STRUCTURE OF VINCANIDINE AND VINERVINE

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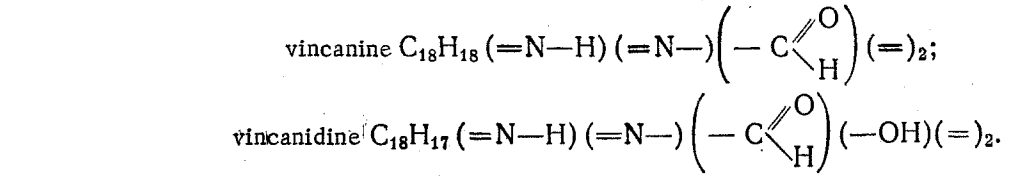
1. Vincanidine and vinervine are α-methylindole derivatives. Heated with hydrochloric acid they afford an indolenine base, desformylvincanidine, and this on reduction, depending on the conditions, gives indoline and indole derivatives. Formation of 4-methoxy-N-oxalylanthranilic acid by oxidation of the O-methyl ether of desformyldihydrovincanidine established the position of the phenolic hydroxyl group in vincanidine and vinervine.

2. The structures and absolute configurations of vincanidine and vinervine are established by the formation of indolenine, indoline, and indole bases from them, and by UV, IR, and mass spectroscopy, as well as by the formation of tetrahydroacuammicine from tetrahydrovinervine.

Vincanidine, $C_{19}H_{20}O_2N_2$, $[\alpha]_D^{30}$ -848° (methanol) is extracted from the roots of Vinca erecta [1]. The IR spectrum of vincanidine has bands at 1565 and 1660 cm^{-1}, indicating the presence of an aldehyde group along with a double bond [2]. The methyl iodide derivative of vincanidine exhibits a band at 3380 cm^{-1}, due to its hydroxyl group, and the secondary nitrogen atom gives a band at 3160 cm^{-1}. Ozonolysis of the base shows the presence of an ethylidene group. Reduction using Adams' catalyst gives dihydrovincanidine, the UV spectrum of which is identical with that of vincanidine; hence it is the double bond of the ethylidene group which is reduced.

Comparison of the UV and IR spectra, as well as the compositions of vincanine [3] and vincanidine [4] show that the latter is hydroxyvincanine-1 (R = H).

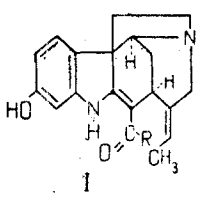


vincanine $C_{18}H_{18}(=N-H)(=N-)\left(-C\begin{matrix}O\\H\end{matrix}\right)(=)_2$;

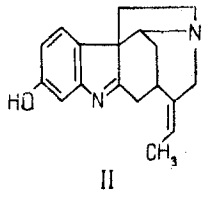
vincanidine $C_{18}H_{17}(=N-H)(=N-)\left(-C\begin{matrix}O\\H\end{matrix}\right)(-OH)(=)_2$.

The phenolic hydroxyl of vincanidine is not methylated by diazomethane, but is methylated by methyl iodide in the presence of sodium methylate, giving the methiodide of the O-methyl ether of vincanidine, with mp 280-282°, $[\alpha]_D^{27}$ -615° (water). The IR spectrum of the latter exhibits bands of a 1, 2, 4-trisubstituted benzene at 815; 860 cm^{-1}. Hence the hydroxyl group of vincanidine occupies position 10 or 11.

Heating vincanidine with hydrochloric acid gives the indolenine base desformylvincanidine ($C_{18}H_{20}ON_2$), $[\alpha]_D$ -176° (ethanol) (II) [4]. In the IR spectrum the hydroxyl group exhibits a band at 3570 cm^{-1}. Desformylvincanidine forms a methiodide of the O-methyl ether, $C_{20}H_{25}ON_2I$.



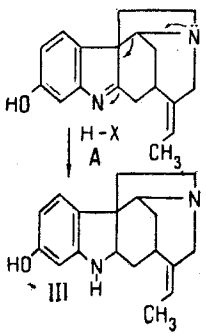
I



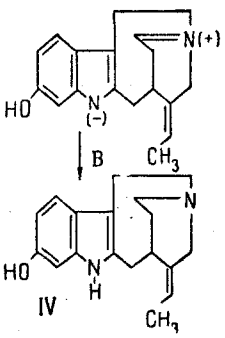
II

Sodium borohydride reduction of desformylvincanidine in acid medium, or reduction with zinc and hydrogen chloride in absolute methanol gives the indoline base desformyldihydrovincanidine $C_{18}H_{22}ON_2$ (III). The IR spectrum of the latter contains band of a hydroxyl group at 3570 cm^{-1} and a secondary nitrogen atom at 3300 cm^{-1}, so that the double bond $-N=C\langle$ is reduced. Methylation with diazomethane gives the O-methyl ether $C_{19}H_{24}ON_2$, $[\alpha]_D^{26}$ -116° (chloroform). Reduction of desformylvincanidine with sodium borohydride in alkaline medium gives the indole base desformyldihydrovincanidine $C_{18}H_{22}ON_2$ (IV).

The formation of indoline and indole bases by reduction of desformylvincanidine shows that there is an equilibrium A ⟷ B:



III



IV

On methylation with methyl iodide in the presence of sodium methylate the indole base IV forms the methiodide of an O-methyl ether, $C_{20}H_{27}ON_2I$. The IR spectrum of the latter exhibits bands for the secondary nitrogen atom at 3280 cm^{-1} and for 1,2,4-trimethylbenzene at 815 and 860 cm^{-1}.

The formation of desformylvincanidine and, after reduction, of indoline and indole bases from vincanidine is quite likely. The alkaloid acuammicine exhibits similar degradation reactions [5].

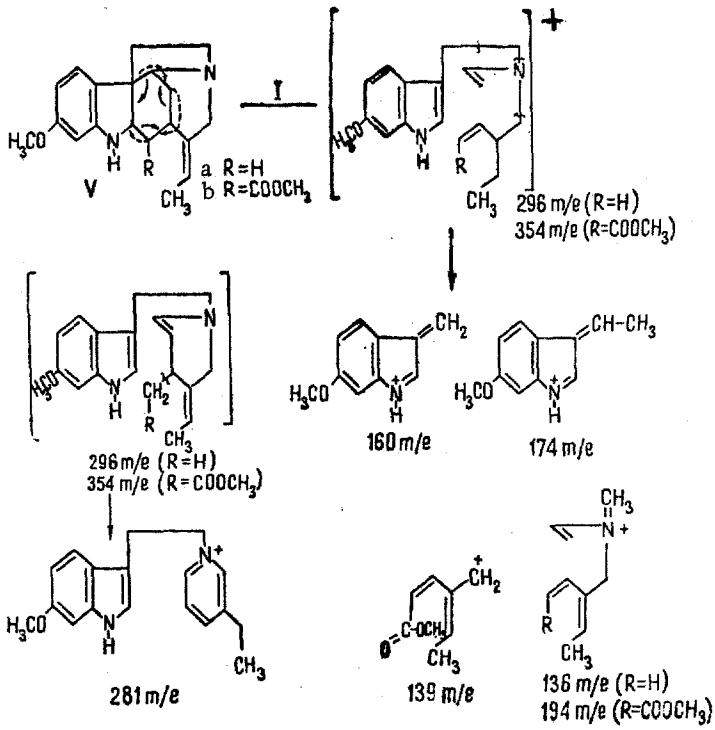
Structure I for vincanidine (R = H) is fully confirmed by mass spectrum analysis of the O-methyl ether of desformyldihydrovincanidine (Va). Electron impact on compound Va gives two types of molecular ions.

Type I. It is postulated that under electron impact the primary splitting is in ring C/D, with rupture of the C_3-C_7, C_2-C_{16}, and C_{14}-C_{15} bonds, and formation of a molecular ion with 296 m/e. Further scission of bands C_5-C_6 and C_5-N_4 in the molecular ion gives fragments of the indole part of the molecule having masses 160 and 174 m/e, and a fragment of the non-indole part of the molecule, mass 136 m/e. The 160 and 136 m/e fragments form a molecular ion mass, 296 m/e.

Type II. Ring C is decomposed under electron impact with splitting of bands C_3-C_7 and C_2-C_{16}, migration of one hydrogen atom from C_{14} to C_{16}, and formation of a molecular ion of the second type. Subsequently, splitting off of a methyl group from C_{15} leads to complete aromatization of ring D and formation of a stable ion of mass 281 m/e.

The fragmentation scheme for the O-methyl ether of desformyldihydrovincanidine is in agreement with the decomposition of decarbomethoxy-1,2-dihydroacuammicine [6]. Fragments of the indole part differ by a methoxyl group of 30 m/e.

Formation of 4-methoxy-N-oxalylanthranilic acid by oxidation of the O-methyl ether of desformyldihydrovincanidine shows that vincanidine is 11-hydroxyvincanine-1 (R = H): -



Vinervine, $C_{20}H_{22}O_3N_2$, $[\alpha]_D^{32}$ -505° (methanol), is isolated from the above-ground portion of V. erecta [7]. It contains one methoxyl group and two active hydrogen atoms. The IR spectrum of vinervine shows the presence of an ester carbonyl group, conjugated with a double bond, at 1690 cm^{-1} [8], a hydroxyl group at 3440 cm^{-1}, and a secondary nitrogen atom at 3380 cm^{-1}.

Sodium borohydride reduction of vinervine in acid medium gives dihydrovinervine $C_{20}H_{24}O_3N_2$; $[\alpha]_D^{30}$ -29.2° (methanol), while further reduction with Raney nickel in a current of hydrogen affords tetrahydrovinervine $C_{20}H_{26}O_3N_2$. In the IR spectrum of dihydrovinervine the carbonyl ester band has a maximum at 1730 cm^{-1}.

Methylation of vinervine with diazomethane gives an O-methyl ether $C_{21}H_{24}O_3N_2$, $[\alpha]_D^{28}$ -533° (methanol). In the IR spectrum there is an ester carbonyl maximum at 1690 cm^{-1}, and a secondary nitrogen atom maximum at 3380 cm^{-1}.

The UV spectra of vinervine and its O-methyl ether exhibit three maxima. The nature of the absorption curves

affords a basis for considering it to be an α-methyleneindoline derivative.

The high specific levorotation and the low frequency of the carbonyl ester band in vinervine and its O-methyl ether, and also the marked drop in specific rotation and the shift of the carbonyl group band in the dihydro- derivative indicate that vinervine is related to the α-methyleneindoline group of alkaloids, conjugated with an ester group.

A comparison of UV and IR spectra and of the composition and properties of vinervine and acuammicine [9], provided the basis for considering vinervine as hydroxyacuammicine: -

acuammicine $C_{18}H_{18}(=N—H)(=N—)(COOCH_3)(=)_2$;

vinervine $C_{18}H_{17}(=N—H)(=N—)(COOCH_3)(OH)(=)_2$.

Heating vinervine in a sealed tube with hydrochloric acid gave an indolenine base identical with desformylvincanidine (II). Consequently vinervine and vincanidine are based on the same heterocyclic system, and the structure of vinervine is I (R = OCH_3). This was confirmed by mass spectrum analysis of the O-methyl ether of dihydrovinervine, with an intensive molecular ion peak at 354 m/e. In the high mass region there is a peak of average intensity at 295 m/e, corresponding to the splitting off of a carbomethoxy group ($M^+ - 59$), and another at 281 m/e, corresponding to splitting off of the group CH_2-$COOCH_3$ ($M^+ - 73$). There are also peaks of indole fragments at 160 and 174 m/e, and of non-indole ones at 139 and 194 m/e. The O- methyl ether of desformyldihydrovincanidine does not give rise to a similarly structured fragment with 139 m/e. The schemes for fragmentation of the O-methyl ether of dihydrovinervine and of the O- methyl ether of desformyldihydrovincanidine are similar.

The final structures and absolute configurations of vinervine and vincanidine were ascertained by transforming vinervine into tetrahydroacuammicine [9].

Treated with toluene sulfonyl chloride, tetrahydrovinervine gives the crystalline tosyl ester $C_{27}H_{32}O_5N_2S$, and reduction of this with hydrogen and Raney nickel gives tetrahydroacuammicine [7]. Acuammicine (0.01%) has been isolated from the aerial part of V. erecta collected at the village of Shargun', Surkhandar'ya province.

Experimental

Vincanidine crystallizes from methyl and ethyl alcohols, and chars without melting at 250-280°. In paper chromatography using the system n-butanol–acetic acid–water (100:5:100) R_f = 0.75. In thin-layer chromatography using ethyl acetate- -methanol (1:1) R_f = 0.18. In UV light it appears bright yellow. $[\alpha]_D^{30}$ -848.6° (c = 0.853; methanol).

UV spectrum λ, mμ (in alcohol): 242; 291; 375 (log ε 3.95; 3.26; 4.13).

Found %: C 73.10; 73.20; H 6.50; 6.51; N 8.90; 9.10; H_{act} 0.58; 0.52; mol. wt. 309.7; 309.23. $C_{19}H_{20}O_2N_2$. Calc. %: C 73.99; H 6.53; N 9.08; $2H_{act}$ 0.64; mol. wt 308.36.

19,20-Dihydrovincanidine. 200 mg base in 50 ml ethyl alcohol was reduced with hydrogen and Raney nickel on a steam bath. 0.17 g non-crystalline dihydrovincanidine was isolated, with R_f = 0.64 using n-butanol-acetic acid-water (100:5:100).

19,20-dihydrovincanidine hydrochloride was prepared by mixing an alcohol solution of the base with an alcoholic solution of hydrogen chloride. Mp 280° (decomp., from alcohol).

Found %: Cl 9.80; 9.80. $C_{19}H_{22}O_2N_2 \cdot HCl$. Calc. %: Cl 10.23.

Ozonolysis of vincanidine. Ozonolysis of 81 mg of the base gave 36 mg 2,4-dinitrophenylhydrazone acetaldehyde, mp 136-139°.

Vincanidine O-methyl ether methiodide. 1 g of the base was dissolved in the calculated amount of sodium methylate in methanol, and heated for 3 hr with 3 ml methyl iodide on a steam bath. On cooling 0.82 g crystals came down, mp 280-282° (from methanol). Paper chromatography with n-butanol-acetic acid–water (100:5:100) gave R_f = 0.7. Thin-layer chromatography with ethyl acetate- -methanol (1:1) gave R_f = 0.4. $[\alpha]_D^{27}$ -615° (c = 0.715; water).

Found %: I 27.1; 27.2; OCH_3 7.90, 8.00; N-CH_3 3.20; 3.20; $C_{21}H_{25}O_2N_2I$. Calc. %: I. 27.33; OCH_3 6.68; N-CH_3 3.23.

From the mother liquor, we isolated vincanidine methiodide with mp 310-313° (decomp., from alcohol.) In paper chromatography with n-butanol-acetic acid-water (100:5:100) R_f = 0.73.

Desformylvincanidine. 3 g vincanidine was dissolved in 70 ml 20% hydrochloric acid, and heated for 3 hr in a sealed tube at 115-120°. The reaction mixture was made alkaline with a 25% ammonia solution, and extracted with ether. Crystals of desformylvincanidine (1.81 g) were obtained, mp 185-188° (decomp., from acetone). R_f = 0.64 with n-butanol-acetic acid–water (100:5:100) (paper chromatography) and R_f = 0.28 with ethyl acetate–methanol

(1:1) (thin-layer chromatography). $[\alpha]_D^{14}$ -176° (c = 1.328; methanol).

UV spectrum λ, mμ (in alcohol): 222, 262 (log ε 4.30; 3.66).

Found %: C 76.70; 76.90; H 7.37; 7.61; N 10.07; 9.96; $C_{18}H_{20}ON_2$. Calc. %: C 77.11; H 7.71; N 9.99.

Desformylvincanidine O-methyl ether methiodide. 500 mg base were dissolved in the calculated amount of sodium methylate in 20 ml methanol and heated for 2 hr with 2 ml methyl iodide. The product was evaporated to dryness, the residue dissolved in water, and extracted with chloroform. After distilling off the chloroform 0.61 g crystals were obtained, with mp 242-245° (decomp., from methanol).

Paper chromatography with n-butanol-acetic acid—water (100:5:100) gave R_f = 0.61. Thin-layer chromatography using ethyl acetate-methanol (1:1) gave R_f = 0.36. $[\alpha]_D^{26}$ -29.37° (c = 0.71; methanol).

UV spectrum λ, mμ (in alcohol) 220; 260 (log ε 4.42; 3.52).

Found %: I 28.00; 29.05; OCH_3 6.80; 7.10. $C_{20}H_{25}ON_2I$. Calc. %: I 29.08; OCH_3 7.11.

Sodium borohydride reduction of desformylvincanidine in acid: Desformyldihydrovincanidine (indoline base). 200 mg desformylvincanidine were dissolved in 15 ml 5% hydrochloric acid, and with constant stirring 200 mg sodium borohydride were added over 1 hr. The reaction mixture was made alkaline with ammonia solution, and extracted with ether. After distilling off the ether there were isolated 140 mg crystals with mp 240-242° (decomp., from alcohol). Paper chromatography gave, with n-butanol-acetic acid – water (100:5:100), R_f = 0.77, while thin-layer chromatography using methanol-chloroform (1:1) gave R_f = 0.41. $[\alpha]_D^{14}$ -106.6° (c = 0.919; ethanol).

UV spectrum λ, mμ (in alcohol) 245; 292 (log ε 3.91; 3.49).

Found %: C 76.20; 76.10; H 7.84; 7.83; N 9.91; 10.02; H_{act} 0.62; 0.61; mol. wt. 275.2; 282.5. $C_{18}H_{22}ON_2$. Calc.%: C 76.59; H 7.86; N 9.92; $2H_{act}$ 0.70; mol. wt. 282.366.

Reduction of desformylvincanidine with zinc and methanolic sulfuric acid. 500 mg base were dissolved in 500 ml 10% absolute methanolic sulfuric acid, and 30 g zinc dust added. The mixture was heated for 1 hr on a steam bath. The precipitate was filtered off, and the filtrate evaporated to small volume in a vacuum. Fifty ml water were added, the solution made alkaline with a saturated solution of sodium carbonate, and extracted with ether. On concentration the ether solution afforded 350 mg desformyldihydrovincanidine, with mp 240-242°. In thin-layer chromatography using methanol-chloroform(1:1), R_f = 0.41.

Desformyldihydrovincanidine O-methyl ether. 300 mg of the base were dissolved in 25 ml of a 2:1 mixture of alcohol and chloroform. An excess of ethereal diazomethane solution was added, and the mixture left for 24 hr at 0°; the solvent was then distilled off in a vacuum, the residue dissolved in 5% hydrochloric acid, 5% potassium hydroxide solution added until the mixture was alkaline, and the whole extracted with ether. After distilling off the ether crystals were obtained with mp 150-151° (from acetone – petroleum ether, 1:3). Thin-layer chromatography using methanol-chloroform (1:1) gave R_f = 0.54, while paper chromatography using n-butanol–acetic acid – water (100:5:100) gave R_f = 0.80. $[\alpha]_D^{26}$ -116° (c = 0.99; chloroform).

Found: Mol. wt. (mass spectrometer) 296.0. $C_{19}H_{24}ON_2$. Calc.: Mol. wt. 296.4.

The mass spectrum of the O-methyl ether of desformyldihydrovincanidine was determined with a MKh-1303 mass spectrometer with an inlet at 160°, and 23 ev ionizing voltage.

Alkaline sodium borohydride reduction of desformylvincanidine: desformyldihydrovincanidine (indole base). 400 mg desformylvincanidine were dissolved in 15 ml 3% aqueous potassium hydroxide. 400 mg sodium borohydride was added over 2 hr. The alkaline solution was acidified with 10% hydrochloric acid, 25% ammonia added till the mixture was alkaline, and the whole extracted with ether. After evaporating off the ether, 280 mg of a base was isolated with mp 160-161° (from acetone-petroleum ether, 2:1). Paper chromatography using n-butanol-acetic acid—water (100:5:100) gave R_f = 0.77. Thin-layer chromatography with ethyl acetate – methanol (9:1) gave R_f = 0.17.

UV spectrum λ, mμ (in alcohol): 226; 276; 294 (log ε 4.48; 3.66; 3.48).

Found %: C 76.70; 76.90; H 7.78; 7.74; N 9.59; 9.71; $C_{18}H_{22}ON_2$. Calc. %: C 76.59; H 7.86; N 9.92.

O-methyl ether of desformyldihydrovincanidine (indole base). 500 mg base were dissolved in 250 ml dry ether, an excess of ethereal diazomethane solution added, and the mixture left for 72 hr. The ethereal solution was washed with a 3% potassium hydroxide solution, and the solvent completely removed. Crystals were obtained (from acetone) with mp 200-201°. Thin-layer chromatography using methanol-chloroform (1:1) gave R_f = 0.51.

Methiodide of O-methyl ether of desformyldihydrovincanidine (indole base). 510 mg desformyldihydrovincanidine (indole base) were dissolved in the calculated amount of sodium methylate in 50 ml methanol, and heated for 3 hr on a

steam bath with 2 ml methyl iodide. The solvent was distilled off, the residue taken up in water, and extracted with chloroform. On distilling off the chloroform, 550 mg of the O-methyl ether of desformyldihydrovincanidine methiodide, with mp 257-258°, were obtained.

Paper chromatography using n-butanol-acetic acid-water (100:5:100) gave R_f = 0.74, and thin-layer chromatography using ethyl acetate-methanol (1:1) gave R_f = 0.42. $[\alpha]_D^{18}$ -34.4° (c = 0.61; methanol).

Found %: C 53.70; 53.50; H 6.55; 6.32; N 6.22; 6.34; OCH_3 6.80; 6.80; I 28.30; 28.0; $C_{20}H_{27}ON_2I$. Calc. %: C 54.69; H 6.29; N. 6.39; I 28.84; OCH_3 7.08.

Vinervine mp 154-155° (decomp., from ether) was obtained from purified vinervine hydrochloride or sulfate. Paper chromatography using n-butanol-acetic acid-water (100:5:100) gave R_f = 0.81. $[\alpha]_D^{32}$ - 505° (c = 1.053, chloroform).

UV spectrum λ, mμ (in alcohol): 234; 290; 336 (log ε 4.22; 3.86; 4.22).

Found: mol. wt. 338.3; 336.59. $C_{20}H_{22}O_3N_2$. Calc.: mol. wt. 338.4.

Vinervine hydrochloride is obtained by mixing vinervine base with an aqueous solution of hydrochloric acid. Mp 199-200°, from methanol – water (2:1). $[\alpha]_D^{32}$ -511.4° (c = 1.447; methanol).

Found % : Cl 9.25. $C_{20}H_{22}O_3N_2 \cdot HCl$. Calc. %: Cl 9.40.

Vinervine sulfate is precipitated when a sulfuric acid solution of the total alkaloids is neutralized with ammonia. Mp 182-183° (decomp., from methanol).

Vinervine O-methyl ether. 300 ml ethereal solution of diazomethane were added to 2 g of vinervine, and the mixture left for 72 hr. The ethereal solution was washed with 5% potassium hydroxide solution. After the ether was distilled off, there remained 0.8 g of vinervine O-methyl ether with mp 188-189° (from methanol). $[\alpha]_D^{28}$ -533° (c = 1.11; methanol).

UV spectrum λ, mμ (in alcohol): 235; 290; 338 (log ε 4.17; 3.86; 4.27).

Found %: C 71.40; 71.50; H 7.37; 7.22; N 7.71; 8.1; OCH_3 17.18; 17.04. $C_{21}H_{24}O_3N_2$. Calc. %: C 71.56; H 6.95; N 7.97; $2OCH_3$ 17.50.

2,16-dihydrovinervine. Over 1.5 hr, 1 g sodium borohydride was added to 1 g vinervine in 150 ml 15% hydrochloric acid. The acid solution was made alkaline with ammonia and extracted with ether. 650 mg 2,16-dihydrovinervine were isolated, mp 268-270° (decomp., from methanol). Paper chromatography using n-butanol-acetic acid—water (100:5:100) gave R_f = 0.73. $[\alpha]_D^{30}$ -29.2° (c = 0.588; methanol).

UV spectrum λ, mμ (in alcohol): 248; 296 (log ε 3.80; 3.36).

Found %: C 70.50; 70.80; H 7.59; 7.40; N 8.10; 8.36; $C_{20}H_{24}O_3N_2$. Calc. %: C 70.58; H 7.10; N 8.22.

Tetrahydrovinervine. 200 mg dihydrovinervine were dissolved in 10 ml alcohol, and then heated for 3 hr in a current of hydrogen with Raney nickel. The catalyst was filtered off, and the alcohol removed in a vacuum. 170 mg tetrahydrovinervine were obtained, mp 262-263° (decomp., from methanol). Paper chromatography with butanol-1 – acetic acid – water (100:5:100) gave R_f = 0.79.

O-methyl ether of 2,16-dihydrovinervine. 2 g vinervine O-methyl ether were dissolved in 50 ml 20% hydrochloric acid and 2 g sodium borohydride added over 1.5 hr. When the reaction ended, the mixture was made alkaline with 25% ammonia and extracted with ether. After distilling off the ether there remained 1.8 g O-methyl 2,16-dihydrovinervine, mp 143-144° (from methanol); $[\alpha]_D^{21}$ -26.9° (c = 0.52; methanol).

Found %: C 71.3; 71.2; H 7.90; 7.94; N 8.15; 8.25; mol. wt. 354 (mass spectroscopy). $C_{21}H_{26}O_3N_2$. Calc. %: C 71.16; H 7.43; N 7.90.

Ozonolysis of vinervine. 50 mg vinervine gave on ozonolysis 15 mg 2,4-dinitrophenylhydrazone acetaldehyde, with mp 138-140°.

Decarbomethoxyvinervine (desformylvincanidine). 0.4 g vinervine were dissolved in 30 ml 15% hydrochloric acid, and heated for 2.5 hr at 100° in a sealed tube. The contents were made alkaline with ammonia and extracted with ether. Evaporation of the ether gave 170 mg desformylvincanidine with mp 185-187° (decomp., from ether). Paper chromatography with n-butanol – acetic acid – water (100:5:100) gave R_f = 0.64. Thin-layer chromatography using ethyl acetate – methanol (1:1) gave R_f = 0.28.

Tetrahydrovinervine tosylate. 1 g of the base was dissolved in 20 ml dry pyridine, 1.5 g toluene sulfonyl chloride were added, and the whole left for 24 hr, after which 100 ml water were added, and the mixture extracted with ether. The ether extract was washed with 5% potassium hydroxide solution and water. The extract then was dried and

distilled, and the residue of pyridine distilled off in a vacuum, to give 1.3 g tosyl ester, with mp 270-271°(from acetone).

Found %: S 8.8. $C_{27}H_{32}O_5N_2S$. Calc. %: S 6.7.

Tetrahydroacuammicine. 1.3 g tosyl ester were dissolved in 50 ml 85% alcohol, and reduced with hydrogen and Raney nickel while heating on a steam bath. The reduction product was separated from the catalyst, and the alcohol reduced to small volume, when 200 mg tetrahydrovinervine tosylate were precipitated. After drying the mother liquor was treated with petroleum ether. Evaporation gave 200 mg tetrahydroacuammicine with mp 126-127°, mixed mp with tetrahydroacuammicine undepressed. Paper chromatography with n-butanol-acetic acid – water (100:5:100) gave R_f = 0.81. Thin-layer chromatography using ethyl acetate-methanol (1:1) gave R_f = 0.35.

IR spectrum (cm^{-1}): N-H 3380; $COOCH_3$ 1735; 1255, indoline 1610, o-disubstituted benzene 745.

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