530. Aconitum *and* Delphinium *Alkaloids. Part I. The Environment of the Nitrogen Atom in Delpheline.*

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The heptacyclic molecule of delpheline has been shown to contain a *N*-ethylpiperidine ring with a methylene group in the ring on one side of the nitrogen atom, and a five-membered ring bearing a secondary hydroxyl group which must be close to the nitrogen atom.

Plant material identified as *Delphinium elatum*, L., has yielded to different investigators a remarkable variety of different, but obviously closely related, alkaloids. Keller and Völker [1] isolated from the seeds a crystalline base, probably delpheline. From green parts of the same species collected in Russia, Rabinovich [2] isolated eldeline, the acetate ester of eldelidine, $C_{25}H_{39}O_7N$: Feofilaktov and Alekseeva [3] isolated delphelatine, the propionate of an alkamine, $C_{24}H_{43}O_8N$: Kuzovkov [4] isolated elatine, an ester of elatidine, $C_{25}H_{41}O_7N$, which could be hydrolysed to formaldehyde and lycoctonine. Goodson [5] separated three alkaloids from "the seeds of a horticultural species, *D. elatum*," methyl lycaconitine (an ester of lycoctonine [6]), delpheline, $C_{25}H_{39}O_6N$,[7] and in small amount delatine, $C_{19}H_{25}O_3N$. Careful comparison of the published properties of the alkamines shows that none is identical.

The source of our alkaloids was the seeds and the aerial portion of the common giant perennial *Delphinium* of horticulture, which is not a genetically pure strain of *D. elatum*, but a hybrid of *D. elatum* with *D. cheilanthum*, *D. formosum*, and many other species. Presumably the seeds extracted by Goodson were from a similar mixture of hybrids, and by his procedure we had no difficulty in isolating methyl-lycaconitine and delpheline in yields similar to his. A much more convenient and efficient method of extraction, avoiding crushing of the seeds and percolation with large volumes of organic solvents, is described in the Experimental part of this paper.

Goodson [7] assigned to delpheline the formula, $C_{25}H_{39}O_6N$, which we have confirmed by analysis of many derivatives and transformation products. He showed that it contained three methoxyl groups, and formed a basic monoacetate, indicating the presence of a hydroxyl group. Since delpheline gave Gaebel's test and on treatment with strong acid liberated about a mol. of formaldehyde, the two remaining oxygen atoms were placed in a methylenedioxy-group, although other interpretations are obviously possible.

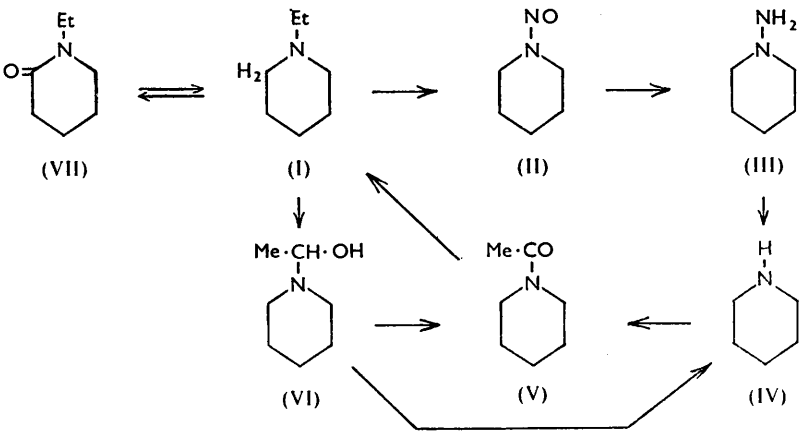
[1] Keller and Völker, *Arch. Pharm.*, 1925, **263**, 274.
[2] Rabinovich, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 1702.
[3] Feofilaktov and Alekseeva, *ibid.*, 1954, **24**, 738.
[4] Kuzovkov, *ibid.*, 1955, **25**, 422.
[5] Goodson, *J.*, 1943, 139.
[6] Cookson, Page, and Trevett, *J.*, 1954, 4028.
Goodson, *J.*, 1944, 665.

The production of ethyl iodide from delpheline and hydriodic acid in the normal Herzig–Meyer estimation of *N*-alkyl groups suggests that the tertiary nitrogen atom bears a side chain of two carbon atoms, but does not distinguish between an ethyl group and, for example, a 2-methoxyethyl group. We have now proved in two independent ways that delpheline does contain a simple *N*-ethyl group.

Nitrous acid [8] converted delpheline (cf. I) into de-ethyl-*N*-nitrosodelpheline (cf. II), characterised by its neutrality and characteristic [9] absorption spectrum, $\lambda_{max.}$ 238—239 mμ (ε 8200) and 354—355 mμ (ε 100). An attempt to increase the efficiency of the conversion by use of nitrosyl chloride in benzene gave no neutral product, but by repeated treatment of unchanged delpheline with nitrous acid up to 80% could be converted into the *N*-nitroso-compound. The sensitivity of delpheline to strong acid ruled out direct removal of the *N*-nitroso-group by hydrolysis.[8] The substance was resistant to hydrogenation at atmospheric pressure and to the action of zinc and dilute acid, but was reduced by lithium aluminium hydride, sodium and alcohol, or, best, lithium in ammonia to *N*-aminode-ethyldelpheline (cf. III), which could be hydrogenolysed to de-ethyldelpheline (cf. IV). Acetylation of the secondary base (cf. IV) yielded a neutral monoacetyl derivative (cf. V) that regenerated delpheline on reduction with lithium aluminium hydride.

The starting point of a second cycle for removal and replacement of the *N*-ethyl group was to oxidise delpheline with mercuric acetate. Among the products was a water-soluble base, $C_{25}H_{39}O_7N$, crystallising with one mol. of water. It was identified as α-hydroxydelpheline (cf. VI) by oxidation with potassium permanganate to the *N*-acetyl derivative (cf. V) and by cleavage with dilute acid to de-ethyldelpheline (cf. IV).

Oxidation of delpheline with potassium permanganate in acetone afforded the neutral oxodelpheline (cf. VII), the carbonyl stretching frequency of which at 1648 cm.$^{-1}$ shows that the lactam ring is of six (or more) atoms, so that the nitrogen atom in delpheline must be situated as in partial formula (I). Lithium aluminium hydride reduced oxodelpheline very slowly to delpheline.



The presence of a hindered hydroxyl group in delpheline was established by its acetylation with acetyl chloride, but not, or only very slowly, with acetic anhydride and pyridine, to a basic acetate that regenerated delpheline on hydrolysis. The secondary nature of the hydroxyl group followed from the oxidation of delpheline to dehydrodelpheline with the loss of two hydrogen atoms. The infrared spectra of the two substances were very similar except that the band at 3500 cm.$^{-1}$ in delpheline was replaced by one at 1748 cm.$^{-1}$ in dehydrodelpheline, which therefore has a carbonyl group in a five-membered ring. The ketone could be reduced back to the alcohol with lithium aluminium hydride, sodium and

[8] Abubakirov and Yunusov, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **24**, 733; cf. Jacobs and Craig, *J. Biol. Chem.*, 1940, **136**, 323; Speyer and Walther, *Ber.*, 1930, **63**, 852.

[9] Goldberg and Kirchsteiner, *Helv. Chim. Acta*, 1943, **26**, 288; Briggs, Harvey Locker, McGillivray, and Seelye, *J.*, 1950, 3013; Haszeldine and Jander, *J.*, 1954, 691.

alcohol, or lithium and ammonia, but it formed no carbonyl derivatives. The oxidation could be carried out not only by chromic acid in acetic acid, or, the best reagent, *N*-bromosuccinimide, but also by such mild reagents as silver oxide (which also gave dehydro-oxodelpheline) and mercuric acetate (which also gave α-hydroxydelpheline). Rather unexpectedly, chromic anhydride in pyridine [10] oxidised delpheline to oxodelpheline, not dehydrodelpheline. Oxodelpheline could be further oxidised by the reagent to the keto-amide, dehydro-oxodelpheline, also produced by treatment of dehydrodelpheline with potassium permanganate in acetone. Lithium aluminium hydride reduced dehydro-oxodelpheline to oxodelpheline and ultimately to delpheline.

The physical properties of derivatives of delpheline with different functions at the nitrogen and carbinol-carbon atoms showed that these two parts of the molecule are close enough to influence each other quite strongly. The basicities of delpheline, acetyldelpheline, and dehydrodelpheline fall sharply in that order (apparent pK_a in 50% ethanol 7·6, 6·9, and 5·5 respectively). That is most simply interpreted as indicating progressive withdrawal of electrons from the nitrogen atom. The ultraviolet absorption of the dehydro-compounds illustrates equally clearly the interaction between the carbonyl group and the nitrogen atom. When the function of the latter is changed from tertiary amine to ammonium salt to amide, the maximum due to the carbonyl group changes from 269 mμ (ε 160) to 259 mμ (ε 200) to 313 mμ (ε 44). The Table shows that the stretching frequencies of the amide- and the ketone-carbonyl groups are also to some extent dependent on the nature of the other group in the molecule. Finally, the molecular-rotation difference for

Stretching frequencies of CO *groups* (*cm.*$^{-1}$ *in* CS_2).

Compound	Amide	Ketone
Oxodelpheline	1649	—
Dehydro-oxodelpheline	1656	1760
Dehydrodelpheline	—	1748
Dehydrodelpheline hydrochloride	—	1752 (in Nujol)

oxidation of the secondary hydroxyl group is −120° for delpheline but −470° for oxodelpheline.

An obvious possibility is that the amino- and the hydroxyl group in delpheline are attached to adjacent carbon atoms. This interpretation was supported by the remarkable similarity of the ultraviolet spectrum of dehydrodelpheline in acid solution to that of piperidinoacetone, which had its maximum at an even shorter wavelength (254 mμ) in the same solvent. The presence of the group, N·CH·CH(OH), in delpheline might also have accounted for its easy oxidation * by silver oxide or mercuric acetate [12] to dehydrodelpheline through an intermediate, $^{+}$N:C·CH(OH). We subsequently found that salts of aminocamphor and its derivatives, which with a *cyclo*pentanone ring should be much safer models for dehydrodelpheline, did not absorb at an abnormally short wavelength. And de-ethyldelpheline, which would be expected to consume periodic acid and lead tetra-acetate if it were an α-hydroxy-secondary amine,[13] was quite inert to those reagents. More decisive evidence against the presence of an α-hydroxy-amine group in delpheline will be reported later.

Since dehydrodelpheline does not absorb radiation in the O–H stretching region the two inert oxygen atoms must both be ethereal. Delpheline in acid solution has a very low extinction coefficient at 210 mμ, and oxodelpheline is inert to ozone at 0° and absorbs no perbenzoic acid, so that delpheline is saturated and contains seven rings.

Experimental

Unless otherwise noted optical rotations were measured in $CHCl_3$, ultraviolet spectra in EtOH, and apparent dissociation constants in aqueous ethanol (1 : 1 by volume).

*. The oxidation seems not to be simply a case of steric acceleration,[11] since 11β-hydroxy-steroids or -trimethylsteroids are not oxidised under the same conditions.

[10] Cf. Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[11] Schreiber and Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1529.
[12] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439, and references given there.
[13] McCasland and Smith, *ibid.*, 1951, **73**, 5164, and references given there.

Extraction of Delphinium *Hybrids.—Seeds.* Non-viable seed (13 kg.) from Carters Tested Seeds Ltd., Raynes Park, labelled "*Delphinium elatum hybridum*, Splendid Mixed," was crushed and then percolated with light petroleum followed by ethanol. The extracts were worked up essentially as described by Goodson,[5] to yield methyl-lycaconitine hydriodide (135·2 g., 1·04%) and delpheline (31·9 g., 0·25%). In addition, lycoctonine (20·4 g., 0·16%) was isolated by hydrolysis with boiling, aqueous-alcoholic alkali of the material in the mother-liquors from crystallisation of the methyl-lycaconitine hydriodide.

A much more convenient method of isolation, that also gave a rather higher yield of alkaloids, involved extraction of the whole, uncrushed seeds with dilute acid. The seeds (10 kg.) were soaked in 2½% acetic acid for 2 days. The liquor was drained from the much swollen seeds, neutralised by the addition of solid sodium hydrogen carbonate, and extracted with ether. After removal of gelatinous matter suspended in the ether layer by addition of kieselguhr, the ether was evaporated and the partly crystalline residue was crystallised from acetone, to yield delpheline.

The aqueous layer from the ether-extraction was extracted with ethyl acetate, the mother-liquors of acetone from which the delpheline had crystallised were added, and the solvents were removed under reduced pressure. The residue was redissolved in ethanol and carefully neutralised with 40% hydriodic acid. Methyl-lycaconitine hydriodide separated from the solution kept at 0°.

The aqueous layer that had been extracted with ethyl acetate was then made strongly alkaline with sodium hydroxide and extracted with chloroform to remove the stronger bases. Gelatinous matter in any of the organic extracts could be coagulated and removed by addition of kieselguhr.

The seeds were extracted twice more for periods of 7 days with 2½% acetic acid, and the liquors were worked up in the same way. The third extraction yielded only negligible amounts of alkaloids other than delpheline, so that only the bicarbonate–ether extraction was carried out later.

The mother-liquors from all the crystallisations were combined and the ester alkaloids presumably present were hydrolysed with boiling aqueous-alcoholic alkali. Lycoctonine and more delpheline were isolated from the product.

The total basic content of the seeds was 219·7 g. (2·2%). The crystalline alkaloids were delpheline (29·35 g.), methyl-lycaconitine hydriodide (104·0 g.), and lycoctonine (19·9 g.).

Young shoots. New shoots from *Delphinium* plants were gathered in the Spring when they were about 1 ft. high. Extraction of the dried shoots with 2½% acetic acid, as for the seeds, produced delpheline (0·44%). The total basic content was 0·86%, but no methyl-lycaconitine hydriodide and only a trace of lycoctonine could be isolated. Just under 3 cwt. of shoots (weighed before drying) gave 58 g. of delpheline. Extraction of the dried shoots with methanol gave a lower yield of delpheline.

A sample of only stalks and stems contained much less delpheline than the entire shoots (0·16% of dry weight). The green leaves and stalks of a mature plant collected after flowering in late July contained almost no basic material. The only crystalline products isolated were mannitol (0·34%), and a glycoside crystallising from aqueous ethanol in clusters of pale yellow needles (0·1%), m. p. 196—210° (decomp.), $[\alpha]_D$ +31° (*c* 1·2 in EtOH); the aglycone formed yellow crystals, m. p. 310—315° (decomp.).

The unsaponifiable part of the neutral oil extracted from the seeds with light petroleum was chromatographed on alumina. Chloroform–benzene (1 : 1 v/v) eluted a crude sitosterol (0·47% of the oil), m. p. 132—133°, $[\alpha]_D$ −23°. The acetate after recrystallisation from ethanol had m. p. 124—125°, undepressed by a genuine sample of β-sitosteryl acetate.

Delpheline.—After several recrystallisations from aqueous ethanol or acetone delpheline had m. p. 216—219°, undepressed by a sample from Goodson's collection kindly given by Mr. T. M. Sharp, $[\alpha]_D$ −27° or −26° (in EtOH), $\lambda_{max.}$ (apparent) 212·5 mμ (ε 1600 in ethanol, ε 70 in dilute HCl), p*K*′ 7·6 (Found: C, 66·45; H, 8·5; *C*-Me, 5·1. Calc. for $C_{25}H_{39}O_6N$: C, 66·8; H, 8·7; 2*C*-Me, 6·7%).

Dilution, with ethyl acetate, of a solution of delpheline neutralised with hydriodic acid in methanol caused separation of *delpheline hydriodide*, m. p. 213—214° (decomp.; after sintering at 210°), when recrystallised from methanol–ethyl acetate (Found: C, 51·9; H, 7·0. $C_{25}H_{39}O_6N$,HI requires C, 52·0; H, 6·8%).

Acetyldelpheline.—Delpheline was boiled with acetyl chloride for 1·5 hr. Isolation with chloroform and several recrystallisations from aqueous ethanol or light petroleum afforded acetyldelpheline, m. p. 122—123°, $[\alpha]_D$ −32°, p*K*′ 6·9 (Found: C, 66·1; H, 8·3. Calc. for

$C_{27}H_{41}O_7N$: C, 66·0; H, 8·4%). The acetate was stable at 200°, failing to undergo the " pyro " reaction of aconitine and delphinine.[14]

Delpheline was unchanged by two days' treatment with a large excess of methyl iodide in nitromethane in presence of sodium hydrogen carbonate at 100°, or by 8 hours' boiling with cyanogen bromide in benzene.

Titrations with Perbenzoic Acid.—The substance (about 25 mg.) and perbenzoic acid (about 3·5 atom equiv. of O) in chloroform (10 ml.) were kept at 0°. The consumption of per-acid, compared with an appropriate blank solution, was as follows (time in days–uptake in atoms of O) : delpheline 1–2·98, 1·5–3·13, 2–3·26; acetyldelpheline 1–0·98, 8–1·05; dehydrodelpheline 1–3·08; oxodelpheline 2–0·00, 4–0·09, 8–0·13.

Acetyldelpheline (46 mg.) in chloroform (5 ml.) containing perbenzoic acid (1 atom equiv. of O) was left at 0° for 18 hr. The resulting *acetyldelpheline* N-*oxide* (20 mg.), crystallised from acetone–ether, had m. p. 220—225° after sintering at 216°, $[\alpha]_D$ −53° (in EtOH) (Found : C, 59·5; H, 8·4. $C_{27}H_{41}O_8N,2H_2O$ requires C, 59·6; H, 8·3%).

De-ethyl-N-*nitrosodelpheline.*—Sodium nitrite in water (2 ml. of 60% solution) was added to a solution of delpheline (200 mg.) in acetic acid (2 ml.) and water (6 ml.), and the mixture was left at room temperature overnight. The basic part of the product consisted of unchanged delpheline (140 mg.). The neutral part was eluted from active alumina with benzene–ethyl acetate (1 : 1) to give *de-ethyl*-N-*nitrosodelpheline* (28 mg.) as needles from ether–acetone or ethyl acetate–*cyclo*hexane, m. p. 253—254°, $[\alpha]_D$ −137°, $\lambda_{max.}$ 238—239 mμ (ε 8200) and 353—354 mμ (ε 100) (Found : C, 61·4; H, 7·4; N, 5·9. $C_{23}H_{34}O_7N_2$ requires C, 61·3; H, 7·6; N, 6·2%).

The yield was hardly affected by variation in reaction time from 4 to 48 hr. or by the proportion or mode of addition of the reagents. Gradual addition of the nitrite to the delpheline solution at 90° almost doubled the yield, but then very little delpheline could be recovered.

N-*Aminode-ethyldelpheline.*—De-ethyl-*N*-nitrosodelpheline (250 mg.) in dioxan (4 ml.) and ether (20 ml.) was added to lithium (200 mg.) in ammonia (30 ml.). Three hours later the lithium was destroyed by ethanol. The product, isolated with chloroform, was split into a neutral fraction of unchanged nitroso-compound (90 mg.) and a basic fraction of N-*aminode-ethyldelpheline* (150 mg.), which crystallised from ether. After recrystallisation from chloroform–ether it had m. p. 203—204°, $[\alpha]_D$ −34° (Found : C, 63·4; H, 8·5; N, 6·3. $C_{23}H_{36}O_6N_2$ requires C, 63·3; H, 8·3; N, 6·4%).

The reduction could be carried out also with sodium and ethanol or with lithium aluminium hydride in ether–dioxan (3 hours' boiling) but with recovery of a larger proportion of unchanged nitroso-compound.

De-ethyldelpheline.—*N*-Aminode-ethyldelpheline (56 mg.) and a large excess of zinc wool in ethanol (3 ml.), water (17 ml.), and concentrated hydrochloric acid (5 ml.) remained at room temperature overnight. The basic product (56 mg.), isolated with chloroform, was soluble in the whole range of solvents from water to light petroleum. Slow crystallisation from a small volume of ether produced cube-like crystals of *de-ethyldelpheline*, m. p. 87—89°, $[\alpha]_D$ −16° (Found : C, 65·3; H, 8·2. $C_{23}H_{35}O_6N$ requires C, 65·5; H, 8·4%).

N-Aminode-ethyldelpheline (100 mg.) in acetic acid (10 ml.) containing perchloric acid (3 drops) was shaken with Adams's catalyst (70 mg.) under hydrogen for 5 hr. A solution of the basic product (73 mg.) in acetic anhydride (5 ml.) was left at room temperature overnight. The resulting N-*acetylde-ethyldelpheline* (70 mg.) melted at 233—234° after crystallisation from ethyl acetate–*cyclo*hexane, and had $[\alpha]_D$ −53°, $\nu_{max.}$ 1628 cm.$^{-1}$ (in $CHCl_3$) (Found : C, 64·8; H, 8·2; N, 3·2. $C_{25}H_{37}O_7N$ requires C, 64·8; H, 8·05; N, 3·0%).

Reduction of N-*Acetylde-ethyldelpheline.*—A solution of the amide (48 mg.) and lithium aluminium hydride (500 mg.) in ether (35 ml.) and dioxan (5 ml.) was boiled for a day. The basic fraction recrystallised from acetone had $[\alpha]_D$ −25°, m. p. 203—208°, undepressed by an authentic sample of delpheline (yield 28 mg.).

Oxidation of Delpheline with Mercuric Acetate.—Delpheline (1·0 g.) and mercuric acetate (5·0 g.) in water (20 ml.) and acetic acid (0·5 ml.) were heated on a steam-bath. Mercurous acetate rapidly separated. After an hour the mixture was cooled and the filtrate was made alkaline with ammonia. Extraction with chloroform afforded a gum which was chromatographed on alumina.

[14] Reviewed by Stern, " The Alkaloids," Ed. Manske and Holmes, Academic Press Inc., New York, 1954, Vol. IV, p. 275.

Benzene–ethyl acetate (9 : 1) removed *dehydrodelpheline* (402 mg.), crystallising from aqueous ethanol in blades, m. p. 140°, $[\alpha]_D$ −72° or −55° (in EtOH), $\lambda_{max.}$ 269 mμ (ε 170) or 260 mμ (ε 200, in dilute HCl), p*K'* 5·5 (Found : C, 67·3; H, 8·2; N, 3·1. $C_{25}H_{37}O_6N$ requires C, 67·1; H, 8·3; N, 3·1%).

A solution of dehydrodelpheline in ethyl acetate treated with hydrogen chloride deposited prisms of the *hydrochloride*, m. p. 179—182° (Found : C, 62·9; H, 8·1. $C_{25}H_{37}O_6N$,HCl requires C, 62·0; H, 7·9%).

Ethyl acetate eluted from the alumina column *α-hydroxydelpheline* (339 mg.), m. p. 92—107° after crystallisation from water, $[\alpha]_D$ −18·5° (Found, air-dried : C, 62·5; H, 8·45. $C_{25}H_{39}O_7N$,H_2O requires C, 62·1; H, 8·55%. Loss in weight on drying at 100° *in vacuo*, 3·6. $1H_2O$ requires 3·7%).

Oxidation of α-Hydroxydelpheline.—α-Hydroxydelpheline (46 mg.) in acetone (5 ml.) and acetic acid (3 drops) was treated with potassium permanganate (10·5 mg.) at room temperature. The neutral product was *N*-acetylde-ethyldelpheline (19 mg.), m. p. and mixed m. p. 213—217°, $[\alpha]_D$ −56°.

Hydrolysis of α-Hydroxydelpheline.—A solution of α-hydroxydelpheline (70 mg.) in methanol–ethyl acetate (1 : 3) was made just acid with hydrochloric acid. A week later the free base was crystallised from ether, to give de-ethyldelpheline (20 mg.), m. p. and mixed m. p. 85—89°.

Oxidation of Delpheline with Potassium Permanganate.—Delpheline (3·0 g.) in acetone (300 ml.) and acetic acid (4 ml.) was treated gradually with powdered potassium permanganate (2·0 g.) during 20 min. An hour later the mixture was diluted with water (300 ml.) and decolorised with sulphur dioxide. On evaporation under reduced pressure to about 100 ml. cube-like crystals of *oxodelpheline* (1·63 g.), m. p. 202—205°, were obtained. More (0·24 g.) was got by acidifying the mother-liquors, extracting them with chloroform, and crystallising the product from aqueous ethanol. Recrystallised several times from aqueous ethanol oxodelpheline had m. p. 204—208°, $[\alpha]_D$ −26·5° or −29° (in EtOH) (Found : C, 63·3, 63·2; H, 8·1, 8·2; N, 3·3, 3·1; *C*-Me, 4·35. $C_{25}H_{37}O_7N$,$\frac{1}{2}H_2O$ requires C, 63·5; H, 8·1; N, 3·0; 2*C*-Me, 6·35%).

In routine preparations the total neutral product was eluted from active alumina with benzene–ethyl acetate (1 : 1). Oxodelpheline, m. p. 200—205°, crystallised in 70% yield on removal of the solvent, and was used for further experiments after being washed with ether.

In Nujol suspension oxodelpheline had bands at 3500 and 3420 and at 1658 and 1628 cm.$^{-1}$ which might have been due to a secondary amide. However, a saturated solution in CS_2 (about 0·1%) had bands only at 3500 and at 1648 cm.$^{-1}$, so that the splitting observed in Nujol must have been caused by intermolecular hydrogen bonds in the crystal.

Oxidation of Delpheline with Silver Oxide.—Delpheline (3·9 g.) and neutral silver oxide (from 20 g. of silver nitrate) in ethanol (200 ml.) and water (50 ml.) were boiled for 7 hr. The product was divided into basic (3·46 g.) and neutral (0·66 g.) fractions, which were separately chromatographed on alumina. The basic part consisted of dehydrodelpheline, m. p. 137—138° (from aqueous ethanol). From the neutral fraction 3% ethyl acetate in benzene eluted *dehydro-oxodelpheline* which, recrystallised from aqueous ethanol, had m. p. 113—116° (hydrated) and 186—189° (anhydrous), $[\alpha]_D$ −129° or −120° (in EtOH), $\lambda_{max.}$ 313 mμ (ε 44) (Found, anhydrous : C, 64·6; H, 7·7; N, 2·8. $C_{25}H_{35}O_7N$ requires C, 65·05; H, 7·6; N, 3·0%).

Oxodelpheline was recovered unchanged from treatment with silver oxide in the same way.

Oxidation of Delpheline with Chromic Oxide in Pyridine.—A mixture of delpheline (533 mg.) and chromic oxide (500 mg.) in pyridine (10 ml.) that had been left at room temperature overnight was diluted with water and treated with sulphur dioxide. The neutral product (530 mg.) was chromatographed on alumina. Benzene–ethyl acetate (1 : 1) eluted oxodelpheline, m. p. 205—209°, not depressed by a sample made with permanganate.

Delpheline (229 mg.), oxidised with chromic oxide (507 mg.) in pyridine (7 ml.) as before, gave a gum (130 mg.) that crystallised from aqueous ethanol as dehydro-oxodelpheline, m. p. and mixed m. p. 115—117° and 184—186°, $[\alpha]_D$ −114° (in EtOH).

Identical dehydro-oxodelpheline (100 mg.) was also made by addition of potassium permanganate (160 mg.) to dehydrodelpheline (160 mg.) in acetone (100 ml.) and acetic acid (0·5 ml.); or by oxidation of oxodelpheline with an equal weight of chromic oxide in pyridine.

Oxidation of Delpheline with Chromic Acid in Acetic Acid.—Delpheline (209 mg.) in acetic acid (1 ml.) was treated with chromic oxide (34 mg.) in water (3 drops) and acetic acid (2 ml.). After three days the solution was diluted with water and extracted five times with chloroform, which was then washed with dilute ammonia to remove acetic acid. The involatile part of the extract crystallised from aqueous ethanol as prisms of the weak base, dehydrodelpheline (59 mg.), m. p. and mixed m. p. 137—139°.

The aqueous layer was made alkaline with ammonia and extracted with chloroform, to give back delpheline (123 mg.).

Oxidation of Delpheline with N-*Bromosuccinimide.*—Delpheline (2·0 g.) and *N*-bromosuccinimide (0·91 g.) in dioxan (40 ml.), water (20 ml.), and acetic acid (4 ml.) were allowed to react at room temperature overnight. When the solution was made alkaline with ammonia and the flask scratched, dehydrodelpheline (0·88 g.) crystallised (m. p. 130—133°). Chromatography on alumina of the base in the mother-liquor gave, on elution with 3% ethyl acetate in benzene, more dehydrodelpheline (0·505 g.). The combined fractions, when recrystallised from aqueous alcohol, had m. p. and mixed m. p. 139—140°.

Elution of the column with ethyl acetate gave delpheline (0·36 g.).

Reduction of Dehydrodelpheline.—Dehydrodelpheline (105 mg.) in dioxan (5 ml.) and ether (25 ml.) was added to lithium (54 mg.) in ammonia (25 ml.). Fifteen minutes later ammonium chloride was added and the product was isolated with ether. Delpheline (98 mg.), crystallised from chloroform–ether, had m. p. and mixed m. p. 203—210°.

Delpheline (m. p. 215—218°) was produced also by reduction with sodium in boiling propan-1-ol, and with lithium aluminium hydride (6 hours' boiling in ether).

Reduction of Oxodelpheline.—Oxodelpheline (995 mg.), boiled for 4 days with lithium aluminium hydride (2·0 g.) in ether (50 ml.), afforded delpheline (593 mg.), m. p. and mixed m. p. 217—219° after crystallisation from aqueous ethanol.

Dehydro-oxodelpheline was reduced to delpheline in the same way.

Some of the earlier experiments were done by the late Mr. A. Busby in 1952. Dr. B. J. Langdon very kindly arranged the collection and despatch of a generous supply of *Delphinium* shoots from the nurseries of Messrs. Blackmore and Langdon, Bath. We are also grateful to the Central Research Fund for a grant for the purchase of *Delphinium* seed, and to Professor D. H. R. Barton, F.R.S., for his valuable advice and encouragement.

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