2H, aromatic protons); m/e 357 (M^+).

(\pm)-Galanthamine from Ia.

A mixture of 0.7 ml. of 37% formalin, 0.7 ml. of 85% formic acid, and 16 mg. of Ia was heated on a water-bath for 3.5 hours, basified with 5% sodium bicarbonate, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 12 mg. (70% yield) of (\pm)-galanthamine. Recrystallization from ether gave colorless needles, m.p. 121° , the physical and spectral data of which were in good accord with the authentic sample previously synthesized.

Catalytic Hydrogenation of Ia.

A mixture of 12 mg. of Ia, 6 mg. of 5% palladium-charcoal, and 20 ml. of ethanol was vigorously shaken in a current of hydrogen for 2 hours. Filtration of the catalyst and evaporation of the solvent gave 10.5 mg. of Ib as a pale yellow oil, which was crystallized with chloroform to give crystals, m.p. $122\text{-}128^\circ$, ν max (chloroform) cm^{-1} : 3550 (OH), 3350 (NH); nmr (deuteriochloroform) δ : 3.88 (s, 3H, OCH_3), 4.26 (s, 1H, H_X), 6.70 ppm (s, 2H, aromatic protons).

Anal. Calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_3 \cdot 0.5\text{ H}_2\text{O}$: C, 67.61; H, 7.75.

Found: C, 67.22; H, 7.47.

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