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THE TOTAL SYNTHESIS OF SOME PYRROLYZIDINE ALKALOIDS AND THEIR ABSOLUTE CONFIGURATION

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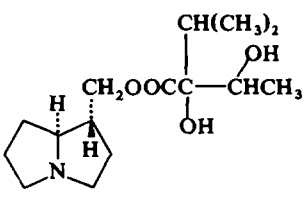
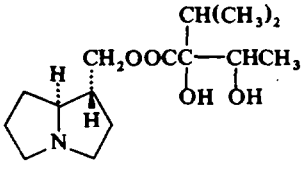
Abstract—The number of known pyrrolyzidine alkaloids of the ester type is on the increase (e.g. Leonard[1]), but their total synthesis, which could finally prove the relative and absolute configuration, has not yet been accomplished. Now we report the first total synthesis of the simplest group of ester alkaloids containing isomeric 1-hydroxymethylpyrrolyzidines as necines, esterified by isomeric 2-isopropyl-2,3-dihydroxybutyric acids. The relative and absolute configuration of the compounds has been determined.

The synthesis of the alkaloids involves the preparation of optically active necines, the synthesis of optically active acids and esterification of necines with the corresponding acids. Using this route, the complete synthesis of trachelanthamine (I), viridiflorine (II) and lindelofine (III) has been achieved.



I



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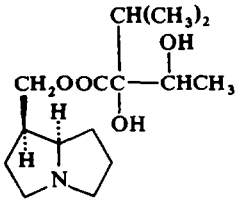


III

THE PREPARATION OF OPTICALLY ACTIVE NECINES

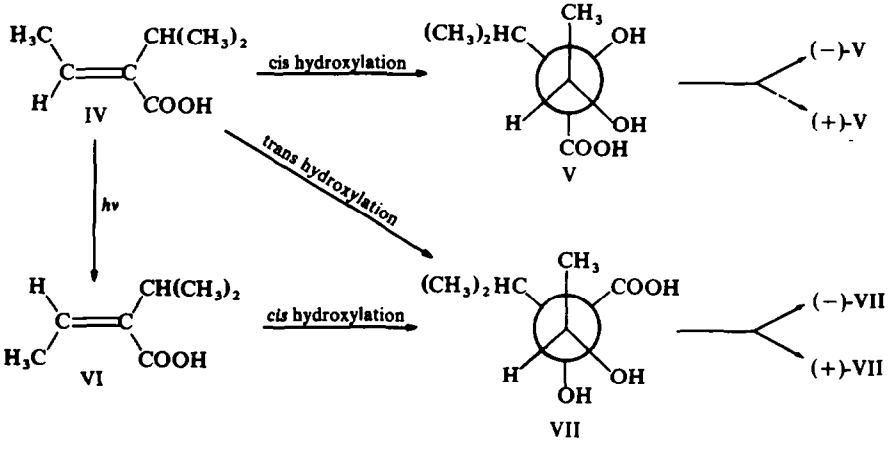
THE synthesis of (±)-trachelanthamidine was performed earlier in this laboratory[2,3] starting from γ-butyrolactone. Fractional crystallization of its acid dibenzoyltartrates afforded both laburnine and (−)-trachelanthamidine, the latter being the constituent of trachelanthamine (I) and viridiflorine (II).

From the mixture of diastereomeric 1-hydroxymethylpyrrolyzidines, obtained as described earlier,[2] (±)-isoretronecanol was isolated which was resolved into antipodes, i.e. lindelofidine and isoretronecanol, by means of fractional crystallization of its acid dibenzoyltartrates. Properties of the optically active necines obtained correspond to those of the natural necines either occuring in the free state in some plants [laburnine, (−)-trachelanthamidine, (−)-isoretronecanol] or prepared by hydrolysis of the corresponding alkaloids.

SYNTHESIS OF OPTICALLY ACTIVE 2-ISOPROPYL-2,3-DIHYDROXY-BUTYRIC ACIDS

Stereospecific synthesis of (+)-trachelanthic and viridifloric acids, constituents of alkaloids I–III, could prove conclusively their relative configuration, since some doubt about this point still remained.

Trans-2-isopropylcrotonic acid (IV) was obtained from ethyl 2-isopropyl-3-hydroxybytizoate with some modifications of known procedure[4] (see Experimental). The NMR-spectrum of IV contains a doublet at δ 1·82 ppm (CH_3-group)



and a quartet at δ 6·81 ppm (β–H); the latter value is characteristic for *trans*-configuration of a double bond (cf. Lit.[5]). *cis*-Hydroxylation of IV with OsO_4 in the presence of chloric acid,[6] treatment with anionite IRA-410 (OH^-) followed by crystallization afforded homogeneous trachelanthic acid (V). Its IR-spectrum contains two wide peaks (895, 922 cm^{-1}) and an inflexion (955 cm^{-1}) in accord with the data for 2,3-dihydroxybutyric acids.[7] Taking into account *trans*-configuration of IV and the known mechanism of hydroxylation with OsO_4[8] the acid V obtained should be the (±)-threo-isomer. It has been resolved by crystallization of its salts with (−) and (+)-α-phenylethylamines, the (+)-isomer being identical to the natural (+)-trachelanthic acid, thus proving the configuration of the latter as (+)-threo-2-isopropyl-2,3-dihydroxybutyric acid.

Acid IV was converted into the *cis*-isomer by UV-irradiation. This transformation may be easily controlled by changes in the NMR-spectrum, since the β–H–*trans* exhibits a quartet centred at δ 6·81 ppm while that of β–H–*cis* is centred at δ 6·01 ppm (cf. Refs. 5 and 6). Shift of the β–CH_3-signal is smaller, but large enough to evaluate the composition of the reaction mixture. Thus, the amount of the *cis*-isomer was found to be about 80% after 150 hr of irradiation. *cis*-Hydroxylation of the *cis*-isomer (VI) with OsO_4–$HClO_3$ afforded (±)-erythro-2-isopropyl-2,3-dihydroxybutyric acid (VII). A completely identical compound has been obtained by *trans*-hydroxylation of the *trans*-acid IV with pertungstic acid according to Adams[4] or with H_2O_2 at pH 7–8.[9] Racemic VII was resolved[10] by crystallization of its salts with (+)- and (−)-α-phenylethylamines; the antipodes appeared to be identical to the known (+)- and (−)-viridifloric acids.[4]

It was not known which of the two viridifloric acids is the constituent of alkaloid viridiflorine, the problem being complicated by the possibility of racemization of either of the viridifloric acid antipodes which could occur during hydrolysis of the alkaloid.

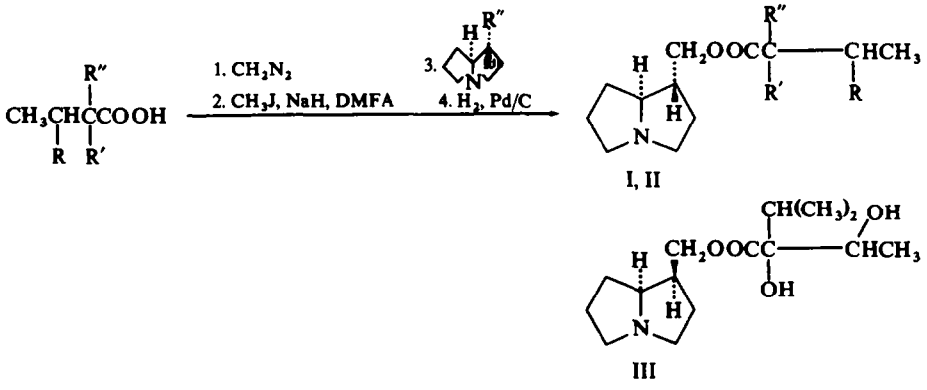
To solve the problem, alkaloid viridiflorine was hydrolyzed under conditions described in the literature,[11] and (−)-viridifloric acid identical to that described in the literature was isolated. The O-methyl derivative of the ester of synthetic (+)-VII and that of natural viridifloric acid obtained from viridiflorine[12] show the opposite specific rotation value (cf. Table 1), thus ruling out the possibility of racemization; thus the constituent of alkaloid viridiflorine is (−)-viridifloric acid.

TABLE 1. COMPARISON OF THE CONSTANTS OF THE DERIVATIVES OF NATURAL AND OF (+)-VIRIDIFLORIC ACIDS VII

Compound	From natural acid		From (+)-acid	
	B.p.	$\lvert\alpha\rvert_D$	B.p.	$\lvert\alpha\rvert_D$
VIII	95–96°/20 mm	+44·6° (23°; c, 3, ethanol)	85–86°/10 mm	44·9° (23°; c, 3 ethanol)
IX	81–82°/1 mm	+42·0° (20°; c, 1,5 ethanol)	81–82°/1 mm	−42·6° (20°; c, 1 ethanol)

SYNTHESIS OF THE ALKALOIDS

The synthesis of the aforementioned alkaloids (I–III) was accomplished by esterification of necines with the corresponding acids according to the following scheme:



I: $R = R^{II} = OH$; $R^{I} = CH(CH_3)_2$; $R^{III} = H$; $R^{IV} = CH_2OH$
II: $R = R^{I} = OH$; $R^{II} = CH(CH_3)_2$; $R^{III} = H$; $R^{IV} = CH_2OH$
III: $R = R^{II} = OH$; $R^{I} = CH(CH_3)_2$; $R^{III} = CH_2OH$; $R^{IV} = H$.

The optically active acids (V, VII) were transformed into the methyl esters by treatment with diazomethane. The latter were benzylated with benzyl chloride in dimethylformamide in the presence of sodium hydride. Methyl 2,3-di-O-benzyl-2-isopropyl-2,3-dihydroxybutyroates were re-esterified with the corresponding 1-hydroxymethyl-pyrrolyzidines in the presence of catalytic amounts of sodium

methoxide, and 2,3-di-O-benzylalkaloid derivatives obtained were debenzylated by hydrogenolysis over palladium on charcoal. By this route, trachelanthamine(I)[6] was obtained by re-esterification of the natural (+)-trachelanthic acid [(+)-IV] with trachelanthamidine and alkaloid lindelofine (III)[13]—by re-esterification with lindelofidine. Viridiflorine (II)[10] was obtained from the derivative of (−)-viridifloric acid and (−)-trachelanthamidine.

Properties (Table 2) and IR-spectra of the synthetic alkaloids were identical to those of the natural ones. Thus, the method developed seems to be suitable for synthesis of alkaloids of this type independently of the stereochemistry of necines and acids.

TABLE 2. COMPARISON OF THE NATURAL AND SYNTHETIC ALKALOIDS

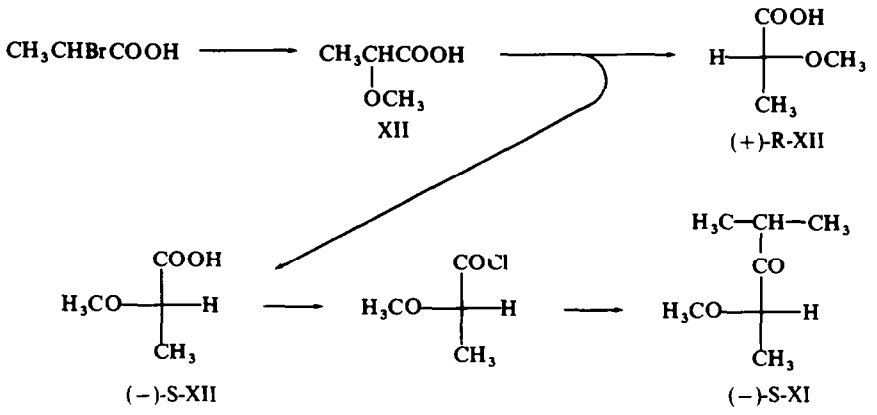
Constant / Alkaloid		m.p.	R_f^*	$\lvert\alpha\rvert_D$ (C = 1, ethanol)	m.p. of picrate
Trachelanthamine,	synth.	91–92°	0·78	−17·2	153–155°
I	nat.	91–92°	0·78	−18·1°	155–156°
Viridiflorine,	synth.	102–103°	0·73	−12·0°	—
II	nat.	102·5–103·5°	0·73	−11·73°	—
Lindelofine	synth.	105–106°	0·62	+49·1°	122–123°
III	nat.	106–107°	0·62	+50·0°	123–123·5°

* n-BuOH:AcOH:H_2O (4:1:5).

ABSOLUTE CONFIGURATION

The absolute configuration of the natural hydroxymethylpyrrolyzidines was established earlier (e.g. [14]). Hence, to determine the total absolute configurations of the ester pyrrolyzidine alkaloids of the type I–III it is necessary to establish only the absolute configurations of the corresponding necinic acids. Since the relative configurations of the acids are also known, it is enough to determine the absolute configuration of one of the asymmetric centres for each of the isomeric pairs.

It has been demonstrated earlier,[15] and finally confirmed by the results of the present studies, that trachelantic acid [(+)-V] and the heliotrinic acid [(−)-X] has the same threo-configuration. Heliotrinic acid may be converted into (+)-2-methyl-4-methoxypentanone-3 (XI), $[\alpha]_D$ 22·5° [16] by oxidative destruction with PbO_2. Since the β-carbon atom is not involved in this reaction, its absolute configuration in trachelanthic and heliotrinic acids and in ketone XI is the same. Stereospecific synthesis of this ketone was performed according to the following scheme

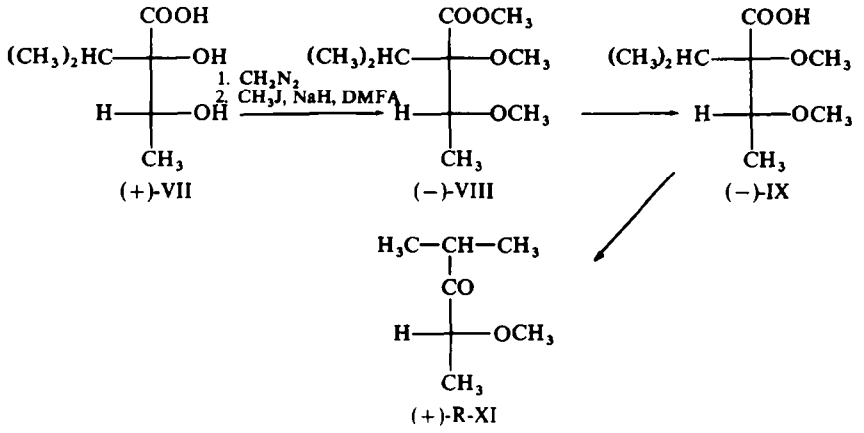


Racemic α-methoxypropionic acid (XII) was obtained by the known method.[17] The optically pure (−)-α-methoxypropionic acid was obtained by crystallization of the salt with (−)-α-phenylethylamine; from the mother liquor the (+)-acid could be isolated. On the basis of the unequivocal evidence for the configuration of lactic acid,[18–20] the (−)-α-methoxypropionic acid obtained must be regarded as possessing S-configuration. Treatment of (−)-XII with thionyl chloride resulted in acid chloride (cf. Ref. [21]), which was subsequently transformed to ketone (−)-XI by reaction with $(CH_3)_2CHMgCl$.

On the inverse addition of reagents at −35–45° ketone XI was obtained in 45% yield. The hindered position of carbonyl group in XI prevents its further reaction with Grignard reagent thus providing the high yield of ketone. The ketone obtained has $[\alpha]_D$ −23·5° and thus it must be named (−)-[4S]-2-methyl-4-methoxypentanone-3. As suggested by the optical rotation value, no racemization of the compound takes place during the synthesis in accord with the earlier evidence obtained for a related reaction (cf. McKenzie[22]). Hence, the ketone (+)-XI, obtained by degradation of (−)-X acid has the R-configuration, and so β-carbon atom of the acids (−)-X and (+)-V has also R-configuration and the acids (V, X) must be named: (+)-[2S, 3R]-2-hydroxy-2-isopropyl-3-hydroxybutiric[(+)-V] (−)-[2R,3S]-2-hydroxy-2-isopropyl-3-hydroxybutiric [(−)-V] and (−)-[2S, 3R]-2-hydroxy-2-isopropyl-3-methoxybutiric acids [(−)-X].

From the knowledge of the β-carbon atom configuration in lasiocarpinic acid to be the same as that in heliotrinic and trachelanthic acids,[23] the data obtained prove also the R-configuration for the β-carbon atom of lasiocarpic ([4R]-2-3-dihydroxy-2-methyl-4-methoxypentancarbonic-3) acid.

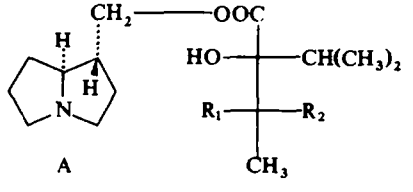
Since the relative configuration of viridifloric acid is known, its absolute configuration follows from absolute configuration of any of the asymmetric centres. Attempted proof of the configuration based upon selective oxidation with *tert*-butylchromate,[24] and subsequent correlation of the configuration of α-hydroxy-β-ketoacid was unsuccessful. Configuration of the β-carbon atom has been established by conversion of (+)-viridifloric acid ((+)VII) into 2-methyl-4-methoxypentanone-3 according to the following scheme:

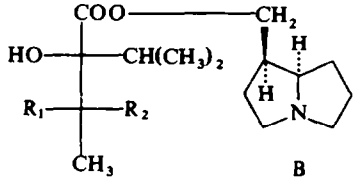


Methylation of methyl ester of (+)-viridifloric acid obtained by action of diazomethane (+)-VII with methyl iodide in the presence of NaH. followed by saponification with aqueous methanolic alkali, gave rise to (−)-2-isopropyl-2,3-dimethoxybutyric acid [(−)-IX)]. Oxidative decarboxylation of (−)-IX by heating with PbO_2 in 5% H_3PO_4[16] afforded the (+)-ketone-XI, having properties identical to the published ones. Hence, the degradation of (+)-viridifloric acid results in (+)-[4R]-2-methyl-4-methoxypentanone-3, and the viridiflorine constituent acid is (−)-[2S,3S]-2-hydroxy-2-isopropyl-3-hydroxybutyric acid.

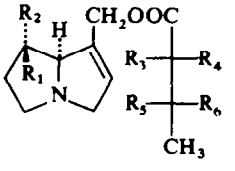
As far as we know, the oxidative degradation of α-alkoxy carboxylic acids has not yet been described; it may present some interest as a new degradation procedure for studies of the structure of some natural compounds.

On the basis of the above data the absolute configuration of a large group of ester pyrrolyzidine alkaloids may be deduced. Their structures are presented below.



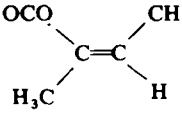


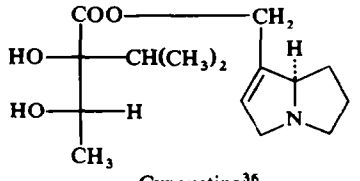
Trachelanthamine: $R_1 = H$; $R_2 = OH$[11]. A.
Lindelofine: $R_1 = H$; $R_2 = OH$[35]. B
Viridiflorine: $R_1 = OH$; $R_2 = H$[26]. A.
Cynaustraline: $R_1 = OH$; $R_2 = H$[36]. B.



Supinine: $R_1 = R_2 = R_5 = H$; $R_3 = R_6 = OH$; $R_4 = CH(CH_3)_2$.[15,37]
Heleurine: $R_1 = R_2 = R_5 = H$; $R_3 = OH$; $R_4 = CH(CH_3)_2$; $R_6 = OCH_3$[15]
Amabiline: $R_1 = R_2 = R_6 = H$; $R_3 = R_5 = OH$; $R_4 = CH(CH_3)_2$.[36]

Rinderine: $R_1 = R_5 = H$; $R_2 = R_3 = R_6 = OH$; $R_4 = CH(CH_3)_2$.[38]
Echinathine: $R_1 = R_6 = H$; $R_2 = R_3 = R_5 = OH$; $R_4 = CH(CH_3)_2$.[34o]
Heliotrine: $R_1 = R_5 = H$; $R_2 = R_3 = OH$; $R_4 = CH(CH_3)_2$; $R_6 = OCH_3$.[39]
Indicine: $R_1 = R_4 = R_5 = OH$; $R_2 = R_6 = H$; $R_3 = CH(CH_3)_2$.[40]

Echiumine: $R_1 =$  ; $R_2 = R_5 = H$; $R_3 = R_6 = OH$; $R_4 = CH(CH_3)_2$.[41]



Cynaustine[36]

EXPERIMENTAL

Resolution of (±)-trachelanthamidine

Dibenzoyl-(+)-tartaric acid (9·06 g) was added to a solution of (±)-trachelanthamidine (3·25 g) in dry ethanol (8·9 ml). The mixture was boiled under reflux for 10 min and 8 g of salt fell out on cooling, $(\alpha)_D^{22}$ −75° (*c*, 1 in dry EtOH), m.p. 139–149°. After recrystallizations from ethanol (+)-trachelanthamidine salt (1·71 g) had $[\alpha]_D^{20}$ −73·17° (*c*, 1 in absolute EtOH) and m.p. 153·5–154·5°. The salt was treated with 1 ml of 40% KOH and solution extracted with ether. Evaporation of ethereal extract results in 0·5 g of laburnine, b.p. 134°/12 mm, $[\alpha]_D^{20}$ +17·01° (*c*, 1 in absolute EtOH).

Analogous treatment of (±)-trachelanthamidine (1·8 g) with 4·93 g of dibenzoyl-(−)-tartaric acid afforded (−)-trachelanthamidine, b.p. 134°/12 mm, $[\alpha]_D^{20}$ −14·91° (*c*, 1 in absolute EtOH).

Literature: laburnine,[25] b.p. 140–141°/14 mm, $[\alpha]_D^{20}$ +13·6° (*c*, 1·22 in EtOH); (−)-trachelanthamidine,[26] b.p. 139–140°/15 mm, $[\alpha]_D^{20}$ −14·95° (*c*, 12 in EtOH).

(±)-Isoretronecanol. A mixture of diastereoisomeric 1-hydroxymethylpyrrolyzidines (15 g) obtained as described earlier[2] was transformed into picrates. Seven recrystallizations from EtOH afforded 10 g of (±)-isoretronecanol picrate, m.p. 189–190°. (Ref. 27: m.p. 190–191°). The picrate was dissolved in hydrochloric acid, picric acid was continuously extracted with ether, aqueous solution evaporated *in vacuo*, residue treated with diluted alkali and base extracted with ether. After removal of solvent, 3·71 g of (±)-isoretronecanol were obtained, b.p. 108–110°/2 mm (Lit.[28]: m.p. 108–110°/2·5 mm).

Resolution of (±)-isoretronecanol

Lindelofidine. A mixture of (±)-isoretronecanol (3·71 g), dibenzoyl-(+)-tartaric acid (10·35 g) and 12 ml EtOH was boiled under reflux for 10 min, EtOH evaporated and residue recrystallized from dry *n*-butanol. After three crystallizations lindelofidine salt of dibenzoyl-(+)-tartaric acid (0·85 g) was obtained, m.p. m.p. 149–150°, $[\alpha]_D^{20}$ −56·8° (*c*, 1 in EtOH). Found: C, 62·54; H, 5·62. $C_{26}H_{29}NO_7$ requires: C, 62·60; H, 5·97%. The salt was treated with 40% KOH and base extracted with ether. Evaporation of ethereal solution afforded 0·25 g of lindelofidine, b.p. 116–117°/2 mm, $[\alpha]_D^{23}$ +72·01° (*c*, 1 in EtOH).

Isoretronecanol. The mother liquor after the first crystallization in the above experiment was evaporated, and 1·8 g of isoretronecanol, $[\alpha]_D^{20}$ −13·0° (*c*, 1 in EtOH) isolated as described above. The amino-alcohol isolated was resolved as described above, using 5·1 g of dibenzoyl-(−)-tartaric acid and 0·95 g of isoretronecanol salt, m.p. 149–150°, $[\alpha]_D^{21}$ +57° (*c*, 1 in EtOH) was obtained. Found: C, 62·35; H, 5·93; N, 3·07. $C_{26}H_{29}NO_7$ requires: C, 62·60; H, 5·97; N, 2·99%. Isoretronecanol (0·3 g), b.p. 116–117°/2 mm $[\alpha]_D^{23}$ −71·6° (*c*, 1 in EtOH) was obtained from the salt by the method analogous to that described above. Lindelofidine,[29] b.p. 116–117°/2 mm $[\alpha]_D^{20}$ +77·5° (*c*, 2·5 in MeOH); isoretronecanol,[29] b.p. 116–117°/2 mm, $[\alpha]_D^{20}$ −77·5° (*c*, 2·5 in MeOH).

α-Isopropylacetoacetic ester was obtained by alkylation of acetoacetic ester (520 g) in dry EtOH (2 l) with isopropyl bromide (724 g) in the presence of sodium iodide. After purification from the O-alkyl-derivative by treatment with equal volume of 2 N HCl ester (445 g) was obtained, b.p. 93–94°/18 mm Lit.[30]: b.p. 96–98°/20 mm).

Ethyl ester of α-isopropyl-β-hydroxybutyric acid was obtained as described earlier,[31] b.p. 69–72°/1 mm, n_D^{20} 1·4320.

α-Isospropylcrotonic acid (IV). Ethyl α-isopropyl-β-hydroxybutyroate (152 g) was dehydrated with phosphoric anhydride,[31] and the mixture of unsaturated acid ethyl esters subjected to alkaline hydrolysis. Fractional low-temperature crystallization (freezing) afforded 20 g of IV. The residue was boiled under reflux for 20 hr with 175 g of KOH in 777 ml of dry EtOH, and additional portion of acid IV (26·7 g) was obtained additionally by freezing. Overall yield 46·7 g, m.p. 54°. Ref. 31: m.p. 54° (from 25% EtOH).

(±)-Trachelanthic acid (V). α-Isopropylcrotonic acid IV (9·1 g) in 500 ml of water was hydroxylated with 30–50 mg of OsO_4 in presence of chloric acid (3·2 g). In 48 h, 1 g of chloric acid was introduced additionally. The reaction mixture was extracted with benzene, and acid V isolated from the aqueous layer (Amberlite IRA-410, OH^--form, elution with 2·5% CH_3COOH). Evaporation of the eluate afforded 8 g of (±)-acid V, m.p. 116–118° (after sublimation at 90°/0·3 mm). Found: C, 52·03; H, 8·12. $C_7H_{14}O_4$ requires: C, 52·17; H, 8·07%. Lit.[32]: m.p. 119–121° (sublimed).

Resolution of (±)-trachelanthic acid

(+)-Trachelanthic acid [(+)-V]. The solution of (±)-acid (5 g) in dry EtOH (3 ml) was treated with (−)-α-phenylethylamine (4 g) in 2 ml of EtOH, the mixture boiled under reflux for 30 min and left overnight. EtOH was evaporated and 20 ml of dry ether were added to the residue. On storage at 5°, the mixture crystallized to afford 5·65 g of the salt. Recrystallization from ethanol afforded 2·34 g of the salt, m.p. 156–158°, $[\alpha]_D^{22}$ −9·4° (*c*, 1 in EtOH). Found: C, 63·60; H, 8·80; N, 4·97. $C_{17}H_{14}O_4 \cdot C_8H_{11}N$ requires: C, 63·57; H, 8·83; N, 4·94%.

This salt was dissolved in minimum amount of water, acidified with HCl and continuously extracted with ether. Evaporation of ethereal extract afforded 1·33 g (52%) of the acid (+)-V, m.p. 80°. After recrystallization from light petroleum–benzene, m.p. 89–90°, $[\alpha]_D^{24}$ +3·8° (c, 1 in water). Lit.[32]: m.p. 89–90°, $[\alpha]_D^{20}$ +2·2° (in EtOH):[4] m.p. 89°, $[\alpha]_D^{25}$ +2·9° (*c*, 2·5 in H_2O).

(−)-Trachelanthic acid [(−)-V]. In an analogous manner, 0·55 g (50%) of acid (−)-V was obtained from 2·2 g of (±)-acid and 1·77 g (+)-α-phenylethylamine; m.p. 90–91°, $[\alpha]_D^{22}$ −2·4° (*c*, 1 in H_2O). Lit.[4]: m.p. 89°, $[\alpha]_D^{25}$ −3·4° (*c*, 2·5 in H_2O).

(±)-Viridifloric acid (VII). (a) Obtained by hydroxylation of *trans*-isopropylcrotonic acid IV (5 g) with tungsten trioxide (50 mg) and 30% H_2O_2 (4·5 ml), as described earlier.[4] Yield 3·65 g (58%) (calc. for acid entering the reaction), m.p. 150° (from ether–light petroleum).

(b) To the solution of acid IV (1·28 g) in acetonitrile (20 ml), 10 ml of hydrogen peroxide, 10 ml of water and 1 ml of potassium nitrate were added, pH adjusted to 7·6 and mixture stirred for 48 hr. The mixture was acidified with 0·1 N HCl to pH 6·5, evaporated to a small volume, the residue saturated with potassium chloride and extracted with ether. Evaporation of the dried ethereal solution afforded a partially crystalline oil. The starting acid IV was separated, the remaining oil dissolved in 10 ml of water and heated for 4 hr on the steam-bath. The solution was evaporated to afford 0·16 g of the acid VII, m.p. 150° (ether–light petroleum).

(c) The solution of acid IV (0·8 g) in *n*-heptane (15 ml) was irradiated by UV-light for 150 hr. The oil obtained was suspended in 25 ml of water and hydroxylated under conditions, analogous to those used for the preparation of (±)-trachelanthic acid to afford 0·7 g of acid (VII); m.p. 150° (twice recrystallized from ether–light petroleum). Found: C, 51·90; H, 8·55. $C_7H_{14}O_4$ requires: C, 51·85; H, 8·64%. Ref.[4]: m.p. 150° (from ether–light petroleum). Mixed m.p. of the three preparations of acid (VII) with each other shows no depression.

Resolution of (±)-viridifloric acid VII

(+)-Viridifloric acid (+)-VII. To a solution of acid (VII) (7·77 g) in 10 ml of dry EtOH, 6·22 g (−)-α-phenylethylamine in 2 ml of dry EtOH was added and the mixture boiled under reflux for 10 min. On cooling, 9·0 g of the salt of (+)-acid VII deposited, m.p. 137–141°, $[\alpha]_D^{20}$ −9·88° (*c*, 1 in EtOH). Recrystallization from EtOH afforded 2·92 g of the salt, m.p. 158–159°, $[\alpha]_D^{20}$ −3·5° (*c*, 1 in EtOH). Found: C, 63·48; H, 8·88; N, 4·99%. $C_7H_{14}O_4 \cdot C_8H_{11}N$ requires: C, 63·57; H, 8·89; N, 4·94%. The salt was dissolved in water, acidified with HCl and continuously extracted with ether. 1·54 g of (+)-VII was obtained, m.p. 126–127°, $[\alpha]_D^{21}$ +1·97° (*c*, 1 in water). Found: C, 52·21; H, 8·75. $C_7H_{14}O_4$ requires: C, 51·85; H, 8·64%.

(−)-Viridifloric acid (−)-VII. The first mother liquor of the above experiment was evaporated, 3·24 g of acid isolated from residue as described above, and resolved using (+)-α-phenylethylamine, as described above. Recrystallization from EtOH afforded 2·15 g of salt, m.p. 158–159°, $[\alpha]_D^{21}$ +8·5° (*c*, 1 in EtOH).

Found: C, 63·87; H, 8·87. $C_7H_{14}O_4$. $C_8H_{11}N$ requires: C, 63·57; H, 8·89%. 1 g of (−)-VII was isolated from the salt obtained, m.p. 126–126·5°, $[\alpha]_D^{21}$ −2·0° (*c*, 1 in H_2O). Found: C, 52·13; H, 8·81. $C_7H_{14}O_4$ requires: C, 51·85; H, 8·64%. Ref. 4: (+)-acid, m.p. 127·5, $[\alpha]_D^{26}$ +1·8° (*c*, 1 in H_2O); (−)-acid, m.p. 127·5°, $[\alpha]_D^{26}$ −1·6° (*c*, 1 in H_2O).

Natural viridifloric acid VII has been obtained by hydrolysis of viridiflorine II (0·8 g) with 10% ethanolic KOH (8 ml)[11] for 3 hr under reflux. Yield 100%, m.p. 122–123°, $[\alpha]_D^{20}$ −1·7° (*c*, 1·6 in H_2O). The mixture of equal amounts of natural VII and of (+)-VIII had m.p. 146–148°, of natural VII and (−)-VII–123–126°.

Methyl ester of 0,0′-*dimethylviridifloric acid* VIII

Natural viridifloric acid (0·5 g) was methylated with diazomethane and the product treated with 1·27 g of methyl iodide in 7 ml of dry DMFA in the presence of 0·26 g sodium hydride (90% purity) at −30–40° After 1 hr stirring at −30–40° the mixture was left overnight, treated with 50 ml of mixture of water with ether (1:1) and acidified. (+)-VIII (0·34 g) was obtained by evaporation of the ethereal solution (see Table 1).

By an analogous procedure 3·79 g of ester (−)-VIII were obtained from 4·3 g of (+)-viridifloric acid VII. Found: C, 58·62; H, 9·83. $C_{10}H_{20}O_4$ requires: C, 58·79; H, 9·87% (see Table 1).

0·0′-*Dimethylviridifloric acid* IX. (+)-VIII (3·2 g) was hydrolyzed with alkali in MeOH aq and acid (+)-IX (2·42 g) was obtained. By an analogous procedure 2·85 g of (−)-IX acid was obtained from 3·4 g of (−)-VIII. Found: C, 57·14; H, 9·64. $C_9H_{18}O_4$ requires: C, 56·83; H, 9·53% (see Table 1).

Trachelanthamine (I), *viridiflorine* (II) *and lindelofine* (III). Solution of (+)-trachelanthic acid (+)-V (1·75 g) in acetone (20 ml) was treated with 1·6 g diazomethane in 60 ml of ether. In 24 hr the solution was evaporated and the methyl ether V ($[\alpha]_D^{22}$ +7·98°, (*c*, 1 in EtOH)) dissolved in 30 ml of DMFA. At −20°. 0·73 g of sodium hydride (90% purity) were added followed by 3·32 g of benzyl chloride in 15 min. The mixture was stirred during 3·5 hr at room temperature, poured into water–ether, acidified with HCl and extracted with ether. Evaporation of the ethereal solution afforded 20 g of chromatographically homogenous methyl ester of 0·0′-dibenzyl-(+)-trachelanthic acid. 0·4 g of the derivative obtained and 0·16 g of (−)-trachelanthamidine were boiled with 2·5 mg of sodium methoxide in 10 ml of dry *n*-heptane during several hours with removal of the distilled MeOH and several additions of fresh solvent. The cooled mixture was filtered, solvent evaporated and the oil obtained purified by chromatography on alumina. The purified product was dissolved in 50–70 ml of MeOH and hydrogenated over Pd/C until consumption of the theoretical volume of hydrogen. The reaction mixture was filtered and evaporated to afford 0·1 g of trachelanthamine (I). Found: C, 62·70; H, 9·50; $C_{15}H_{27}NO_4$, requires: C, 62·91; H, 9·50%. Picrate: Found: N, 10·88. $C_{15}H_{27}NO_4$. $C_6H_3N_3O_7$ requires: N, 10·89%.

In an analogous manner 0·06 g of lindelofine (III) have been obtained from 0·49 g of 0·0′-dibenzyl-(+)-trachelanthic acid methyl ester and 0·20 g of lindelofidine. Found: C, 62·93; H, 9·43; N, 5·38. $C_{15}H_{27}NO_4$ requires: C, 62·91; H, 9·50; N, 4·91%. *Picrate.* Found: N, 11·03; $C_{15}H_{27}NO_4$. $C_6H_3N_3O_7$ requires: N, 10·89%.

In an analogous manner, 0·74 g of 0·0′-dibenzyl-(−)-viridifloric acid methyl ester have been obtained from (−)-viridifloric acid and subsequently transformed by reaction with 0·3 g of (−)-trachelanthamidine into 0·19 g of viridiflorine 11. Found: C, 62·61; H, 9·48; N, 5·15. $C_{15}H_{27}NO_4$ requires: C, 62·91; H, 9·50; N, 4·51%. The properties of the alkaloids obtained are presented in Table 2.

(±)-α-*Methoxypropionic acid* XII was obtained from α-bromopropionic acid and sodium methoxyde as described earlier.[17] Yield 83·5%, b.p. 106–108°/30 mm. Lit.[33]: b.p. 108–110°/30 mm.

Resolution of (±)-α-*methoxypropionic acid* (XII) (−)-[S]-α-*Methoxypropionic acid* (−)-XII.

The solution of acid (XII) (13·5 g) and (−)-α-phenylethylamine (15·65 g) in MeOH (10 ml) was heated to boiling, MeOH evaporated, residue (29·15 g, m.p. 89–95°, $[\alpha]_D^{22}$ −9·56° (c, 1, in EtOH) was five times recrystallized from benzene to afford 9·2 g of (−)-amine salt with (−)-[S]-α-methoxypropionic acid, m.p. 124–125°, $[\alpha]_D^{22}$ −34·8° (*c*, 1·5 in EtOH). The salt obtained was dissolved in water, acidified with hydrochloric acid and extracted with ether. The ethereal extract was evaporated to afford 3·5 g of (−)-[S]-α-methoxypropionic acid ((−)-XII, b.p. 88–89 /15 mm, $[\alpha]_D^{20}$ −70·5° (pure liquid)) n_D^{21} 1·4131. Lit.[33], b.p. 106–110°/30 mm $[\alpha]_D^{20}$ −75·47° (pure liquid).

(+)-[R]-α-*Methoxypropionic acid* [(+)-XII]. From the first mother liquor of the above experiment, 1·5 g of (+)-α-methoxypropionic acid were isolated as described above, b.p. 86–88°/15 mm, $[\alpha]_D^{22}$ +24° (pure liquid), n_D^{21} 1·4131. Lit.[21]: b.p. 113–115°/30–32 mm, $[\alpha]_D^{22}$ +72° (pure liquid).

(−)-[S]-α-*Methoxypropionic acid chloride* was obtained by reaction of 5·6 g thionyl chloride with 3·5 g

of (−)-[S]-α-methoxypropionic acid (−)-XII during 16 hr at 0 . Thionyl chloride was evaporated to afford 3·13 g of acid chloride, b.p. 57–59°/125 mm. Lit.[21]: b.p. 38–39°/41 mm.

(−)-[S]-4-*Methoxy*-2-*methylpentanone*-3[(−)-XI)]. 3·2 g of isopropylmagnesium chloride in 22·2 ml of dry ether were added dropwisely during 1·5 hr at −60–70° and vigorous stirring to solution of 3·1 g (−)-[S]-α-methoxypropionic acid chloride in 5 ml of dry ether. Usual treatment afforded 1·55 g 48·4% of (−)-[S]-ketone ((−)-XI), b.p. 67–70°/48 mm, n_D^{24} 1·4039, d_4^{18} 0·8915 g/cm³, $[\alpha]_D^{24}$ −23·5° (pure liquid). 2-4-*Dinitrophenylhydrazone*—m.p. 116–117°, $[\alpha]_D^{22}$ −226° (c, 1 in acetone). Lit.[16]: b.p. 140–142°, $[\alpha]_D$ +22·5° (pure liquid).

Oxidation of 0·0′-*dimethylviridifloric acid* (−)-IX. 2·5 g of (−)-IX, 6·5 g PbO_2 and 26 ml 5% phosphoric acid were heated until cessation of CO_2 evolution. The distillate alkalinied with 1N NaOH and oil extracted with ether. Residue after ether evaporation was dried by evaporation with dry benzene to afford 0·6 g (31·2%) of ketone (+)-XI, b.p. 65–67°/47 mm, n_D^{23} 1·4103, d_4^{18} 0·8915 g/cm³, $[\alpha]_D^{23}$ +26·02° (pure liquid).

2,4-*Dinitrophenylhydrazone*: m.p. 116–118·5° (from EtOH), 119–120° (from light petroleum), $[\alpha]_D^{20}$ +230° (*c*, 1 in acetone). Found: C, 50·65; H, 5·81; N, 17·99. $C_{13}H_{18}N_4O_5$ requires: C, 50·82; H, 5·85; N, 18·06%. IR-spectrum identical to that of 2,4-dinitrophenylhydrazone of ketone-(−)-XI. Lit.: b.p. 140–142°, $[\alpha]_D$ +22·5°[16]; 2,4-dinitrophenylhydrazone; m.p. 123–124° (from light petroleum), $[\alpha]_D^{20}$ +236° (*c*, 0·3 in EtOH[23]).

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