THE DITERPENOID ALKALOIDS OF *DELPHINIUM TATSIENENSE* FRANCH

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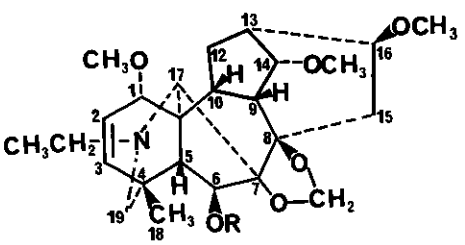
Abstract: From the roots of *Delphinium tatsienense* Franch (Ranunculaceae) two new and six known alkaloids have been isolated. The isolation and structure determination of deacetylambiguine (2) and a novel C_{19}-diterpenoid alkaloid designated as tatsiensine (1) are described. The structure of tatsiensine was established on the basis of spectroscopic data and correlation with delpheline (12). Deacetylambiguine (2) has been isolated for the first time from a natural source. The known alkaloids that were isolated are the C_{19}-diterpenoid alkaloids, browniine (3), delcosine (4), lycoctonine (8), and the C_{20}-alkaloids ajaconine (6), hetisine (7) and hetisinone (5).

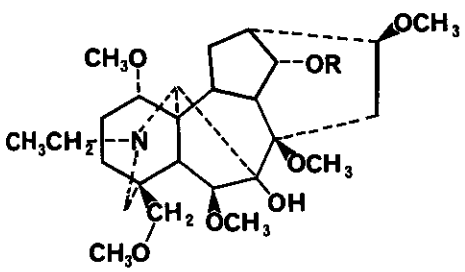
In continuation of our earlier studies on the diterpenoid alkaloids of Chinese Ranunculaceae plants[1], we wish to report in this communication the chemical investigation of the roots of *Delphinium tatsienense* Franch. No work has been reported on the chemical constituents of this plant.

The roots were extracted with 90% ethanol and the crude alkaloid fractions were isolated at pH 8 (E_1) and pH-12 (E_2 and E_3). Chromatographic separation of E_1 gave new alkaloids designated as tatsiensine (1), and deacetylambiguine (2)[2], β-sitosterol, and three known alkaloids which were identified as browniine[3] (3), delcosine[4] (4) and hetisinone[5] (5).



1 R = Ac **Tatsiensine**

11 R = H

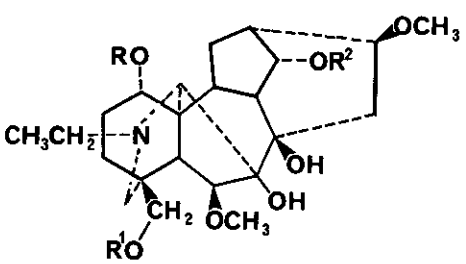


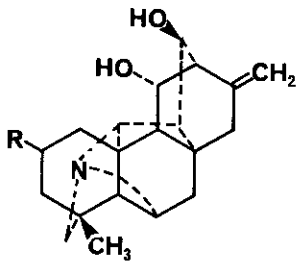
2 R = H

2a R = Ac

+ On leave from the University of Warsaw, Warsaw, Poland.

Deacetylambiguine (2) was prepared earlier by the hydrolysis of ambiguine (2a) which was isolated from the plant, *Consolida ambigua*.[2] This is the first report of the occurrence of 2 from a natural source. Ambiguine has not been chemically correlated with any lycoctonine-type alkaloid and therefore the configuration of the methoxyl group at C(1) has not yet been firmly established. However, since all the known lycoctonine-type alkaloids have been shown to have the C(1)-methoxyl group in the α-configuration, compounds (2) and (2a) in all probability have the C(1)-methoxyl group α-oriented.[3,6†]





3 R = R¹ = CH₃ ; R² = H

4 R = R² = H ; R¹ = CH₃

8 R = R² = CH₃ R¹ = H

5 R = =O

7 R = --OH

The crude alkaloids E_2 and E_3 yielded on chromatographic separation the C_{19}-diterpenoid alkaloid lycoctonine[6] (8)[3a,6] and the C_{20}-alkaloids ajaconine[7] (6) and hetisine[8] (7). The ^{13}C nmr spectral data for compounds (5) and (7) are recorded in the Experimental Section.

Tatsiensine was isolated as an amorphous compound having $[\alpha]_D^{25}$ + 17.4°. Its molecular formula $C_{27}H_{39}NO_7$ was deduced from the mass spectral, ^1H nmr, and ^{13}C nmr spectral data. The ^1H nmr spectrum (for details see the Experimental Section) indicated the following functional groups in the molecule: one tertiary methyl, an ethyl group attached to a nitrogen atom, a methylenedioxy group, an O-acetate and three methoxyl groups. Tatsiensine is unsaturated as shown by two olefinic protons at δ 5.62(d) and 5.91(d,d). On biogenetic considerations, tatsiensine was assumed to be a C_{19}-or C_{20}-diterpenoid alkaloid. Considering a total of eight carbons due to three methoxyls, an acetate, an ethyl and a methylenedioxy group, tatsiensine should be a C_{19}-diterpenoid alkaloid. A methylenedioxy group located at C(7)-C(8) is present only in lycoctonine-type alkaloids.[9] Tatsiensine should therefore possess an oxygen function at C(6). This is present as an acetoxyl group as is evident from the chemical shift of the C(6)-proton in the ^1H nmr spectrum (δ 5.39, br s). This proton moves upfield and appears at δ 4.25(s) in the hydrolysis product (*vide infra*). The C(6)-proton has negligible coupling (J = <1 Hz) with the C(5)-proton indicating that the acetoxyl group at C(6) in tatsiensine should be β-oriented. The $J_{5,6}$ coupling is very small and not resolved, in agreement with the torsional angle of ~ 92° in the above conformation. Similarly, the

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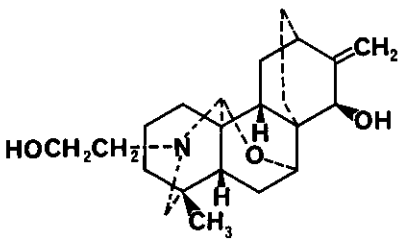
† Dr. S. Sakai has informed us (10th April 1982) that as shown in the diagram in ref. 3[a], the conversion of gigactonine into delphatine has never been achieved. We wish to make this correction by deletion of the indicated arrow.

C(6α)-proton situated on an acetoxyl group appears as a broad singlet at δ 5.5 in dictyocarpine and deltaline. The ^1H nmr spectrum also indicated that tatsiensine contains an N-ethyl group and a tertiary methyl at the C(4)-position.

The problem of locating three methoxyl groups and an olefinic double bond in tatsiensine remains. All three methoxyls are situated on methylenes, since the ^{13}C nmr spectrum (see table) shows doublets at 83.6, 80.2 and 81.9 ppm, due to carbons bearing methoxyl groups. As almost all lycoctonine-type alkaloids contain an oxygen function at C(14) and C(16), a partial structure (**9**) can be written for tatsiensine. No diterpenoid alkaloids have been found that are substituted with an



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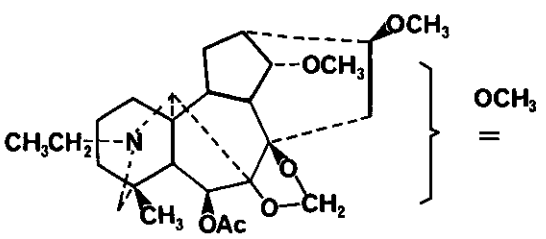

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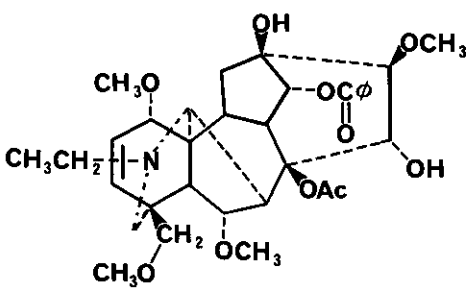
oxygen function at the C(2)- and C(12)-positions. Secondly, only the aconitine-type of alkaloids are oxygenated at the C(3)- and/or C(15)-positions. The third methoxyl group should therefore be placed at C(1). In all probability this has an α-configuration, as in other lycoctonines.[3a] The ^1H nmr and ^{13}C nmr spectral data indicated a unique structure (**1**) with the olefinic double bond at the C(2)-C(3) position.

The ^{13}C nmr spectrum of tatsiensine (**1**) (see Table 1) shows C(1), C(2), and C(3) at 83.6, 124.6 and 137.4 ppm, respectively. These values are close to those reported for these carbons in anhydroaconitine (**10**), viz: C(1): (83.9), C(2): (125.3), and C(3): (137.6).[10]



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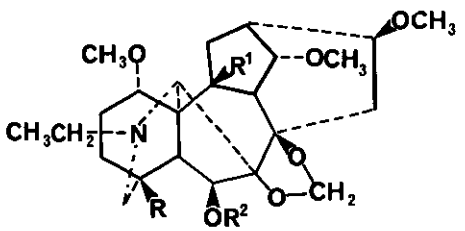

12 R = CH_3 ; R^1 = R^2 = H ; **Delpheline**

13 R = CH_2OCH_3, R^1 = R^2 = H ; **Delcorine**

14 R = CH_3 ; R^1 = OH ; R^2 = Ac ; **Deltaline**

In order to confirm the structure (**1**) assigned for tatsiensine, it was hydrolyzed in methanolic

potassium hydroxide to afford in quantitative yield deacetyltatsiensine (**11**), $C_{25}H_{37}NO_6$, m.p. 236-238°C. The ^1H nmr spectrum (see Experimental Section) and the ^{13}C nmr spectral values (see Table) are in agreement with the proposed structure. Hydrogenation of **11** in the presence of 10% Pd/c gave a reduction product in a yield of 90%. Purification on thick layer plate afforded **12**, m.p. 213-215°C (M^+ m/e 449), $[\alpha]_D$ -26.8°, identical in all respects with synthetic delpheline. A sample of natural delpheline was not available, but was prepared by reaction of deltaline (**14**) with thionyl chloride and treatment of the resulting product with lithium aluminium hydride.[11] ^{13}C nmr spectral data for compounds **1**, **11**, **12** and delcorine[12] (**13**), which is structurally similar to delpheline (**12**), are given in Table 1.

Tatsiensine is the second example of a diterpenoid alkaloid having a double bond between C(2) and C(3). Besides takaonine[13] two other unsaturated pyrodelphinine-type alkaloids are known: falaconitine and mithaconitine[14], possessing unsaturation between C(8) and C(15). Probably these are

TABLE 1. ^{13}C nmr chemical shifts in ppm are given downfield from TMS; solvent - $CDCl_3$

	Compound			
Carbons	**1**	**11**	**12**	**13**
C(1)	83.6	83.6	83.1	83.1
C(2)	124.6	124.6	26.9	26.4
C(3)	137.4	137.8	36.9	31.8
C(4)	34.8(s)	34.6	33.9	38.1
C(5)	54.8	55.9	55.5	52.6
C(6)	78.5	79.5	79.3	78.9
C(7)	91.3(s)	92.3	92.8	92.7
C(8)	84.3(s)	84.9	84.6	83.9
C(9)	47.4	47.4	47.9	48.1
C(10)	40.0	40.2	40.3	40.3
C(11)	50.8(s)	50.8	50.4	50.2
C(12)	28.3	27.9	28.1	28.1
C(13)	38.7	38.4	37.9	37.9
C(14)	80.2	80.7	81.9	82.5
C(15)	34.2	34.0	33.5	33.3
C(16)	81.9	82.3	82.9	81.8
C(17)	61.5	61.1	63.7	63.9
C(18)	23.2	23.1	25.3	78.9
C(19)	57.6	58.3	57.3	53.7
N-CH_2	48.7	48.9	50.2	50.7
CH_3	13.0	12.9	13.9	14.0
O-CH_2-O	93.4	93.3	92.8	92.9
C(1)'	55.9	55.9	56.2	55.5
C(14)'	57.6	57.7	57.8	57.8
C(16)'	56.2	56.2	56.8	56.3
C(18)'	-	-	-	59.6
C(6)-O-C=O	169.9(s)	-	-	-
CH_3	21.7	-	-	-

*Values given for primed carbons refer to chemical shifts for methoxyls.

biogenetic precursors of veratroylpseudaconitine and indaconitine or are artifacts formed during isolation. However, since none of the lycoctonine-type of alkaloids has an oxygen function at C(3), the formation of tatsiensine appears to be of much biogenetic interest.

EXPERIMENTAL

M.p.s are corrected. Spectra were recorded on the following instruments: IR, Perkin-Elmer PE-599; ^{1}H nmr, Perkin-Elmer EM-390, 90 MHz; ^{13}C nmr, JEOL FT Models FX-60 and FX-90 Q; and mass-spectra, Finnegan Quadrupole 4023.

Extraction and separation. - Air dried and powdered roots of *D. tatsienense*† (10.9 kg) were extracted with 90% ethanol (3x10 l) by cold percolation. The solvent was evaporated *in vacuo* to give approx. 1.5 kg of concentrates. Part of this residue (500 g) was dissolved in 1.5% aqueous sulfuric acid (1 l) and extracted with a 1:1 mixture of CH_2Cl_2: $CHCl_3$ (6 x 400 ml). The acidic layer was basified (pH-8) with saturated Na_2CO_3 solution and extracted with $CHCl_3$ to afford a crude alkaloid residue (E_1; 16 g). The aqueous layer was made alkaline (pH-12) with sodium hydroxide solution and extracted with $CHCl_3$ (5 x 300 ml) to give a crude alkaloid fraction (E_2; 3 g). The organic layer from the first extraction was again extracted with 1.5% sulfuric acid and, after basification with sodium hydroxide solution, the solution was extracted with $CHCl_3$ (5 x 100 ml) to give another alkaloid fraction (E_3; 2.3 g).

Fraction E_1 (15 g) was chromatographed on an alumina column (Act. III; 700 g) and eluted with toluene containing increasing amounts of methanol (0.4 - 2.5%). Fractions (500 ml each) were collected and the chromatographic separation was monitored by t.l.c.

Isolation of tatsiensine (1), β-sitosterol, and deacetylambiguine (2). - Fractions 28-31 (toluene: 0.4% MeOH) were combined to give a residue (1.6 g) which was chromatographed over alumina (Act. III; 40 g) and eluted with toluene containing (5 to 50%) ether. Fractions (250 ml) were collected. From fractions 2 and 3 (5 and 10% ether), a mixture of three compounds was obtained. This mixture was shaken with 5% sulfuric acid and extracted with CH_2Cl_2. The solvent was removed from the organic layer and the residue was crystallized from ethanol to afford colorless needles (72 mg), m.p. 139-140°C; $[\alpha]_D^{20}$ - 38° ($CHCl_3$), that were identical with β-sitosterol by comparison of the m.m.p., t.l.c. and ir with those of an authentic sample. The acidic solution on basification with dilute sodium hydroxide and extraction with CH_2Cl_2 afforded a gum which showed two compounds on t.l.c. It was separated on a preparative t.l.c. plate (1 mm thick layer Al_2O_3) to give tatsiensine (1) as an amorphous product that showed a single spot on t.l.c.; $[\alpha]_D^{25}$ + 17.4° (c 0.3, EtOH); ir (nujol) 1740, 1715, 1455, 1370, 1360, 1240, 1220, 1190, 1120, 1075, 1040, 1010, 955 and 930 cm^{-1}. Its ^{1}H nmr spectrum (90 MHz; $COCl_3$, TMS) displayed the following signals: (δ) 1.0 (s, 3H, CH_3-18), 1.08 (3H, t, J=7 Hz, CH_2-CH_3), 3.2 (1H, d, J=4 Hz, H-1), 2.05 (3H, s, $OCOCH_3$), 3.3, 3.35, 3.42 (3H each, s, OCH_3), 3.69 (2H, m, H-14, H-16), 4.93 (2H, br s, O-CH_2-O), 5.39 (1H, br s, H-6α), 5.62 (1H, d, $J_{2,3}$ = 10 Hz, H-3), 5.91 (1H, dd, $J_{2,3}$ = 10 Hz; $J_{1,2}$ = 4 Hz, H-2). Its mass spectrum (MS) showed the following peaks: m/z (M^+ + 1, 490, 60%), 489 (M^+, 27), 476(26), 458(48), 446(95), 430(74), 400(24), 361(23) and 111(100). For the ^{13}C nmr spectrum see Table 1.

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† The roots were collected in Giao-jia (Yunnan) China and the plant was authenticated. A herbarium specimen of *D. tatsienense*, voucher specimen No. 151476, is deposited in the Herbarium of the Department of Botany, University of Georgia, Athens, Ga. 30602.

The other compound separated on the preparative t.l.c. plate was deacetylambiguine (**2**) (amorphous, 100 mg), $[\alpha]_D^{25}$ + 36.6° (c 0.38, EtOH); MS: m/z 481 (M^+, 10%), 480(15), 466(15), 450(100), 434(16), 418(16). Its ^{13}C nmr spectrum was identical with the values reported earlier for synthetic deacetylambiguine.[2]

Isolation of browniine (**3**). - Fractions 41-44 (toluene: 0.8% MeOH) were combined (1.05 g), rechromatographed on alumina (Act. III; 100 g) and eluted with CH_2Cl_2: ether (1:1) containing increasing percentages of methanol. Fractions (500 ml each) were collected and fraction 6 (elution with 1.8% MeOH) gave a foam (0.38 g), $[\alpha]_D^{25}$ + 40.2° (c 2.5, EtOH), which was identified as browniine (**3**) by comparison of the ^{13}C nmr values with those reported.[3]

Isolation of delcosine (**4**). - Fractions 52-61 (toluene: 1.3% MeOH) were pooled (2.5 g), chromatographed on a short column, and crystallized from acetone to afford delcosine (**4**, 1.5 g), m.p. 197-198°C; $[\alpha]_D^{20}$ + 56.2° (c 1.94, $CHCl_3$); ir (nujol) 3520, 3475, 3350, 1465, 1400, 1380, 1350, 1320, 1300, 1270, 1220, 1190, 1165, 1135, 1108, 1050, 1035, 1010, 1000, 970, 950, 875, 856, 810 cm^{-1}. ^1H nmr ($CDCl_3$, TMS) showed the following signals: (δ) 1.11 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.34, 3.37, 3.37 (3H each, s, $O\underline{CH_3}$). MS: m/z 453 (M^+, 5%), 438(40), 420(40), 111(30), 98(40), 71(50), 58(100). The m.m.p., ir, and ^{13}C nmr spectrum were identical with those of an authentic sample.

Isolation of hetisinone (**5**). - Fractions 62-70 (toluene: 2% MeOH) (1.06 g) on crystallization from acetone afforded colorless plates (0.45 g), m.p. 267-269°C; its m.m.p., t.l.c., and ir spectrum were identical with those of an authentic sample. The ^{13}C nmr spectrum (CD_3OD, TMS) showed the following signals: (ppm) 214.3 (s, C-2), 145.4 (s, C-16), 108.2 (t, C-17), 75.6, 71.5, 70.3, 65.2, 64.4, 60.4, 55.7 (s, C-10), 55.0, 52.0, 50.8, 49.9, 45.2, 44.4 (s, C-8), 42.4 (s, C-4), 36.1, 33.9, 28.7 (q, C-18).

The crude alkaloid fraction E_2 (1.3 g) was chromatographed over alumina (Act. III; 90 g) and eluted with toluene containing 2-4% methanol:

Isolation of ajaconine (**6**) and hetisine (**7**). - Elution with toluene containing 2% methanol (750 ml) gave on crystallization ajaconine (**6**; 215 mg); m.p. 165°C; $[\alpha]_D^{26}$ - 116° (EtOH); MS: m/z 359 (M^+, 10%), 342(5), 328(100), 316(15), 300(20), 288(15), 195(25), 165(30). Comparison of the m.m.p., ir and ^{13}C nmr spectra[7] with those of an authentic sample of ajaconine showed them to be identical.

The fraction (500 ml) obtained by elution with toluene: 4% methanol, on crystallization afforded hetisine (**7**, 820 mg); m.p. 259°C; MS: m/z 329 (M^+, 100%), 312(65), 300(20), 294(15), 283(45), 260(10), 217(15). Comparison of the m.m.p., t.l.c. and ir spectrum with those of an authentic sample of hetisine showed them to be identical. Its ^{13}C nmr spectrum ($CDCl_3$; TMS) displayed the following signals: (ppm) 146.5 (s, C-16), 107.4 (t, C-17), 76.1 (d), 71.9 (d), 68.1 (d), 66.5 (d), 64.2 (d), 63.4 (t), 61.6 (d), 55.6 (d), 52.5 (d), 50.9 (d), 50.7 (s, C-10), 43.5 (s, C-8), 39.0 (t), 36.6 (s, C-4), 36.6 (t), 34.3 (t), 30.3 (q, C-18).

Isolation of lycoctonine (**8**). - The mother liquors in the separation of compounds (**1**) and (**2**) were combined with the crude alkaloid E_3 and the combined mixture (2 g) was chromatographed on alumina (Act. III, 35 g). The column was eluted with toluene containing increasing percentage (1-50%) of ether. Fractions (400 ml each) were collected and fraction 11 (toluene + 50% ether + 1% MeOH) gave a crystalline solid (120 mg) identified as lycoctonine (**8**); m.p. 126-127°C; $[\alpha]_D^{20}$ +

52.8° (c 0.96, EtOH). Comparison of the m.m.p., ir, and ^{13}C nmr spectrum with those of an authentic sample of lycoctonine showed them to be identical.

Deacetyltatsiensine (**11**). - Tatsiensine (**1**; 30 mg) was dissolved in methanol (10 ml) and a solution of 100 mg of KOH in 5 ml methanol was added and left for 16 h. The solvent was evaporated and the residue was diluted with water and extracted with CH_2Cl_2. The residue on crystallization from ethanol afforded colorless plates (**11**; 28 mg), m.p. 236-238°C; $[\alpha]_D^{25}$ + 28.8° (c 0.34, abs. EtOH). MS: m/z 447 (M^+, 10%), 432(6), 416(3), 402(5), 374(5), 166(8), 141(15), 111(20), 58(100). (Calc. for $C_{25}H_{37}NO_6$, M.W. 447). ir (nujol) 3465, 1460, 1378, 1342, 1322, 1310, 1295, 1259, 1220, 1200, 1190, 1170, 1158, 1130, 1110, 1080, 1070, 1012, 1000, 985, 965, 932 and 930 cm^{-1}. ^1H nmr ($CDCl_3$, TMS): (δ) 1.04 (3H, s, CH_3-18), 1.09 (3H, t, J = 7 Hz, CH_2CH_3), 3.1 (1H, d, J = 2 Hz, H-1), 3.32, 3.41, 3.47 (3H each, s, OCH_3), 3.69 (2H, m, H-14, H-16), 4.25 (1H, s, H-6α), 5.1, 5.13 (2H, each s, O-CH_2-O), 5.68 (1H, d, $J_{2,3}$ = 10 Hz, H-3), 5.94 (1H, dd, $J_{2,3}$ = 10 Hz, $J_{1,2}$ = 4 Hz, H-2). For the ^{13}C nmr spectrum refer to Table 1.

Hydrogenation of **11** to obtain the compound (**12**). - Deacetyltatsiensine (**11**, 25 mg) was dissolved in methanol (6 ml) and after addition of 10% Pd/C (5 mg) the mixture was hydrogenated at atmospheric pressure with magnetic stirring. After 4 h, the solution was filtered, the solvent was evaporated and the residue (25 mg) was chromatographed on a thick-layer (0.25 mm) alumina plate. The homogeneous band gave on crystallization from methanol-hexane, colorless plates (**12**, 12 mg), m.p. 213-215°C, $[\alpha]_D^{26}$ - 26.8° (c 0.27, EtOH); ^1H nmr spectrum ($CDCl_3$, TMS) (δ) 0.93 (3H, s, CH_3-18), 1.03 (3H, t, J = 7.5 Hz, CH_2CH_3), 3.25, 3.35, 3.41 (3H each, s, OCH_3), 3.66 (2H, m, H-14, H-16), 4.18 (1H, s, H-6α), 5.01, 5.08 (2H, each s, O-CH_2-O).

Compound **12** was identical with delpheline as shown by its m.m.p., t.l.c. and ir spectral comparison.

Preparation of delpheline (**12**) from deltaline (**14**). - Deltaline (**14**; 150 mg) was dissolved in benzene (5 ml) and treated with freshly distilled thionyl chloride (1 ml) for 10 h. The solvent was removed, the crude chloride was suspended in ether (150 ml) and refluxed with lithium aluminium hydride (250 mg) for 16 h. The mixture was poured over crushed ice and extracted with ether to afford a solid (100 mg) which showed at least seven spots on t.l.c. (Al_2O_3; $CHCl_3$: 5% MeOH). This was separated on a 3mm thick plate of Al_2O_3 and eluted with $CHCl_3$. The band (Rf 0.2) was cut and extracted with $CHCl_3$ - 10% MeOH to afford a crystalline solid (8 mg), m.p. 210-212°C (reported[11], m.p. 216-219°C).

ACKNOWLEDGMENT. The authors express their appreciation to Dr. S. K. Srivastava for preparation of a reference sample of delpheline from deltaline. We also thank Professor R. C. Cookson for a sample of delphelamone.

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Received, 22nd March, 1983