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Synthesis of Sempervirine, a Pentacyclic Anhydronium Indole Alkaloid

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Summary. Sempervirine (2,3,4,13-tetrahydro-1*H*-benz[*g*]indolo[2,3-*a*]quinolizin-6-ium, **1**) the pentacyclic anhydronium indole alkaloid of *Gelsemium sempervirens* Ait. f. (*Loganiaceae*), has been synthesized in three steps from hexahydroisochroman-3-one (**6**) and N-2-(3-indolyl)-ethylamine (tryptamine, **7**). The condensation product, N-2-(3-indolyl)-ethyl-2-(hydroxymethyl)-*trans*-hexahydrophenylacetamide (**8**) arising from **6** and **7** on double cyclization with phosphoryl chloride yielded the 3,4-dehydroyohimbane derivative **9**. Aromatization of rings C and D of compound **9** with 2,3-dichloro-5,6-dicyanobenzoquinone (*DDQ*) in glacial acetic acid, followed by basification, generated sempervirine (**1**).

Keywords. Sempervirine synthesis; Cyclization; *DDQ*/AcOH; Drug for neuralgia, migraine, and cancer.

Synthese von Sempervirin, einem pentacyclischen Anhydronium-Indolalkaloid

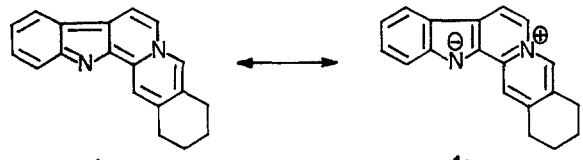
Zusammenfassung. Sempervirin (2,3,4,13-Tetrahydro-1*H*-benz[*g*]indolo[2,3-*a*]chinolizin-6-ium, **1**), das pentacyclische Anhydronium-Indolalkaloid von *Gelsemium sempervirens* Ait f. (*Loganiceae*) wurde ausgehend von Hexahydroisochroman-3-on (**6**) und N-2-(3-Indolyl)-ethylamin (Tryptamin, **7**) in 3 Stufen synthetisiert. Das durch doppelte Cyclisierung von **6** und **7** mit Phosphorylchlorid entstehende Kondensationsprodukt N-2-(3-Indolyl)-ethyl-2-(hydroxymethyl)-*trans*-hexahydrophenylacetamid (**8**) ergab das 3,4-Dehydroyohimbanderivat **9**. Aromatisierung der Ringe C und D von **9** mit 2,3-Dichlor-5,6-dicyanobenzochinon (*DDQ*) in Eisessig und anschließende Einstellung eines basischen *pH*-Werts lieferte Sempervirin (**1**).

Introduction

In continuation of our studies on new approaches to the synthesis of yohimbinoid alkaloids [1,2] we were interested in the synthesis of the physiologically active anhydronium indole alkaloids of the yohimbine series [3a, 3b].

A number of anhydronium indolic bases have been reported to occur in several plant species; *Catharanthus roseus* G. Don (*Apocynaceae*) [4], *Geissospermum velosii* Allem (*Apocynaceae*) [5–10], *Gelsemium sempervirens* Ait. f. (*Loganiaceae*) [11], *Pleiocarpa mutica* Benth. (*Apocyanaceae*) [12,13], *Rauwolfia serpentina* Benth. ex Kurz. (*Apocynaceae*) [14], and *Strychnos melinoniana* Baill. (*Loganiaceae*) [15].

A literature survey revealed that sempervirine **1**, occurring in *Gelsemium sempervirens* Ait. f. (*Loganiaceae*), is an useful drug in relieving severe pain due to neuralgia and migraine [3a]. It is also used in cancer treatment [3b]. In perspective of these therapeutic properties it was thought pertinent to undertake a detailed physiological and pharmacological investigation of sempervirine.



1 1a

Since the yield of sempervirine from natural sources is poor, it was relevant to develop an efficient method for its preparation. A few syntheses of this alkaloid had been published [16–18], but none of them proved to be satisfactory so far with respect to their yields. We have developed a new synthesis of sempervirine with better yield; the results are reported in the present paper.

Results and Discussion

From retrosynthesis, it could be envisaged that for the non-nitrogenous part of **1** hexahydroisochroman-3-one (**6**) would be an appropriate synthon. It was generated from [4.3.0]non-8-one (**5**) by *Baeyer-Villiger* oxidation following a procedure described in the literature [19,20].

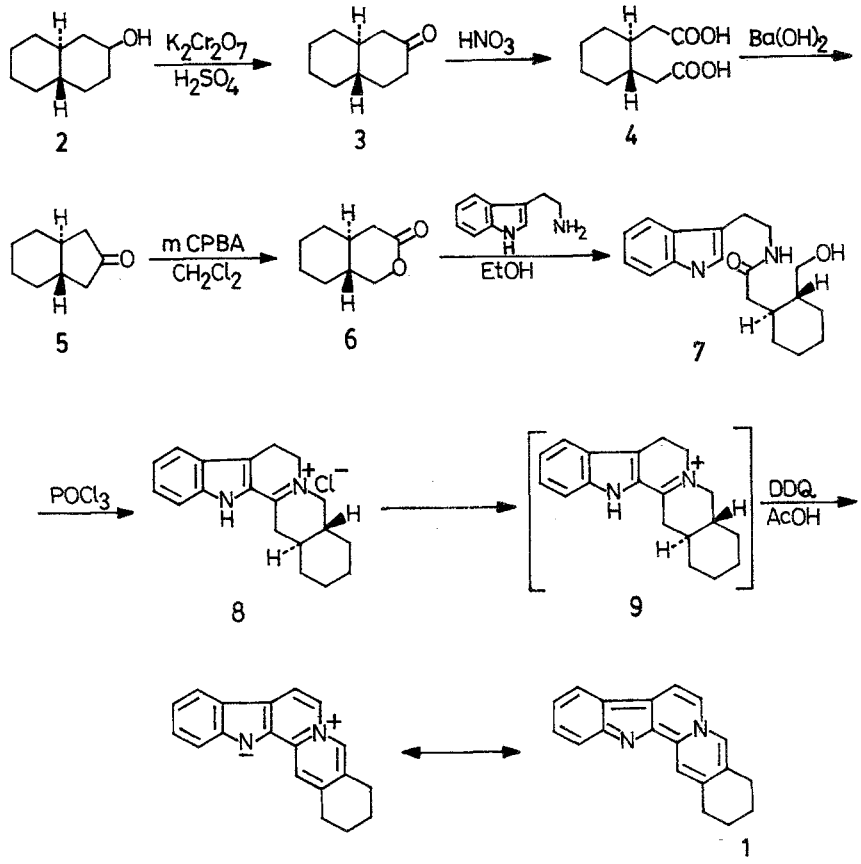
Upon condensation with tryptamine in refluxing ethanol, the lactone *trans*-hexahydroisochroman-3-one (**6**) afforded N-2-(3-indolyl)-ethyl-2-(hydroxymethyl)-hexa-hydrophenylacetamide (**8**). The latter-*via* double cyclization with freshly distilled phosphoryl chloride-yielded the 3,4-dehydro-yohinbinoid derivative **9**, which, on dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone in glacial acetic acid under an N_2 atmosphere followed by basification, afforded the anhydronium alkaloid sempervirine (**1**, Scheme 1). The identity of the anhydronium base was established by comparison with an authentic sample.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 and 75.5 MHz, respectively. The infrared spectra were measured with a Perkin Elmer 782 spectrophotometer. Mass spectra (70 eV) were taken with an AEIMS 3074 mass spectrograph.

N-2-(3-(Indolyl)-ethyl-2-(hydroxymethyl)-trans-hexahydro-phenylacetamide (**7**)

A mixture of tryptamine (1.2 g, 8.33 mmol) and *trans*-hexahydroisochroman-3-one (**6**, 1.2 g, 7.78 mmol) was refluxed in absolute ethanol (40 ml) for 24 h. Alcohol was removed at low temperature (40°C, rotavapor). The residue was dissolved in methylene chloride (5 ml) and chromatographed over silica gel. The fraction which migrated on elution with chloroform-methanol (95:5) afforded 1.96 g (85%) of N-2-(3-indolyl)-ethyl-2-(hydroxymethyl)-trans-hexahydrophenylacetamide (**7**). M.p.: 54°C; IR (KBr): $\nu = 3400, 1630\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 8.84$ (s, 1H), 7.58 (d, $J = 7.8$Hz, 1H), 7.26 (d, $J = 7.8$Hz, 1H), 7.06 (t, $J = 7.8$Hz, 1H), 6.18 (s, 1H), 3.74 (s, 1H), 3.42 (m, 4H), 3.26 (d, $J = 7.2$Hz, 2H), 2.82 (t, $J = 6.6$Hz, 2H), 0.8 – 2.12 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 173.7$ (s), 136.3 (s), 127.2 (s), 122.2 (d), 121.7 (d),



Scheme 1

119.0 (d), 118.3 (d), 112.3 (s), 111.3 (d), 65.3 (t), 44.9 (d), 39.8 (t), 39.7 (t), 35.7 (d), 33.1 (t), 29.7 (t), 26.0 (t), 25.8 (t), 25.0 (t) ppm; MS (70 ev): $m/z = 314$ [M^+]; $C_{19}H_{26}N_2O_2$ (314); calcd.: C 72.61, H 8.28, N 8.91; found: C 72.44, H 8.19, N 8.65.

Sempervirine (2,3,4,13-tetrahydro-1H-benz[g]indolo[2,3-a]-quinolizin-6-ium, **1**)

N-2-(3-indolyl)-ethyl-2-(hydroxymethyl)-*trans*-hexahydro-phenylacetamide (**7**, 1.8 g, 5.72 mmol) was refluxed with $POCl_3$ (10 ml) under N_2 for 3 h. The reaction product was cooled to room temperature under a current of N_2, and excess phosphoryl chloride was removed under vacuum. The residue was dissolved in water, basified with aqueous ammonia, and extracted with chloroform (3 × 50 ml). The organic layer was dried and concentrated in *vacuo* to yield a brown residue (1.1 g; 74%) which was dissolved in methylene chloride (5 ml), chromatographed over silica gel, and eluted with chloroform: ethylacetate (8:2). Upon removal of the solvent, the relevant fractions furnished 1.0 g of a semi-solid (67%). It was found to be homogeneous [M^+: 278] and showed a single spot on TLC (silica gel, Merck, developed with ethylacetate-methanol (8:2), $R_f = 0.78$). The substance, however, failed to crystallize from various solvents and solvent mixtures. It exhibited UV bands characteristic for 3,4-dehydroyohimbinoid derivatives (EtOH, $\lambda_{max} = 292, 235$ nm).

The semi-solid mass of the 3,4-dehydroyohimbinoid derivative **9** (0.8 g) was dissolved in glacial acetic acid (10 ml) to which *DDQ* (4.5 g, 20 mmol) was added. The reaction mixture was boiled under N_2 for 2 h and cooled. Acetic acid was removed at low pressure. The residual orange mass was dissolved in water (100 ml), basified with 20% sodium hydroxide solution, and extracted with chloroform

(3 × 200 ml). The chloroform extract was washed with brine (2 × 15 ml), dried, and the solvent was removed under reduced pressure. The resulting brown mass was chromatographed over neutral alumina ($CHCl_3$:MeOH = 95:5). Upon elution and evaporation, sempervirine **1** was obtained as an orange red powder.

0.62 g (66%); m.p.: 258–60°C; IR (KBr): $\nu = 3400$, 1615, 1460, 1440 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 8.70$ (s, 1H), 8.46 (s, 1H), 8.26 (m, 2H), 8.09 (m, 1H), 7.56 (m, 2H), 7.27 (m, 1H), 3.52 (m, 2H), 3.07–2.92 (m, 2H), 1.8 (m, 4H) ppm; UV (EtOH): $\lambda_{max} = 386$, 350, 290, 240 nm ($\log \varepsilon = 3.28$, 3.53, 3.73, 4.06); MS (70 eV): $m/z = 272$ [M^+]; $C_{19}H_{16}N_2$ (272); calcd.: C 83.82, H 5.88, N 10.29; found: C 83.80, H 5.89, N 10.30.

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