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# SYNTHESES OF TETRAACETYL MALAXIN AND KURAMERINE

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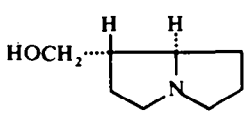
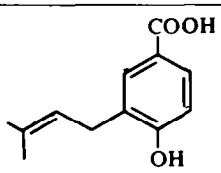
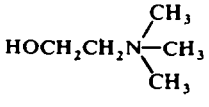
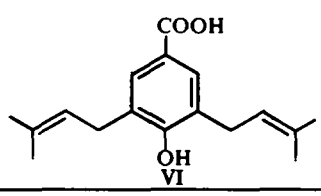
**Abstract**—Among the new Liparis alkaloids isolated from genus Liparidinae in *Orchidaceae*, tetraacetates of malaxin and kuramerine were synthesized.

SOME new alkaloids have been isolated from the plants of Liparis groups belonging to the *Orchidaceae* and their structures established.[1]

These Liparis alkaloids all consist of three moieties: (1) amino alcohol (2) alkyl substituted *p*-hydroxybenzoic acid (3) sugar moiety. The structures of malaxin (I) and kuramerine (II), isolated from *Liparis bicallosa* Schltr. or *Malaxis congesta* Comb. nov. and *Liparis Krameri* Franch et. Sav. respectively, are shown in Table 1.

TABLE 1.

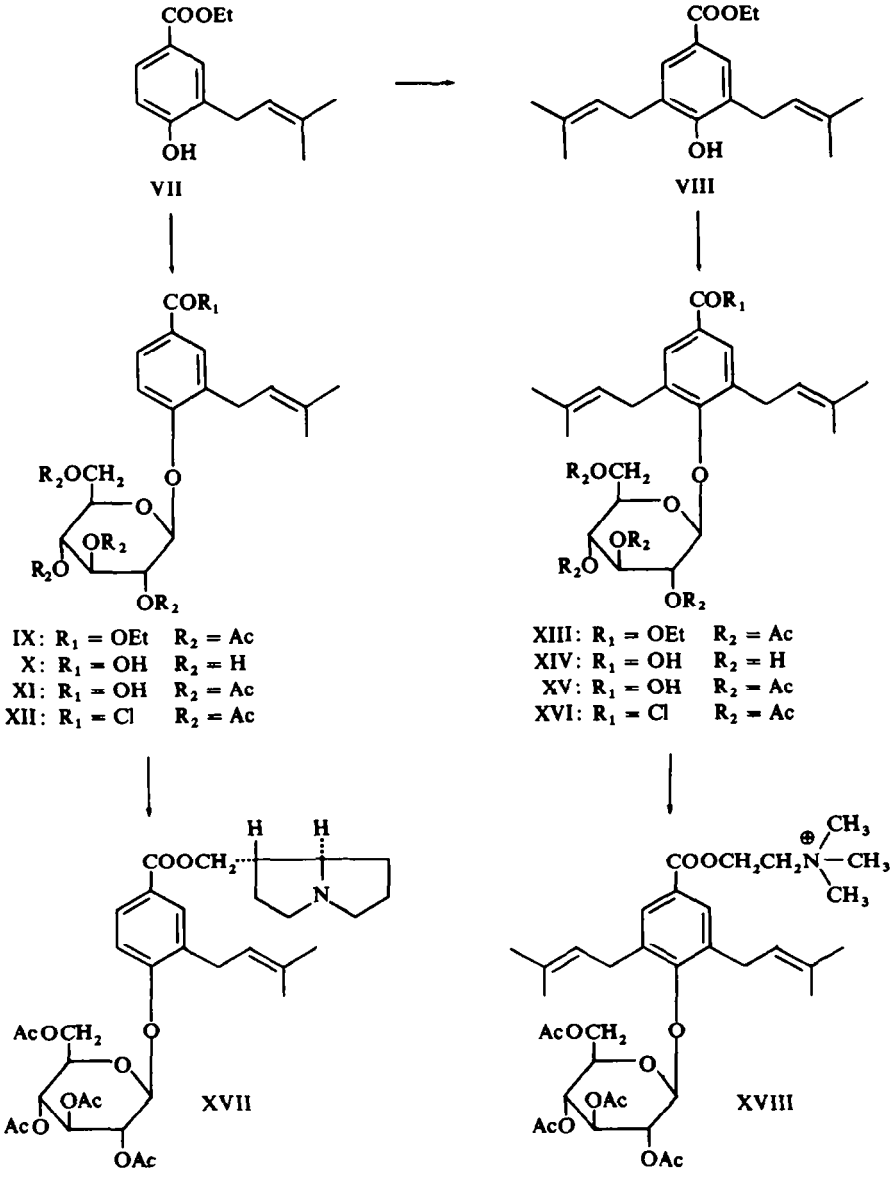
| | 1 | 2 | 3 |
|---|---|---|---|
| malaxin |  |  | D-glucose |
| I | III | V | |
| kuramerine |  |  | D-glucose |
| II | IV | VI | |

This paper deals with the synthetic confirmation of these two new alkaloids as shown in Scheme 1.

Ethyl 3-(3-methyl-2-butenyl)-4-hydroxybenzoate (VII) was prepared from the sodium salt of ethyl 4-hydroxybenzoate and 1·1 eq. of 1-bromo-3-methyl-2-butene in dry benzene at 50° by the slightly modified method of Kaczka *et al.*[2] When a mixture of sodium salt of VII and 2·0 eq. of 1-bromo-3-methyl-2-butene in dry benzene was refluxed for 4 hr, the second 3-methyl-2-butenyl substituent was easily

introduced in the opposite *ortho* position of the OH group in VII to give a 3,5-bis-(3-methyl-2-butenyl) derivative.

However, since separation of the resulting product from the reaction mixture was found to be difficult, the viscous oily product was hydrolysed with 10% NaOH aq to give the corresponding free acid which was then chromatographed on silicic acid. Thus pure 3,5-bis-(3-methyl-2-butenyl)-4-hydroxybenzoic acid (VI) was isolated and identified as natural nervogenic acid[1a] by IR and mass spectra. It was again converted into the ethyl ester (VIII) by heating with EtOH in the presence of a catalytic amount of conc. $H_2SO_4$.



Formation of glucosidic bond was achieved by the Koenigs–Knorr's method:[3] the phenolic compound VII or VIII was reacted with tetra-O-acetyl-α-D-glucopyranosyl bromide in dry quinoline in the presence of silver oxide stereoselectively to give a β-glucosidic compound, IX or XIII.

Hydrolysis of IX or XIII with 10% NaOHaq followed by acetylation gave the corresponding tetraacetate, XI or XV.

The final stages in these syntheses were performed as follows: The free acid (XI) was chlorinated with $SOCl_2$ to the acid chloride (XII) which was reacted with laburnine[4] (III) in dry pyridine to give the desired tetraacetyl malaxin (XVII).

On the other hand, tetraacetyl kuramerine (XVIII) was obtained by heating an intimate mixture of the acid chloride (XVI), prepared from XV and $SOCl_2$, and choline chloride at 160°.

Condensation products, XVII and XVIII, were both isolated as picrates which were proved to be identical with tetraacetates of malaxin and kuramerine picrates derived respectively from natural products.

## EXPERIMENTAL

All m.ps are uncorrected. The spectra were recorded on the following instruments: IR spectra, Nihonbunko IR-S; UV spectra, Perkin–Elmer 202; NMR spectra, Varian A-60; Mass spectra, Hitachi Model RMU-6D mass spectrometer. For column chromatography, Wako-Gel C-100 were used.

*Ethyl 3-(3-methyl-2-butenyl)-4-hydroxy benzoate* (VII). This product (VII) was prepared by the method of Kaczka *et al.*,[2] using benzene as the solvent and a temp of 50° for 8 hr including the time for addition of the reagent (about 3 hr at 50°). The crystalline product (ca. 100 g) obtained from ethyl *p*-hydroxybenzoate (113 g) was purified by silicic acid chromatography using *n*-hexane–$CHCl_3$ (7:3) as the eluting solvent in place of the Kaczka's treatment. Recrystallization from *n*-hexane afforded colourless needles of VII (51 g), m.p. 83–85°*; IR bands, at 3300, 1670, 1605, 1380, 1290, 1120, 1010 $cm^{-1}$ (KBr); NMR signals, at 1·37 (3H, t, $J$ = 7 c/s), 1·76 (6H, d, $J$ = 1·5 c/s), 3·40 (2H, br, d, $J$ = 7·5 c/s), 4·36 (2H, q, $J$ = 7 c/s), 5·34 (1H, br, t, $J$ = 7·5 c/s), 6·83 (1H, d, $J$ = 9 c/s), 7·84 (1H, q, $J_1$ = 9 c/s, $J_2$ = 2 c/s), 7·86 (1H, d, $J$ = 2 c/s) ppm (from internal TMS, in $CDCl_3$); mass, *m/e* 234 ($M^+$).

3,5-*Bis*-*(3-methyl-2-butenyl)-4-hydroxybenzoic acid* (VI). To a vigorously stirred suspension of freshly prepared dry sodium salt of VII (10·7 g) in dry benzene (200 ml) was added gradually 1-bromo-3-methyl-2-butene (12·5 g) at 55° (the time required for the addition was about 5 hr). Stirring was continued for additional 5 hr, the mixture was then refluxed for 4 hr and filtered. The filtrate was evaporated under reduced press to give an oil which was mixed with 10% NaOH aq. (60 ml) and heated at 100° for 1 hr. After cooling, the insoluble substance was removed by extracting with $Et_2O$. The aqueous layer was acidified with dil $H_2SO_4$ and the separated oil was taken up in $Et_2O$. The ether soln was washed with water and dried with water and dried over $Na_2SO_4$. Removal of the solvent gave an oily product which was chromatographed on silicic acid using *n*-hexane–$CHCl_3$ (1:1) as the eluent. Crystals obtained from one of the fractions were recrystallized from *n*-hexane to afford colourless prisms of VI, 3–4 g, m.p. 96–97°; IR bands, at 3500, 1670, 1605, 1325, 1290, 1260, 1185 $cm^{-1}$ (KBr); UV absorption, max at 258 mμ ($\varepsilon$ = 12000) in MeOH, 291 mμ ($\varepsilon$ = 17000) in alkaline MeOH; mass, *m/e* 274 ($M^+$), 257, 230, 219, 203, 175, 159. This product was identical with nervogenic acid (VI) by the IR and mass spectra and mixed m.p.

*Glucosidation of* VII (IX). To a soln of VII (5 g) and tetra-O-acetyl-α-D-glucopyranosyl bromide (10·6 g) in dry quinoline (20 ml), freshly prepared dry $Ag_2O$ (10 g) was slowly added with stirring at room temp. After 30 min, the reaction flask was left in a dessicator (containing $P_2O_5$ as drying agent) over night. The reaction mixture was dissolved in AcOH (70 ml) at about 10° and poured gradually into ice-water (300 ml) with stirring. The ppt collected was washed with water and taken up in $CHCl_3$. The $CHCl_3$ soln was decolorized with norit-A and filtered. Evaporation of the solvent under reduced press gave an oil which was chromatographed on silicic acid. The first fraction eluted from *n*-hexane–$CHCl_3$ (1:4) was recrystallized from *n*-hexane to give colourless needles of IX, 7·2 g, m.p. 105–107°; IR bands, at 1755, 1715, 1605, 1495, 1380, 1230, 1040 $cm^{-1}$ (KBr). (Found: C, 59·62; H, 6·50. $C_{28}H_{36}O_{12}$ requires: C, 59·56; H, 6·43%).

* Kaczka reported at 70–72°.

*Alkaline hydrolysis of* IX. A soln of IX (1·2 g) in EtOH (5 ml) containing 2N NaOH (5 ml) was refluxed for 1·5 hr. After cooling, the reaction mixture was acidified with 0·5N HCl and kept at 0° for several hr. The precipitated crystalline product was recrystallized from AcOEt to give colourless needles of X, 690 mg, m.p. 124–126°; $[\alpha]_D^{20} = -51°$ (*c* 2, MeOH); IR bands, at 3400, 1690, 1605, 1500, 1250, 1130, 1100, 1075, 1040, 1015 $cm^{-1}$ (KBr); UV absorption, max at 251 mμ ($\varepsilon = 14500$) in MeOH, 244 mμ ($\varepsilon = 13000$) in alkaline MeOH. The product was proved to be malaxinic acid by IR spectra.

*Acetylation of* X. To a soln of X (1 g) in dry pyridine (5 ml) was added $Ac_2O$ (3 ml) at 10° with stirring and the reaction temp was gradually raised to room temp. After standing over night, the reaction mixture was poured into ice-water and stirred vigorously for 2 hr. The ppt was collected and washed with water. Recrystallization from 95% EtOH gave colourless crystals of XI, 1·25 g; m.p. 160–161°; IR bands, at 1760, 1690, 1495, 1380, 1230, 1070, 1040 $cm^{-1}$ (KBr). (Found: C, 58·43; H, 6·04. $C_{26}H_{32}O_{12}$ requires: C, 58·20; H, 6·01%).

*Tetraacetylmalaxin* (XVII). A mixture of XI (100 mg) and $SOCl_2$ (100 mg) was heated under reflux. After 20 min, excess $SOCl_2$ was evaporated under reduced press and the residual solid was dissolved in pyridine (2 ml). To this, a soln of laburnine (25 mg) in pyridine (1 ml) was added under cooling and the mixture was kept over night at room temp. The solvent was evaporated under reduced press to give viscous oily product which was poured into ice-water.

The insoluble material was dissolved in a small amount of MeOH (about 1 ml) and precipitated by addition of an excess picric acid aq to afford the picrate of XVII. Recrystallization of the picrate from 80% EtOH gave yellow needles of XVII picrate, 64 mg, m.p. 96–97°. (Found: C, 52·17; H, 4·99; N, 6·06. $C_{34}H_{45}O_{12}N—C_6H_3O_7N_3 \cdot 2H_2O$ requires: C, 51·94; H, 5·23; N, 6·01%). This product was proved to be tetraacetyl malaxin by comparison of IR spectra of the picrate.

*Preparation of glucoside* (XIV). A soln of VI (5 g) in absolute EtOH (50 ml) containing 5 drops of conc $H_2SO_4$ was refluxed for 4 hr. The reaction mixture was cooled and neutralized with solid $NaHCO_3$. Evaporation of the solvent yielded a viscous oil which was dissolved in $Et_2O$. The ether soln was washed with water and then dried over $Na_2SO_4$, followed by concentration to give an oily product of VIII, 4·0 g, mass, *m/e* 302 ($M^+$) (from high resolution of mass spectrum. Found: 302·1955. $C_{19}H_{26}O_3$ requires: 302·1882), 287, 285, 273, 257, 247, 231, 191, 173. This product was mainly one spot on TLC. The glucosidation of VIII was carried out by the same way as in the case of IX. The reaction of VIII (3·5 g) with tetra-O-acetyl-α-D-glucopyranosyl bromide (7·5 g) and $Ag_2O$ (8·0 g) in dry quinoline (20 ml) afforded 2·3 g pure crystalline XIII, m.p. 133–135°; IR bands, at 1755, 1725, 1605, 1380, 1230, 1075, 1045 $cm^{-1}$ (Nujol).

Alkaline hydrolysis of the product gave XIV in quantitative yield, m.p. 103–105°; $[\alpha]_D^{20} = -17°$ (*c* 2, MeOH); IR bands, at 3350, 1690, 1605, 1275, 1180, 1100, 1075, 1040, 1010 $cm^{-1}$ (KBr); UV absorptions, max at 243, 278, 288 mμ ($\varepsilon = 14000, 2300, 2000$) in MeOH, 235 (shoulder), 278, 288 mμ ($\varepsilon = 12500, 2300, 2000$) in alkaline MeOH. Physical data mentioned above were completely identical with natural kurameric acid.

*Acetylation of* XIV. The soln of XIV (200 mg) in dry pyridine (2 ml) was mixed with $Ac_2O$ (1 ml) and the mixture was kept at room temp over night. The reaction mixture was poured into ice-water (30 ml) and the ppt was recrystallized from 80% EtOH as colourless needles of XV, 220 mg, m.p. 170–172°; IR bands, at 1760, 1695, 1605, 1380, 1230, 1070, 1045 $cm^{-1}$ (KBr). (Found: C, 60·03; H, 6·42. $C_{31}H_{40}O_{12} \cdot H_2O$ requires: C, 59·79; H, 6·48%).

*Tetraacetyl kuramerine* (XVIII). An intimate mixture of XVI (100 mg) and choline HCl (45 mg) was heated quickly up to 160°. After evolution of HCl gas was ceased (about 20 min), the reaction mixture was cooled to room temp. The resulting cake was washed several times with $Et_2O$ and the ether washings discarded by decantation. The residue was dissolved in 1 ml MeOH and to the methanolic soln was added aqueous picric acid. The precipitated picrate was recrystallized from 80% EtOH to give yellow needles of XVIII-picrate, 70 mg, m.p. 150–151°. (Found: C, 53·96; H, 5·84; N, 6·01. $C_{36}H_{52}O_{12}N—C_6H_2O_7N_3 \cdot H_2O$ requires: C, 53·83; H, 6·02; N, 5·98%).

This was proved to be tetraacetyl kuramerine by comparison of the IR spectra of the picrates.

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