ACTA CHEMICA SCANDINAVICA 21 (1967) 53–62

Isolation, Structure and Synthesis of Alkaloids from *Valeriana officinalis* L.*

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A method has been worked out for the isolation of the alkaloids of *V. officinalis*. Two alkaloids have been isolated in a pure state and assigned the structures I a (major) and I b. It is suggested that the alkaloid reported by Chichibabin *et al.*[3] is actinidine. The pyridinium chromofore has a characteristic infrared absorption in the 1600–1650 cm^{-1} region, of value for structural elucidation. The major alkaloid has been synthesized.

It has been known for a long time that the medicinal plant *Valeriana officinalis* L. contains alkaloids; however, the attempts by several workers [1–8] to isolate them have either failed or afforded products with conflicting analytical data, Table 1. No structure has been suggested for any of the alkaloids so far. Because of the great amounts of oils and the water solubility of the alkaloids, the isolation caused considerable difficulties and is troublesome. It has been reported that fresh and dried material have different alkaloid composition.[4] Most of the earlier work was carried out on dried roots and this part of the plant was also used in our work.

RESULTS AND DISCUSSION

The alkaloid content of the dried roots is about 0.05 to 0.1 %. Since none of the earlier methods of isolation was satisfactory, a new method was worked out affording a mixture of alkaloids from which the main crude alkaloid was isolated in a yield of about 0.03 %. The yield of the pure compound was about 0.015 %. It turned out to be an optically active quaternary base with the composition $C_{18}H_{22}NOCl$. The data for the alkaloids isolated earlier do not agree with the data for the present alkaloid. However, one of its degradation products agree with an alkaloid reported by the Russian workers,[3] see below.

* A preliminary account of this work was given in *Tetrahedron Letters* **1966** 445.

Table 1. Earlier work on the *Valeriana* alkaloids.

Compounds isolated	Remarks	References
Chatinine, 0.01 %, picr. 97–98°, chloride 115°;. Valerine, 0.002 %, dec.about 100°.	Fresh roots	2
Picr. 147–148°, $C_{10}H_{15}N{\cdot}C_6H_3N_3O_7$, $(C_{10}H_{15}N{\cdot}HCl)_2PtCl_6$, about 0.005 %.	Dried roots, steam distillation insol. in water	3
—	Dried roots, alkaloids sol. in water. Chatinine and valerine were not found.	4
B.p. 211–212°, picr. 141–142°, nitrate, 94°, chloride 111–113°, $C_{17}H_{32}N$.	Roots, water soluble alkaloids	5
—	0.21 % of crude alkaloids were separated by a cation exchanger.	6
Valerine, m.p. 155–158°. Chatinine, m.p. 138°, $C_{10}H_{22}O_2N_2$. picr. 115–116.5°, chloride 105–109°, $[\alpha]_D = -20°(H_2O)$	Roots, water soluble alkaloids, 0.02 %.	7
α-Acetylpyrrole		8
Major alkaloid: chloride, dec. 201–203°, picr. m.p. 151–152°, $C_{18}H_{22}NO^+$. $[\alpha]_D^{22} = +50.5°$ (CH_3OH)	Dried roots, water sol. alk., 0.03 %.	This work.
$\lambda_{max} = 267$ mμ; $\varepsilon = 5500$; $\lambda_{max} = 222$ mμ; $\varepsilon = 12\,000$ (C_2H_5OH).		
Minor alkaloid: chloride dec. 220–223° picr. m.p. 65–70°, $C_{18}H_{22}NO_2^+$ trifluoroacet. m.p. 145–147° $[\alpha]_D^{22} = +19.3°$, (CH_3OH)	0.001 %	

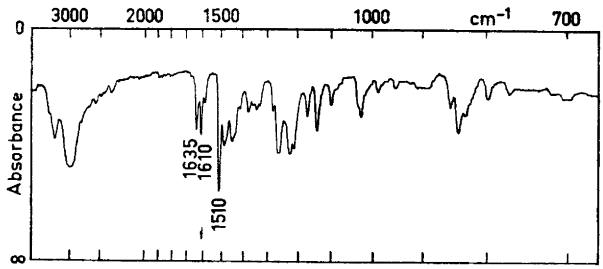


Fig. 1. IR spectrum of the major alkaloid, I a.

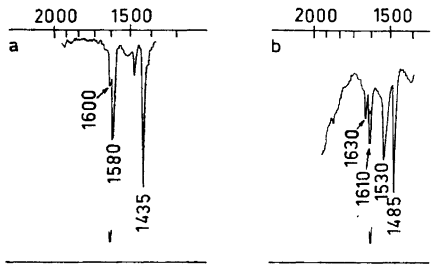


Fig. 2. a) IR spectrum of pyridine, b) pyridinium hydrochloride.

In minute amounts, 0.001 %, a second alkaloid was isolated with the composition $C_{18}H_{22}NO_2Cl$.

The IR spectrum of the main alkaloid (KBr) Fig. 1, shows a strong absorption in the region 3400—2900 cm^{-1} indicating strong hydrogen bonding, two sharp peaks in the olefinic region at 1635 and 1615 cm^{-1} (possibly aromatic) of about the same intensity, and aromatic absorption at 1585, 1515 and 1485 cm^{-1}. The strong out-of-plane bending-absorption at 837 cm^{-1} is most probably due to a 1,4-disubstitution pattern in the aromatic ring. No carbonyl band is present. It was first thought that the absorption at 1635 and 1615 cm^{-1} was due to an olefinic or imine bond but this was excluded by other spectral data. By comparison with the IR spectra of the hydrochlorides of pyridine and pyridine-4-aldehyde [9] it was found that this pair of peaks is characteristic for the pyridinium structure (in some cases only one peak is visible in the region 1615—1650 cm^{-1}), and is of diagnostic value; *cf.* Witkop.[10] Their relative intensity changes in various pyridinium compounds. Fig. 2 shows the characteristic shift in the IR for pyridinium hydrochloride in comparison with the free base. The similarities of the spectra 1 and 2b in the 1600 cm^{-1} region are easily noticeable.

The alkaloid absorbs in the UV region at $\lambda_{max} = 222$ mμ, $\varepsilon = 12\,000$ and $\lambda_{max} = 267$ mμ; $\varepsilon = 5500$ in acid and neutral solution and at $\lambda_{max} = 242$ mμ; $\varepsilon = 16\,000$ and $\lambda_{max} = 292$ mμ; $\varepsilon = 3000$ in alkaline solution. The shift indicated the presence of a phenolic group which was supported by acetylation that gave a product with an IR absorption at 1760 cm^{-1}, within the region of phenolic esters. The shortwave absorption of relatively low intensity excludes a longer conjugated system. The calculated UV curve for the sum of the *p*-cresol and trimethylpyridinium chromophores is in very good agreement with the absorption curve of the alkaloid.

The NMR spectra support the earlier assignments and give further important information about the structure. A total of 22 ($\pm$ 1) protons was counted. In the low field part of the spectrum the 2 and 6 protons of pyridine are located at $\delta = 8.90$ and $\delta = 8.83$ ppm. The two pairs of protons of the *para*-substituted benzoid system are centered at $\delta = 7.04$ and 6.73 ppm forming a typical A_2B_2 spectrum. The triplet at 4.73 ppm is ascribed to a methylene group attached to ammonium and split by another methylene group, $J = 7.3$ c/s. The alkaloid contains two methyl groups, one aromatic, $\delta = 2.34$ ppm, which must be located on the pyridine ring and one aliphatic at $\delta = 1.23$ ppm

split by one hydrogen atom, $J = 6.9$ c/s. The other aliphatic protons form a broad complex band at $\delta = 3.5 - 1.5$ ppm. The NMR spectrum of the methylated product showed the presence of two methoxy groups, which was at first puzzling before it was found out that one of them belonged to the monomethylsulphate ion, coincidentally located exactly at the same place as the aromatic methoxy group. The picrate of the methylated alkaloid has only one methoxy group at $\delta = 3.72$ ppm ($CDCl_3$), Table 2.

Table 2. NMR data for the main alkaloid in deuterated DMSO.

ppm	Protons	Multiplicity	Remarks
8.90	1	s	2 or 6 H in pyridine
8.83	1	s	»
7.04	2	d	A_2B_2 spectrum, 2,3,5,6 H in the
6.73	2	d	*p*-substituted phenol. $J_{AB} = 8.8$ c/s
4.73	2	t	$J = 7.3$ c/s, methylene at N
3.5—2.7	5—6	compl.	
2.34	3	s	$ArCH_3$
2.7—1.5	2—3	compl.	
1.23	3	d	$H-C-CH_3$, $J = 6.9$ c/s.
3.71	6	s	Phenolic OCH_3 of methylated alkaloid and $CH_3OSO_3^-$ ($CDCl_3$)
3.72	3	s	Picrate, phenolic OCH_3 ($CDCl_3$)

The mass spectrum of the trifluoroacetate, which confirms the analysis, shows no molecular ion because the alkaloid is a salt. The highest set of peaks is located at *m/e* 337 and 336, the origin of which might be a decarboxylation (M — 44). Strong peaks are located at *m/e* 268, 267, 147, 132, 121, 120, 107, 91,

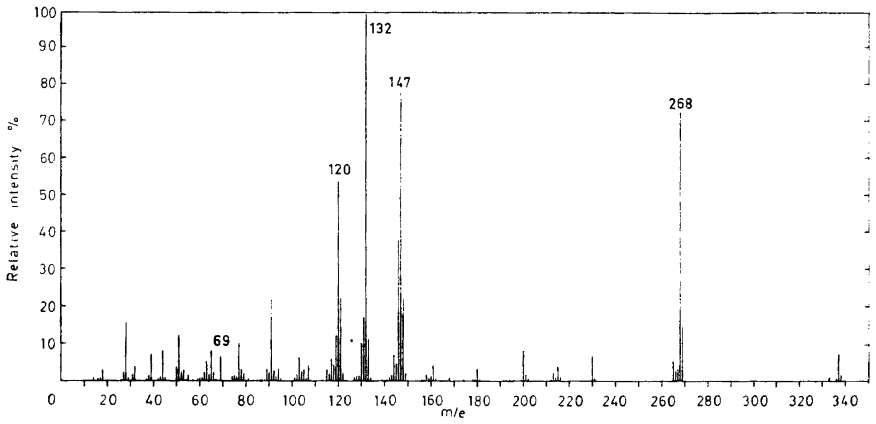
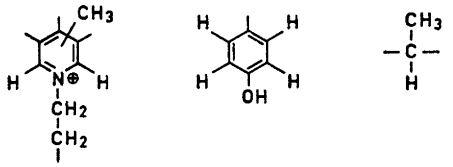


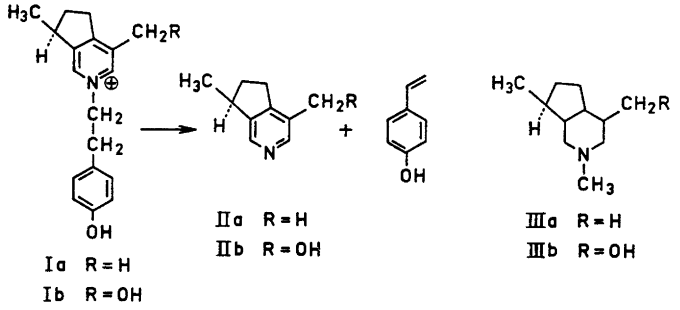
Fig. 3. Mass spectrum of the major alkaloid, I a.

and 77. The presence of the trifluoroacetate ion is supported by the peak at m/e 69 = CF_3^+. M/e 268 is the pyridinium ion (M − CF_3COO^-). The peaks in the middle part of the spectrum confirm the *para*-substituted phenol structure,[11] Fig. 3.

On basis of these data the following structural elements could be derived, which gives us 16 C, 18 H, N, and O:



The remaining two methylene groups must be attached to the pyridine nucleus forming a condensed ring. The alkaloid can thus be represented by the structure I a.



The aliphatic methyl group was placed in the α-position due to biogenetic reasons. With this substitution pattern it can be envisaged that the pyridine fragment is built up by two isoprene units attached head to tail. The β-position is in disagreement with the NMR data. It is expected that this molecule on pyrolysis would decompose into two fragments: *p*-hydroxystyrene (MW 120) and the pyridine derivative (MW 147). This is nicely confirmed by the strong mass peaks at m/e 120 and m/e 147, Fig. 3. The final proof of the structure was obtained by pyrolysis on a larger scale, which afforded the hydrochloride of the pyridine fragment (M^+ = 147) the mass spectrum of which is shown in Fig. 4. This was identical with that of a known alkaloid, actinidine, II a, the structure of which was determined by Sakan *et al.*[12] The optical rotation of the free base and the melting point of the picrate agreed with the values reported.[13] The IR spectra of the picrate and of a picrate obtained from Prof. Sakan were identical. The structure of three other closely related alkaloids have recently been elucidated: skytanthine, III a,[14,15] tecostanine, III b[16] and tecomanine.[17] They occur in families, which are widely separated genetically. This and the monoterpenoid structure of the alkaloids suggests that they are more or less accidentally formed in these plants rather than that they indicate a relationship between the families.[18]

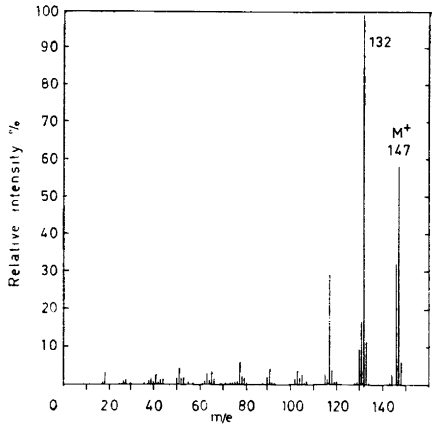


Fig. 4. Mass spectrum of actinidine hydrochloride.

It is most likely that the alkaloid reported by Chichibabin *et al.*[3] is actinidine. The melting point of the picrates agree very well and the composition reported differs only in two hydrogens; found: $C_{10}H_{15}N$, calculated for actinidine: $C_{10}H_{13}N$. They have obtained their alkaloid by steam distillation under alkaline conditions, which causes a degradation of the pyridinium salt to the free base.

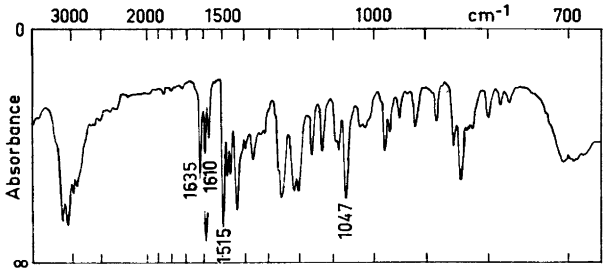


Fig. 5. IR spectrum of the minor alkaloid, I b.

Structure of the minor alkaloid I b. With all the spectral data of the major alkaloid at hand, we were able to determine the complete structure of the minor alkaloid with the minute amount of material (40 mg) we had at our disposal. The infrared spectrum (KBr), Fig. 5, which was similar to that of I a showed the presence of the pyridinium chromophore at 1635 and 1615 cm^{-1} and also suggested the presence of a second hydroxyl group (sharp absorption at 1074 cm^{-1}), which is missing in the spectrum of I a. The NMR spectrum of the picrate (it crystallizes with one mole of ethanol, Fig. 6) was very informative. The aromatic methyl group had vanished but instead a sharp peak (2 H) was visible at $\delta = 4.68$ ppm. (DMSO, region of benzylic alcohols) on top of the triplet at $\delta = 4.80$ ppm, which arises from the methylene

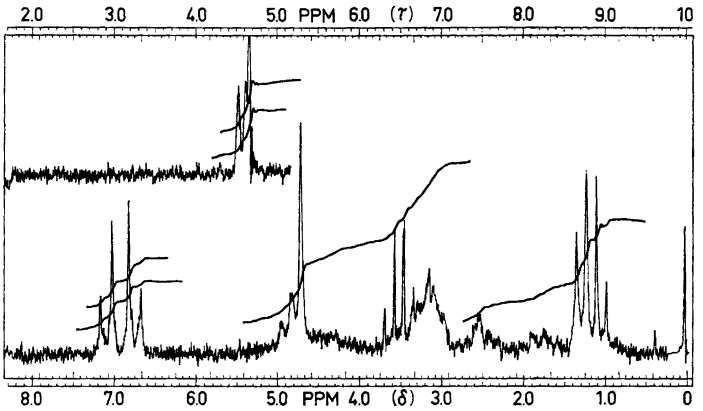


Fig. 6. NMR spectrum of the minor alkaloid, I b, containing one mole of ethanol, $CDCl_3$.

group at N^+. This suggests that the oxygen function is located on the methyl carbon of the pyridinium nucleus as in I b. The other parts of the spectrum were practically identical to that of I a. As expected the mass spectrum of the trifluoroacetate showed a strong peak at *m/e* 163, which is the weight of the pyridine fragment II b. This together with the analytical data confirms the proposed structure I b for the minor alkaloid.

Absolute configuration. Sakan *et al.*[12] have shown that nepetalactone, which is related to (+)-α-methylglutaric acid,[19] and actinidine have the same configuration. Since I a has been degraded to II a of the same optical rotation as Sakan's alkaloid and furthermore I b also has a fairly strong dextrorotatory power it follows that the alkaloids of *Valeriana officinalis* have the absolute configuration depicted in I a and I b.

Synthesis of the major alkaloid, I a. β-(*p*-hydroxyphenyl)ethyl bromide was reacted with actinidine, obtained by pyrolysis of the natural product I a. The bromide of I a was formed in a good yield. The picrate of the product proved to be completely identical with the picrate of the natural product. Since actinidine was synthesized earlier by the Japanese workers the synthesis outlined constitutes a total synthesis of I a.

Physiological action. Extract of *V. officinalis* is used as a mild sedative; however, the active constituents are still unknown. The main alkaloid, I a, is a highly active inhibitor of cholinesterase activity (pI_{50} 5.9; purified esterase from human blood serum) and less active on acetylcholinesterase (pI_{50} 4.4; purified preparation from *Torpedo* electric organ). The compound shows no significant effects *in vivo* (rabbits) indicating an action on cholinesterase.

It is claimed popularly that *V. officinalis* excites cats. Of interest in this connection is the report [12] that actinidine and the closely related monoterpene lactone matatabilactone * have the same effect. The previous statement is thus

* Matatabilactone is recently shown to consist of a mixture of isomeric lactones; *Tetrahedron Letters* **1965** 4097.

supported by chemical evidence and it is quite conceivable that the plant may contain monoterpenes, not yet isolated, which are related to those of *Actinidia polygama* and *Nepeta cataria*.

Since it is known that Mexican Indians for a long time have chewed leaves of *Tecoma* species as an antidiabeticum [20] and it has been shown recently that the related *Tecoma* alkaloids have blood sugar depressing effects,[21] we have submitted our alkaloid to further pharmacological tests, which will be published elsewhere.[22]

EXPERIMENTAL

The infrared measurements were performed with a Perkin Elmer instrument, model 137, and the ultraviolet spectra with a Beckman DB spectrophotometer. The mass spectra were obtained with an instrument of the semicircular type.[23] A Varian A-60 spectrometer was used for the NMR measurements.

Silica gel according to Stahl was used for TLC and Silica gel 0.2—0.5 mm (Merck) and Aluminium oxide, active, neutral (Merck) for the columns.

Isolation. A mixture of dried and ground roots of *V. officinalis* (4.6 kg, Apotekarnes Droghandel, Stockholm, imported from Belgium) and ether (5 l) was left standing at room temperature with occasional stirring for 5 days. After filtration, ether (5 l) was added to the drug and the extraction continued for another 5 days. The ether extracts gave a negative Dragendorff test. The drug was now extracted three times with chloroform/methanol (5 l, 2/1, v/v) for altogether two weeks. Evaporation in a vacuum afforded a viscous oil which was diluted with methanol (100 ml) and then chloroform (150 ml). One litre of ether was added and after standing in a refrigerator overnight, the solvent was decanted and extracted with 1 % hydrochloric acid (100 ml). The water solution was then used for extraction of the oily precipitate, which was then extracted three times with 1 % hydrochloric acid (20 ml). The combined water solutions were neutralized with solid sodium bicarbonate to about pH 8 and extracted twelve times with chloroform/ethanol (75 ml, 3/2, v/v) and evaporated. The residue (75 g) was chromatographed on silica gel (1 kg) with chloroform/methanol (4/1, v/v) as eluent. Fractions of about 50 ml were collected. The first 55 fractions contain compounds that give positive alkaloid reaction but the spots on TLC (ethylacetate:propanol:ammonia 45:35:20) are tailed and weakly coloured. From the 75th fraction the main part of the alkaloids is eluted in a broad interval giving 4—5 closely located spots. Evaporation of the combined main fractions (15 g) and chromatography on alumina (600 g, chloroform/methanol, 9/1, v/v) gave shortly after the front a crystalline fraction (2.4 g) and at the end of this fraction a small amount of a second alkaloid (0.3 g, oily crystals). Only about 20—25 % of the added material could be eluted from the alumina column. The major alkaloid was recrystallized from water or methanol, m.p. 201—203° (decomp.), $[\alpha]_D^{22} = +50.5°$ (CH_3OH). (Found: C 68.11; H 7.57; N 4.24. Calc. for $C_{18}H_{22}NOCl \cdot CH_3OH$: C 68.00; H 7.80; N 4.18, recrystallized fom methanol). The *picrate* melted at 151—152°. (Found: C 57.52; H 4.91. Calc. for $C_{18}H_{22}NO \cdot C_6H_2N_3O_7$: C 58.05; H 4.87). The salt is easily soluble in water or alcohol and difficultly soluble in most other organic solvents.

The *trifluoroacetate* of I a was prepared by dissolving the chloride in excess of trifluoroacetic acid and letting the solution evaporate. The oily residue crystallizes after a while and can be recrystallized from water. (Found: C 63.07; H 5.92; N 3.93. Calc. for $C_{18}H_{22}NO \cdot CF_3COO$: C 63.00; H 5.78; N 3.68).

Acetylation. The alkaloid (chloride, 30 mg) was dissolved in pyridine (1 ml) and acetic anhydride (1.5 ml) and left standing at room temperature for a week. After evaporation of the solvent in a vacuum a blue coloured oil remains, which partly crystallizes. Colourless crystals are obtained from acetronitrile (m.p. 155—160° decomp.), which give a strong infrared absorption at 1760 cm^{-1}.

Methylation. Dimethyl sulphate (0.5 ml) and sodium hydroxide (0.6 g) in water (3 ml) were added simultaneously in small portions to the alkaloid, I a, (130 mg) dissolved in water (0.5 ml). After the last addition the solution was left standing for 4 h with stirring. The reaction was carried out under nitrogen at room temperature. An oil had been formed, which was extracted with chloroform. A crystalline product (80 mg) was

obtained on evaporation. It was recrystallized from ethylacetate, m.p. 111–113°. A few crystals did not melt before 123°. A qualitative sulfur analysis was positive. (Found: C 60.38; H 7.01. Calc. for $C_{19}H_{24}NO{\cdot}CH_3OSO_3$: C 61.03; H 6.94). A *picrate* prepared from the methylated product melted at 143–144°, The NMR data are collected in Table 2.

Pyrolysis of I a. Ca. 50 mg of the chloride was pyrolyzed at 250°/45 torr in a "Kugelrohr". White, somewhat oily crystals were formed on the wall of the glass tube outside the heating block. Resublimation at 170°/45 torr afforded very pure actinidine hydrochloride. Mass spectrum see Fig. 2. It has no definite melting point. $[\alpha]_D^{22} = -7.9°$ (free base, $CHCl_3$). Sakan *et al.*[12] reported $[\alpha]_D^{11} = -7.2°$ ($CHCl_3$). The melting point of the *picrate* was 145–147° (lit.[13] 146–147°). The IR spectra were identical.

Purification of the minor alkaloid, I b. The oily, partly crystalline product (0.3 g) was chromatographed on alumina (90 g) with chloroform/methanol (9/1, v/v) as eluent. The fractionating was followed by TLC and the fractions containing the second alkaloid were combined, evaporated and recrystallized from methanol with one drop of hydrochloric acid and some decolourizing carbon added. Colourless crystals of the chloride (0.04 g) were obtained, m.p. 220–223° (decomp.), easily soluble in water and alcohol, difficultly soluble in most organic solvents.

The *picrate of I b* melts at 60–65° (from ethanol); it resolidifies and melts then at *ca.* 113°.

The *chloride* was regenerated practically quantitatively from the picrate by an ion exchanger, Amberlite IRA 400, HCl, with acetone/water (9/1, v/v) as eluent. The fractions was analyzed by TLC.

The *trifluoroacetate of I b* was obtained from the chloride (29 mg) by adding 1 ml trifluoroacetic acid. Evaporation of the solvent and crystallization of the residue from a small amount of water containing a little trifluoroacetic acid afforded colourless crystals, m.p. 145–147°, $[\alpha]_D^{22} = +19.3°$ (CH_3OH). (Found: C 58.60; H 5.83. Calc. for $C_{18}H_{22}NO_2{\cdot}CF_3COO{\cdot}H_2O$: C 57.83; H 5.82).

Methyl(p-hydroxyphenyl)acetic ester. *p*-Hydroxyphenylacetic acid (5.0 g) was esterified with methanol (15 ml) and dry HCl (2.5 g) for 20 h at room temperature. Evaporation of the solvent and distillation afforded the methyl ester (1.76 g), $b.p._{15}$ 181–182° (lit.[24] $b.p._{0.7}$ 132–134°).

β-(p-Hydroxyphenyl)ethyl alcohol. Methyl (*p*-hydroxyphenyl)acetic ester (1.76 g) was refluxed with lithium aluminium hydride (0.84 g) in tetrahydrofuran for 36 h. The excess of hydride was destroyed with wet tetrahydrofuran and excess of water was then added. Acidification, extraction with ether, drying of the organic layer and evaporation afforded a partly crystalline residue from which the alcohol was obtained by chromatography on silica ($CHCl_3$ + 2 % CH_3OH as eluent), and crystallization from chloroform; 0.75 g, m.p. 87–89° (lit.[25] 92–93°).

β-(p-Hydroxyphenyl)ethyl bromide. β-(*p*-Hydroxyphenyl)ethyl alcohol (0.39 g) was heated with hydrobromic acid, 48 % (2.24 g), for 3 h at 90°. Dark droplets separated. The mixture was poured into ice water and extracted with ether which was washed with water and sodium bicarbonate, dried and evaporated. The residue gave the bromide, 0.45 g, m.p. 86–88° from cyclohexane (lit.[26] 89–91°).

Synthesis of Ia, bromide. Actinidine hydrochloride (30 mg obtained by pyrolysis of Ia, chloride) was neutralized with dry ammonia in chloroform. The solution was filtered and evaporated. The free base was mixed with β-(*p*-hydroxyphenyl)ethyl bromide and heated for 24 h at 45°. The oil solidified on addition of ether and scratching with a glass rod. I a (32 mg) was obtained as a bromide. It was converted to the picrate, m.p. 151–152°, the IR spectrum of which was identical to the spectrum of the natural product.

Acknowledgements. This work has been supported by grants from *Statens Naturvetenskapliga Forskningsråd* and *Granholms stiftelse.* A stipend from the *University of Stockholm* to K. W. is gratefully acknowledged.

Prof. T. Sakan has kindly sent us a sample of actinidine picrate for spectral comparison. The NMR spectra were run by Civ.Ing. K. I. Dahlqvist. We like to thank Dr. K. B. Augustinsson for the cholinesterase tests.

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Received August 4, 1966.