67. Delphinium *Alkaloids. Part IV. The Alkaloids of the Seeds of* Delphinium ajacis.

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From the alkaloids of the seeds of *Delphinium ajacis* five crystalline alkaloids amounting to approximately 20% of the total alkaloids of the seeds have been isolated, *viz.*, ajacine, ajaconine, and bases for the present designated " base B," " base C," and " base D."

As in the case of the total alkaloids of the seeds of *Delphinium staphisagria* (Jacobs and Craig, *J. Biol. Chem.*, **1939**, **127**, 361), so in that of the total alkaloids of the seeds of *Delphinium ajacis*, only a portion has been obtained in crystalline form. From the seeds of *D. ajacis*, Keller and Völker (*Arch. Pharm.*, **1913**, **251**, 209) isolated two crystalline alkaloids, which they named ajacine and ajaconine. Recently, Hunter (*Pharm. J.*, **1943**, **150**, 82, 95) briefly reported the isolation of four crystalline alkaloids, *viz.*, ajacine, $C_{32}H_{44}O_8N_2,2H_2O$, ajaconine, $C_{21}H_{31}O_3N$, a new alkaloid ajacinine, $C_{22}H_{37}O_6N$, and an unnamed base, but gave no details of their properties or analyses.

In the present investigation five crystalline alkaloids have been isolated, including ajacine and ajaconine, the others being for the present called " *base B*," " *base C*," and " *base D*," as one of them, possibly " base C," may prove to be identical with Hunter's ajacinine.† Ajacine has been shown to be acetylanthranoyllycoctonine, $C_{34}H_{46}O_9N_2,2H_2O$ (Goodson, J., 1944, 108). It was then assumed that the alkyl group attached to nitrogen was a methyl group, but as shown by Rabinovich and Konovalova [*J. Gen. Chem. U.S.S.R.*, **1942**, **12**, 231 (English Summary 328)], in the cases of delphamine from species of *Delphinium* and condelphine from *Delphinium confusum*, var. Pop., the alkyl group of ajacine is now found to be an ethyl group. " Base B," $C_{26}H_{39}O_8N$, and " base C," $C_{24}H_{37}O_7N$, also contain an ethylimino-group, both contain three methoxy-groups, and " base B " on hydrolysis gives " base C " and acetic acid. " Base C " may be a demethyllycoctonine, in which case the relationship of the three alkaloids may be expressed by the following formulæ :

Lycoctonine	$C_{19}H_{19}NEt(OMe)_4(OH)_3$	" Alkaloid B "	$C_{19}H_{19}NEt(OMe)_3(OH)_3{\cdot}OAc$
Ajacine	$C_{19}H_{19}NEt(OMe)_4(OH)_2(O{\cdot}CO{\cdot}C_6H_4{\cdot}NHAc)$	" Alkaloid C "	$C_{19}H_{19}NEt(OMe)_3(OH)_4$

Attempts, however, to prove lycoctonine to be a methyl derivative of " base C " by their conversion into the same hydroxy-compound by demethylation or into the same heptamethoxy-compound by complete methylation were unsuccessful.

Potentiometric titration of ajaconine, which is an *N*-methyl base, gave an equivalent of 362, which is in better accord with the formula $C_{22}H_{33}O_3N$ than with Hunter's formula $C_{21}H_{31}O_3N$. It may be that the formula should be doubled, as the figure obtained for methylimino is only half that required for one methylimino-group in a compound of the formula $C_{22}H_{33}O_3N$. The formula of the *hydriodide* of " base D " is provisionally given as $C_{48}H_{66}O_{12}N_2,HI$; the free base appears to be formed from it by the loss of the elements of a molecule of water in addition to one of hydrogen iodide.

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* Obtained by diffusion of acetone-extracted crepe rubber into light petroleum.

† Since the submission of this paper for publication a contribution on the same subject has been made by Hunter (*Quart. J. Pharm.*, 1944, **17**, 302) in which it is seen that the properties of his ajacinine differ somewhat from those of " base C " described above. Direct comparison of a specimen of ajacinine kindly supplied by Dr. Matthew V. Hunter proves it not to be identical with " base C."

EXPERIMENTAL.

The m. p.'s are corrected.

Total Alkaloids.—By the method described below, 31·8 g. of total alkaloids (1·06%) were obtained from 3 kg. of seeds of horticultural origin.

Isolation of Alkaloids.—The crushed seeds (39 kg.) were percolated with 90% alcohol (260 l.). The percolate, concentrated until most of the alcohol had been removed, separated into two layers. The oily layer was extracted three times with 10% hydrochloric acid, and the acid solution added to the main aqueous layer. The united solutions were treated with excess of sodium bicarbonate and extracted twice with an equal volume of chloroform to give the weak bases. The aqueous solution was treated with 25% sodium hydroxide solution and extracted twice with an equal volume of chloroform, yielding the strong bases. The chloroform solutions were shaken with sufficient N-hydrochloric acid to render the mixtures slightly acid to Congo-red paper. In the case of the chloroform solution of the weak bases, both the aqueous layer (A) and the chloroform layer (B) contained hydrochlorides of bases. In the case of the chloroform solution of the strong bases, the hydrochlorides of the bases passed almost completely into the aqueous layer (C). The aqueous layer (A), containing 103 g. of alkaloids (or 0·264% of the seeds), was treated with excess of sodium bicarbonate and extracted six times with an equal volume of ether. The concentrated ethereal solution on long standing deposited 15·1 g. of crystals of crude " base B " (0·0387% of the seeds). The aqueous liquor was extracted three times with an equal volume of chloroform and the alkaloids thus removed were fractionated by shaking the chloroform solution with small quantities of N-hydrochloric acid. The bases, regenerated from the fractions of the hydrochloride, having rotations between $[\alpha]_D$ + 42° and + 50°, on crystallisation from alcohol gave 5·11 g. of crude crystalline " base C " (0·0131% of the seeds).

The chloroform layer (B) was evaporated to dryness, and the residue treated with very dilute hydrochloric acid. The aqueous solution, after separation from tar and purification with charcoal, contained 164 g. of alkaloids (0·421% of the seeds). It was rendered alkaline with sodium bicarbonate and extracted with ether. The ethereal solution on concentration deposited 40·5 g. of crude crystalline ajacine (0·1038% of the seeds) and on further concentration gave 5·8 g. of crude, crystalline " base B " (0·0148% of the seeds). The bases from the mother-liquor were dissolved in alcohol and neutralised with N-hydriodic acid. On keeping in the ice-chest, 7·77 g. (0·0199% of the seeds) of crude crystalline hydriodide of " base D " separated.

"*Base B.*"—The *base*, purified by recrystallisation from alcohol, gave anhydrous crystals, m. p. 195° (sinters at 193°), $[\alpha]_D^{17^\circ}$ + 34·0° (c = 1 in dry alcohol), $[\alpha]_D^{17^\circ}$ + 0·5 (c = 2 in N/5-hydrochloric acid) (Found: C, 63·1; H, 8·4; N, 3·2; OMe, 18·3; NEt, 7·7; Ac, 7·2; equiv., by potentiometric titration, 493. $C_{26}H_{39}O_8N$ requires C, 63·3; H, 8·0; N, 2·8; 3OMe, 18·9; NEt, 8·7; Ac, 8·7%; equiv., 493). The aurichloride crystallised from alcohol in light yellow, six-sided plates of the *trihydrate*, m. p. 205° (decomp., sinters at 203°) (Found: loss at 105° in a vacuum, 6·3. $C_{26}H_{39}O_8N,HAuCl_4,3H_2O$ requires $3H_2O$, 6·2%). The anhydrous *aurichloride* melted at 205° (decomp., sinters at 203°) (Found: C, 38·1; H, 5·3; N, 1·8; Au, 24·2. $C_{26}H_{39}O_8N,HAuCl_4$ requires C, 38·2; H, 4·9; N, 1·7; Au, 24·1%).

Hydrolysis of " base B." The base (1·17 g.) was dissolved in alcohol (10 c.c.) and heated on the water-bath with 2·7 c.c. of N-sodium hydroxide until most of the alcohol had evaporated. The residue was treated with 10 c.c. of water, and after standing overnight and being scratched, 0·675 g. of basic hydrolytic product (" base C ") crystallised in prisms, a further 0·365 g. being obtained by extracting the mother-liquor with chloroform. Acetic acid was shown to be the acid hydrolytic product by the preparation and analysis of the silver salt. The basic product had m. p. 205° (not depressed by " base C "), $[\alpha]_D^{15^\circ}$ + 56·0° (c = 1 in dry alcohol), $[\alpha]_D^{15^\circ}$ + 36·3° (c = 2 in N/5-hydrochloric acid) (Found: C, 63·8; H, 8·5; N, 3·4; OMe, 22·3; NEt, 8·8; equiv., by potentiometric titration, 451. Calc. for " base C," $C_{24}H_{37}O_7N$: C, 63·8; H, 8·3; N, 3·1; 3OMe, 20·6; NEt, 9·5%; equiv., 451).

"*Base C.*"—The base, purified by recrystallisation from alcohol, formed anhydrous prisms, m. p. 206° (sinters at 200), $[\alpha]_D^{18^\circ}$ + 57·0° (c = 1 in dry alcohol), $[\alpha]_D^{18^\circ}$ + 36·4° (c = 2 in N/5-hydrochloric acid) (Found: C, 63·8; H, 8·6; N, 3·5; OMe, 19·5; NEt, 8·2%; equiv., by potentiometric titration, 451). The aurichloride crystallised from dilute alcohol as a *monohydrate* in plates, m. p. 169° (decomp., sinters at 165°) (Found: loss at 105° in a vacuum, 1·6. $C_{24}H_{37}O_7N,HAuCl_4,H_2O$ requires H_2O, 2·2%); the anhydrous *salt* melted at 171° (Found: C, 36·6; H, 5·2; Au, 25·0. $C_{24}H_{37}O_7N,HAuCl_4$ requires C, 36·6; H, 4·8; Au, 24·9%).

Hydriodide of " Base D."—The *hydriodide*, recrystallised from 70% alcohol, gave needles, m. p. 213° (sinters at 207°), $[\alpha]_D^{15^\circ}$ + 32·4° (c = 2 in N/5-alcoholic potassium hydroxide) (Found, in air-dried substance: loss at 105° in a vacuum, 3·5. $C_{48}H_{66}O_{12}N_2,HI,2H_2O$ requires $2H_2O$, 3·5%. Found, in *anhydrous* salt: C, 58·1; H, 6·8; N, 3·0; I, 12·8; OMe, 9·4; NMe, 3·3 or NEt, 4·9. $C_{48}H_{66}O_{12}N_2,HI$ requires C, 58·2; H, 6·8; N, 2·8; I, 12·8; 3OMe, 9·4; NMe, 2·9 or NEt, 4·3%).

"*Base D.*"—The free *base*, liberated from the hydriodide by sodium bicarbonate solution and extracted with chloroform, gave anhydrous crystals from 70% alcohol, m. p. 97° (sinters at 80°), $[\alpha]_D^{15^\circ}$ + 59·3° (c = 2 in dry alcohol) (Found: C, 68·3; H, 7·5; N, 3·5; OMe, 11·3; NMe, 3·3 or NEt, 4·9. $C_{48}H_{64}O_{11}N_2$ requires C, 68·2; H, 7·6; N, 3·3; 3OMe, 11·0; NMe, 3·4 or NEt, 5·0%).

Ajaconine Sulphate.—The sulphate, purified by recrystallisation from dilute acetone, gave six-sided plates of the *heptahydrate*, m. p. 113° (sinters at 110°), $[\alpha]_D^{23^\circ}$ + 5·5° (c = 2 in water) [Found: loss at 70—105° in a vacuum, 12·9. $(C_{22}H_{33}O_3N)_2,H_2SO_4,7H_2O$ requires $7H_2O$, 13·4%]. The anhydrous *sulphate* melted at 231° (decomp., sinters at 214°) (Found: S, 3·9; OMe, nil; NMe, 3·6. $(C_{22}H_{33}O_3N)_2,H_2SO_4$ requires S, 3·9; 2NMe, 7·1%].

Ajaconine.—The base, liberated from the solution of the sulphate by sodium hydroxide solution and extracted by chloroform, crystallised from dilute alcohol in anhydrous prisms, m. p. 172° (sinters at 170°), $[\alpha]_D^{18^\circ}$ − 119·0° (c = 2 in dry alcohol) (Found: C, 73·5; H, 9·2; N, 4·2; OMe, nil; NMe, 3·6; equiv., by titration with N/10-sulphuric acid and methyl-red as indicator, 361·5; equiv., by potentiometric titration, 362. Calc. for $C_{22}H_{33}O_3N$: C, 73·5; H, 9·3; N, 3·9; NMe, 8·1%; equiv., 359).

Hydrogenation of ajaconine. Ajaconine (0·5 g.), dissolvd in acetic acid (20 c.c.) and hydrogenated in presence of palladium-black, took up 28·5 c.c. of hydrogen at 17°/763 mm. ($C_{22}H_{33}O_3N$ for 2H requires 33 c.c.). Lycoctonine and " base C " evolve ethyl iodide (identified by conversion into trimethylethylammonium iodide) in Herzig and Meyer's process for the estimation of methylimino-groups, showing them to be ethylimino-compounds. Ajaconine in like circumstances gives methyl iodide (identified by conversion into tetramethylammonium iodide) and is therefore a methylimino-compound.

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