Tetrahedron. Vol. 26, pp. 715 to 719. Pergamon Press 1970. Printed in Great Britain

SYNTHESIS OF *dl*-SEPTICINE*

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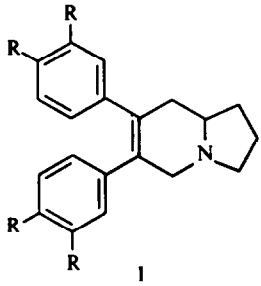
(*Received in the UK* 15 *September* 1969; *accepted for publication* 1 *October* 1969)

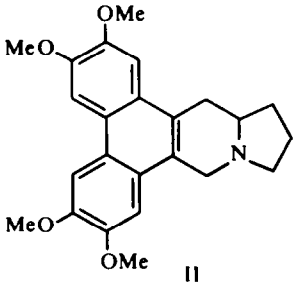
Abstract—The syntheses of *dl*-septicine (Ib) and the model compound Ia are reported.

SEPTICINE,[1] a minor alkaloid isolated from *Ficus septica*, was assigned structure Ib on the basis of its spectral properties and oxidation to veratric acid. On irradiation with an UV lamp, the alkaloid yielded tylophorine (II) which is a congener of septicine in the plant. Septicine is the first instance of an unfused indolizidine alkaloid occurring in nature. We wish to report here the synthesis of *dl*-septicine which confirms the assigned structure.



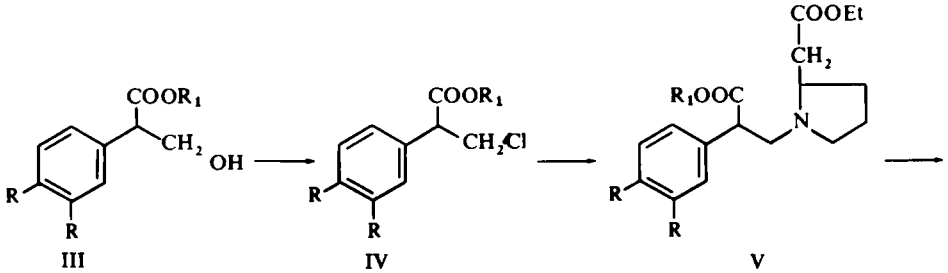
I

a: R = H
b: R = OMe



II

The model compound, $\Delta^{6,7}$-dehydro-6,7-diphenylindolizidine (Ia), was first synthesized as follows. Methyl *dl*-tropate (IIIa) was converted to the chloride (IVa) which was condensed with ethyl 2-pyrrolidinyl acetate to yield the diester (Va). Dieckmann cyclization using triphenylmethyl potassium followed by hydrolysis and decarboxylation yielded the ketoindolizidine (VIa). This was reacted with phenyllithium to give the tertiary carbinol (VIIa). Dehydration of VIIa with sulphuric acid yielded Ia.



III

a: R = H, R_1 = Me
b: R = OMe, R_1 = Et

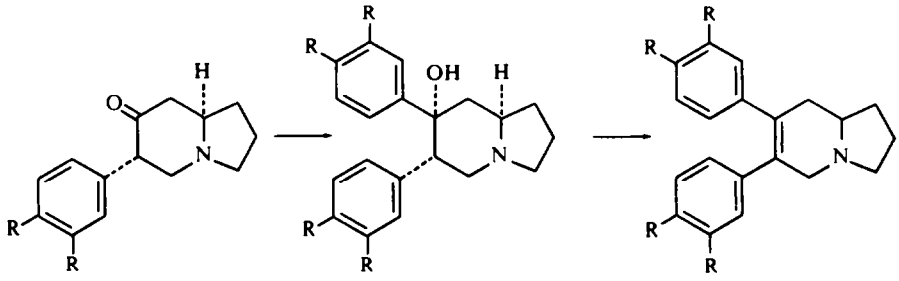
IV

a: R = H, R_1 = Me
b: R = OMe, R_1 = Et

V

a: R = H, R_1 = Me
b: R = OMe, R_1 = Et

* Contribution No. 171 from CIBA Research Centre, Goregaon.

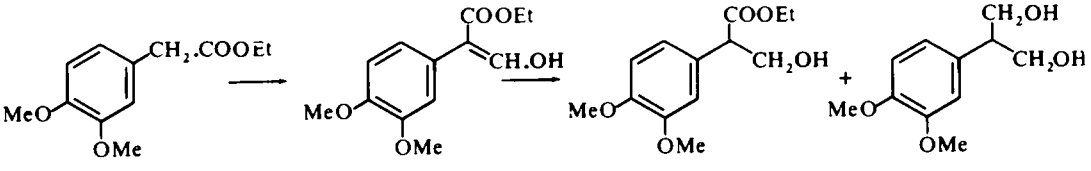


VI
a: R = H
b: R = OMe

VII
a: R = H
b: R = OMe

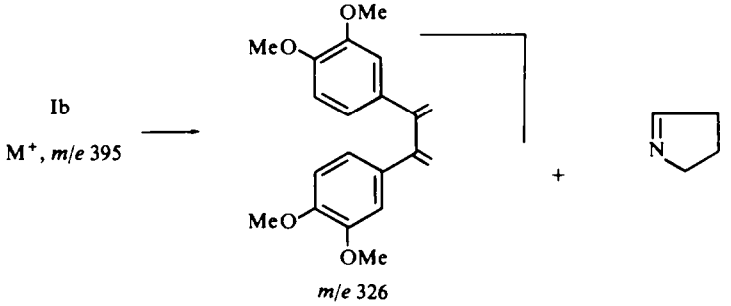
I
a: R = H
b: R = OMe

Septicine itself was synthesized by this method starting from ethyl homoveratrate (VIII). Treatment of VIII with sodium and ethyl formate yielded the hydroxymethylene derivative (IX). Reduction of IX with sodium borohydride under controlled conditions yielded the desired hydroxyester (IIIb) and a small amount of the diol (X). Use of excess borohydride or of higher temperatures during the reduction led to more of X.



VIII IX IIIb X

The hydroxyester (IIIb) was converted to the chloride (IVb) and then reacted with ethyl 2-pyrrolidinyl acetate to yield the diester (Vb). Dieckmann cyclization followed by hydrolysis gave the ketone (VIb.) This was reacted with 3,4-dimethoxyphenyllithium to yield the carbinol (VIIb). Dehydration of the latter yielded *dl*-septicine, m.p. 135–136°, undepressed by admixture with natural *l*-septicine. The two samples also were identical in TLC in three different solvent systems and had identical IR spectra. The mass spectrum of *dl*-septicine showed the molecular ion peak at *m/e* 395 and a very intense peak at *m/e* 326 corresponding to the cleavage shown below:

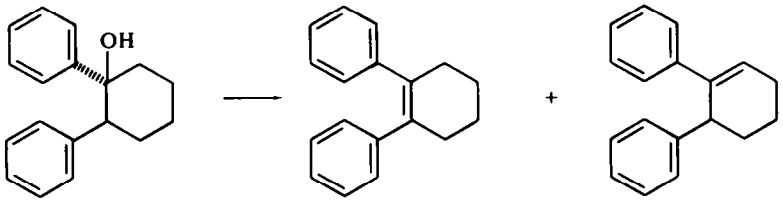


Ib
M^+, *m/e* 395

m/e 326

Tamboulian[2] observed that in the dehydration of 1,2-diphenylcyclohexanol (XI) with thionyl chloride and pyridine both the isomers (XII and XIII) are formed in the ratio of 2:1.

In the dehydration of both VIIa and VIIb, the only crystalline product isolated was the desired stilbene. The styrene isomers were also probably formed but seemed to have undergone decomposition. After this work was complete, Dr. J. H. Russel has informed us that he has synthesized *l*-septicine by a different route.[3]



XI XII XIII

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 421 instrument.

dl-*Methyl tropate* (IIIa). A soln of *dl*-tropic acid (30g) in MeOH (100ml) was treated with excess ethereal diazomethane (from 90g of nitrosomethylurea). Removal of the solvents and distillation of the residue *in vacuo* yielded the methyl ester (26 g), b.p. 145°/2 mm, ν_{max} (CH_2Cl_2) 3680, 3605, 1730 cm^{-1}.

Methyl 3-chloro-2-phenylpropionate (IVa). A soln of methyl tropate (25g) in benzene (100ml) was refluxed for 2 hr with $SOCl_2$ (30g). The solvent and excess $SOCl_2$ were removed *in vacuo*, traces of $SOCl_2$ being removed by adding more benzene and distilling it off. The residual chloride was dried for 3 hr *in vacuo* at 80° and used as such.

Ethyl[1-(2-*carbomethoxy*-2-*phenylethyl*)*pyrrolidinyl*-2-*acetate*] (Va). The above chloride (25 g) and anhyd K_2CO_3 (35 g) were added to a soln of ethyl 2-pyrrolidinyl acetate[4] (12 g) in benzene (150 ml) and the mixture refluxed with stirring in N_2 atmosphere for 8 hr. The soln was filtered, the residue washed well with benzene and the combined filtrate evaporated *in vacuo*. The residual oil was taken up in ether, extracted with 2N HCl and the acid soln basified with ammonia and reextracted with CH_2Cl_2 to give a dark basic oil. This was chromatographed in CH_2Cl_2 over silica gel to yield the *diester* (13 g), ν_{max} (CH_2Cl_2) 1725 cm^{-1}. For analysis, the ester was sublimed at 100°/0·1mm. (Found: C, 67·98; H, 8·11; N, 4·62. $C_{18}H_{25}NO_4$ requires: C, 67·69; H, 7·89; N, 4·39%). For the subsequent reaction, however, the ester which was homogenous by TLC, was dried thoroughly *in vacuo* and used as such without distillation.

7-*Oxo*-6-*phenylindolizidine* (VIa). Potassium (2·8 g) and ferric nitrate (50 mg) were added to anhyd liquid ammonia (60 ml) and the soln stirred for ½ hr in N_2 atmosphere. A soln of triphenylmethane (19 g) in ether (70 ml) was then added and the deep red soln stirred for 1 hr at room temp and then refluxed mildly for 1 hr more. The soln was cooled and a soln of the above diester (13 g) in dry THF (25 ml) was added. The resulting soln was refluxed for 1 hr, then left overnight at room temp and decomposed with 2N HCl (120 ml). The acid soln was separated, extracted with ether to remove non-basic material and then refluxed in N_2 atmosphere for 4 hr. The acid soln was cooled, basified with ammonia and extracted with CH_2Cl_2 to yield a dark brown oil. Chromatography of this in CH_2Cl_2 over silica gel yielded the *ketoindolizidine* (8 g) which was homogenous by TLC, ν_{max} (CH_2Cl_2) 1710 cm^{-1}. The ester was dried well *in vacuo* and used as such for the next reaction. For analysis, a sample was sublimed *in vacuo* at 140°/0·1 mm. (Found: C, 78·12; H, 8·04. $C_{14}H_{17}NO$ requires: C, 78·10; H, 7·96%). Use of NaOEt or K metal for the Dieckmann condensation gave poorer yields of the ketoindolizidine.

6,7-*Diphenyl*-7-*hydroxyindolizidine* (VIIa). Bromobenzene (16 g) was added with stirring to a suspension of Li (2·8 g) in dry ether (100 ml). After the addition the soln was refluxed in N_2 atmosphere for 1 hr. The soln was cooled to 10° and a soln of the above ketoindolizidine (7 g) in dry THF (20 ml) was added. The resultant soln was refluxed for 2 hr, cooled and decomposed with 2N HCl. The acid soln was extracted

with ether to remove non-basic products, cooled, basified with ammonia and re-extracted with CH_2Cl_2 to yield a brownish semi-solid. Addition of ether gave a solid which was filtered (3 g). Crystallization from MeOH-ether gave the *carbinol* as colourless needles, m.p. 173°, ν_{max} (CH_2Cl_2) 3570 cm^{-1}. (Found: C, 82·09; H, 7·76. $C_{20}H_{23}NO$ requires: C, 81·87; H, 7·90%). The *maleate* crystallized from MeOH-ether as hygroscopic needles, m.p. 126–128°. (Found: C, 68·07; H, 7·10. $C_{24}H_{27}NO_5$. MeOH requires: C, 68·00; H, 7·08%). Use of PhMgBr in place of PhLi gave only recovered ketone.

$\Delta^{6,7}$-Dehydro-6,7-diphenylindolizidine (Ia). The above carbinol (2·5 g) was added to a soln containing conc H_2SO_4 (10 ml) and water (5 ml). The reddish soln was heated at 80° for 1 hr in N_2 atmosphere, cooled and poured on ice. Basification with ammonia and extraction with CH_2Cl_2 yielded a gum which was chromatographed over silica gel in CH_2Cl_2 to yield the *diphenylindolizidine* (0·7 g), cream-coloured needles (from MeOH), m.p. 109°, ν_{max}(KBr) 1600 cm^{-1}, λ_{max} 222 (sh), 251 mμ (log ε 4·10, 3·91). (Found: C, 87·60; H, 7·66. $C_{20}H_{21}N$ requires: C, 87·22; H, 7·69%); NMR ($CDCl_3$, 60 mc): δ 7·05 (5H, s), 7·03 (5H, s) (aromatic protons), 3·89 (1H, d, J = 16 cs), 3·1 (1H, d, J = 16 cs) (C═C—CH_2—N).

Ethyl α-hydroxymethylene-3,4-dimethoxyphenyl acetate (IX). Sodium (6·8g) was added to a stirred ice-cooled soln of ethyl homoveratrate (38 g) in dry ether (200 ml.) After ½ hr, ethyl formate (29 g) was added dropwise and the mixture stirred overnight. It was then poured on ice, the aqueous layer separated, acidified quickly and extracted with ether to get a reddish oil (40 g), ν_{max} (CH_2Cl_2) 1710, 1650, 1600 cm^{-1}, which gave a blue colour with $FeCl_3$. It was used as such for the next reaction.

Ethyl 3-hydroxy-2-(3',4'-dimethoxyphenyl) propionate (IIIb). $NaBH_4$ (2·8 g) was added slowly over a period of 20 min to a soln of the above hydroxymethylene ester (20 g) in MeOH (80 ml) at 5–10°. After stirring for 1 hr more, water was added and the mixture extracted with ether to yield a viscous oil. Chromatography of this over silica gel in $CHCl_3$ yielded the *hydroxymethyl ester* (17 g) as a viscous pale yellow oil, ν_{max} (CH_2Cl_2) 3600, 1725 cm^{-1}. For analysis, a sample was sublimed at 180°/0·1 mm. (Found: C, 61·43; H, 7·46. $C_{13}H_{18}O_5$ requires: C, 61·40; H, 7·14%) Elution of the chromatographic column with $CHCl_3$, 5% MeOH yielded 1,3-*dihydroxy*-2-3'4'-*dimethoxyphenylpropane* (X) (0·7 g; needles from benzene-hexane), m.p. 82–83° (lit.[5] m.p. 79–81°) ν_{max} (CH_2Cl_2) 3600, 3460 (broad) cm^{-1}. (Found: C, 62·49; H, 7·92. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60%). Use of more $NaBH_4$ or of higher temps during the reduction resulted in a larger proportion of the diol.

Ethyl 3-chloro-2-(3',4'-dimethoxyphenyl) propionate (IVb). The above ester (12 g) in benzene (100 ml) was refluxed for 2 hr with $SOCl_2$ (12 g). Removal of excess $SOCl_2$ and solvent yielded the *chloride* (9·5 g), which was dried *in vacuo* at 80° and used as such. For analysis, a sample was sublimed at 150°/0·5mm, ν_{max} (CH_2Cl_2) 1725 cm^{-1}. (Found: C, 57·37; H, 6·78. $C_{13}H_{17}O_4Cl$ requires: C, 57·25; H, 6·29%).

Ethyl 1-(2-carbethoxy-2-3', 4'-dimethoxyphenyl)pyrrolidinyl-2-acetate (Vb). The above chloride (30 g), anhyd K_2CO_3 (25 g), ethyl 2-pyrrolidinyl acetate (12 g) and benzene (100 ml) were refluxed in N_2 atmosphere for 14 hr and worked up as usual to yield, after chromatography in CH_2Cl_2 over silica gel, the *ester* (10 g), ν_{max} (CH_2Cl_2) 1720 cm^{-1}. For analysis, a sample was sublimed at 70°/0·1 mm. (Found: C, 64·25; H, 8·37; N, 4·12. $C_{21}H_{31}NO_6$ requires: C, 64·10; H, 7·94; N, 3·56%).

6-(3',4'-Dimethoxyphenyl) 7-oxo-indolizidine (VIb). K (3·2g) and ferric nitrate (50 mg) were added to anhyd liquid ammonia (60 ml.) After stirring for ½ hr, a soln of triphenylmethane (20 g) in dry ether (120 ml) was added. The mixture was stirred at room temp for 1 hr and then refluxed for 1 hr. It was then cooled and a soln of the above ester (11 g) in dry THF (50 ml) added. After refluxing for 2 hr, the mixture was left overnight at room temp. 2N HCl (180 ml) was added and the acid soln refluxed for 6 hr. Working up as for VIIa yielded, after chromatography over Al_2O_3 in CH_2Cl_2 and then over silica gel, the *ketoindolizidine* (5 g) as a viscous liquid, ν_{max} (CH_2Cl_2) 1710 cm^{-1}. For analysis, a sample was sublimed at 180°/0·01 mm. (Found: C, 69·60 H, 7·68. $C_{16}H_{21}NO_3$ requires: C, 69·79; H, 7·69%).

6,7-Di (3',4'-dimethoxyphenyl) 7-hydroxyindolizidine (VIIb). Freshly distilled *n*-BuCl (3·1 g) was added to a suspension of Li (0·7g) in hexane (40 ml) and the mixture refluxed in N_2 atmosphere for 2 hr. The soln was filtered under N_2, evaporated in a stream of N_2 to about 5 ml and dry ether (40 ml) added. The soln was cooled to −40° and 4-bromoveratrole (9 g) added and the soln stirred for ½ hr. The above ketoindolizidine (2g) in dry THF (20 ml) was added and the soln stirred at 20° for 1 hr and then refluxed for 1 hr. The product was decomposed with 2N HCl, the acid soln basified and extracted with CH_2Cl_2 to yield the crude hydroxyindolizidine (2g), ν_{max} (CH_2Cl_2) 3550 cm^{-1}, which was used as such.

dl-*Septicine*[*6,7-di(3',4'-dimethoxyphenyl) $\Delta^{6,7}$-dehydroindolizidine*] (*Ib*). The above crude hydroxyindolizidine (2g) was heated with conc. H_2SO_4 (5 ml) and water (3 ml) at 70° for 20 min in N_2 atmosphere and worked up as for Ia. The crude product was chromatographed once over Al_2O_3, and then over silica gel in CH_2Cl_2. The solid fraction on crystallization from aq MeOH yielded *dl*-septicine (0·5 g), needles,

135–136°, λ_{max} 235 (sh), 284 mμ (log ε 4·20, 4·04). The sample was identical in TLC in three different solvent systems with natural septicine. (Found: C, 72·54; H, 7·49. Calc. for $C_{24}H_{29}NO_4$: C, 72·88; H, 7·39%). The IR spectrum ($CHCl_3$) of the sample was superposable with that of natural septicine, kindly provided by Dr. J. H. Russel; NMR ($CDCl_3$, 60 mc): δ 6·67 (s, 4H), 6·55 (s, 2H), 3,73 (s, 6H), 3·60 (s, 3H), 3·57 (s, 3H); mass spectrum: *m/e* 395 (M^+), 326, 295, 264, 164, 151.

Acknowledgement—We thank Dr. J. H. Russel for providing us a sample of natural septicine, Dr. S. Selvavinayakam for the microanalysis and spectra and Mr. V. Babu Rao, Mr. D. Prakash and Mr. A. R. Sidhaye for technical assistance.

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