602. Aconitum *and* Delphinium *Alkaloids. Part II.* Interrelation of the Functional Groups of Delpheline.*

By R. C. Cookson and M. E. Trevett.

Oxodelpheline is hydrolysed by acid to formaldehyde and demethyleneoxodelpheline, which is shown, mainly from the nature of the products of its reaction with periodic acid and with lead tetra-acetate, to contain the array of atoms indicated in (I). The very close similarity in the chemical and physical properties of demethylenedelpheline and of lycoctonine (XIII) and of their corresponding derivatives allows the speculative structure (XVII) to be advanced for delpheline. The possibility of the biogenesis of lycoctonine and delpheline from a precursor with the atisine skeleton is pointed out.

Goodson [1] showed by the semiquantitative method of Clowes and Tollens [2] that delpheline liberated about one mol. of formaldehyde when treated with strong acid. We were initially rather sceptical of his conclusion that delpheline must therefore contain a methylenedioxy-group, considering that some variant of a reversed Prins reaction or 1 : 3-glycol cleavage [3] was more probable. But in the light of further experiments it seems that the occurrence of an aliphatic methylenedioxy-group in some of them must be admitted as another unique feature of the aconite alkaloids.

We confirmed that delpheline and its oxidation products,[4] dehydrodelpheline, oxodelpheline, and dehydro-oxodelpheline, on treatment with strong acid, all liberated one mol. of formaldehyde, which was identified as its condensation products with dimedone and with 2 : 4-dinitrophenylhydrazine, and was estimated colorimetrically by the chromotropic acid reagent.[5] The products of acid hydrolysis of delpheline, oxodelpheline, and dehydro-oxodelpheline were obtained crystalline, and will be referred to as demethylene compounds. Analytically they differed from their precursors only in the loss of one carbon atom, and like their precursors [4] were saturated.† While delpheline, oxodelpheline, dehydrodelpheline, and dehydro-oxodelpheline did not react with lead tetra-acetate in acetic acid, demethylenedelpheline and demethyleneoxodelpheline (partial formula I) ‡ consumed one mol. almost instantaneously and a second mol. more slowly. Demethyleneoxodelpheline acetate (II) and dehydrodemethyleneoxodelpheline (III) took up one mol. relatively slowly. Demethyleneoxodelpheline (I) also took up one mol. of periodic acid in an hour or two, and (when buffered with sodium hydrogen carbonate) two mols. in a day.

Demethylenedelpheline is therefore a 1 : 2 : 3-triol. Since dehydrodemethyleneoxodelpheline (III) could be reduced by lithium aluminium hydride (but not by sodium borohydride) to demethyleneoxodelpheline, no ketol rearrangement had attended cleavage of formaldehyde from the former, and the secondary hydroxyl group thus demonstrated in the latter was probably the one originally present in delpheline.[4] The failure of dehydrodemethyleneoxodelpheline (III) to reduce bismuth acetate in acetic acid [6] suggested that this secondary hydroxyl group was not adjacent to another. Initial attempts to decide the nature of the other two hydroxyl groups by comparative titration of the demethylene and the parent compounds with chromic acid in acetic acid (see the Experimental section) were inconclusive. All the demethylene compounds took up one equivalent of oxygen

* Part I, *J.*, 1956, 2689. (A preliminary note on part of the matter of this paper appeared in *Chem. and Ind.*, 1954, 1324.)

† Formally " demethylene " denotes replacement of CH_2 by two hydrogen atoms. In the present cases it implies replacement of $-O\cdot CH_2\cdot O-$ by $-OH\ HO-$.

‡ For the sake of clarity the argument is anticipated in this and in some subsequent partial formulæ.

[1] Goodson, *J.*, 1944, 665.

[2] Clowes and Tollens, *Ber.*, 1899, **32**, 2847.

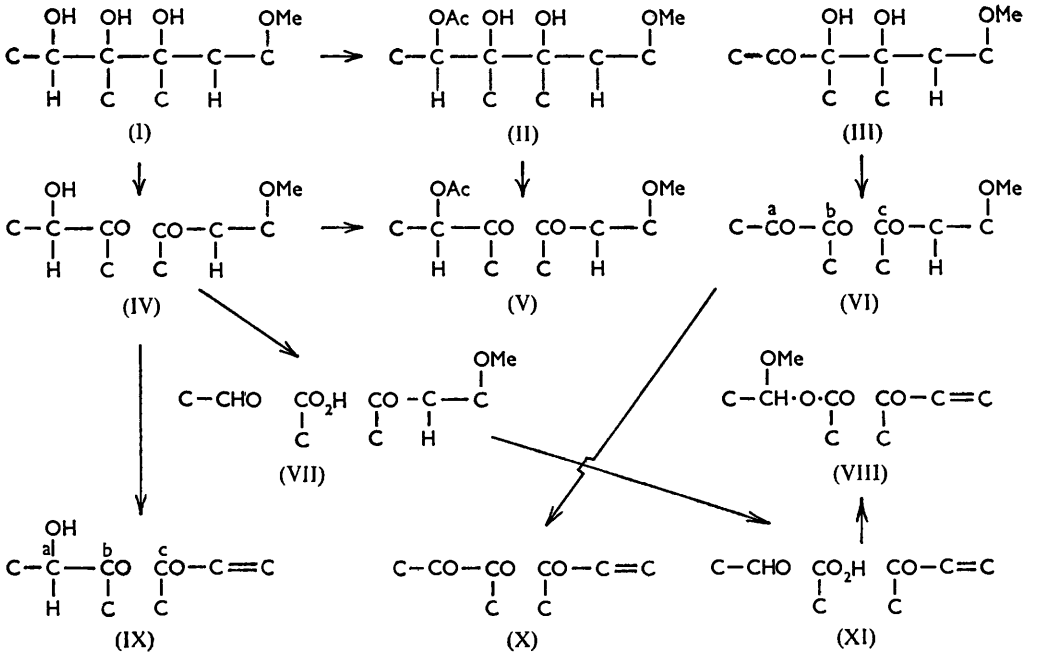
[3] See, amongst many others, Brutcher and English, *J. Amer. Chem. Soc.*, 1952, **74**, 4279; Zimmerman and English, *ibid.*, 1953, **75**, 2367.

[4] Cookson and Trevett, *J.*, 1956, 2689.

[5] Bricker and Johnson, *Ind. Eng. Chem., Analyt. Edn.*, 1945, **17**, 400.

[6] Rigby, *J.*, 1951, 793.

very fast (in the light of later results, this probably involves attack mainly on the ditertiary glycol). The milder reagent, chromic oxide in pyridine,[7] destroyed demethyleneoxodelpheline (I) or dehydrodemethyleneoxodelpheline (III), but left the acetate of the former unaffected, so that (as was subsequently proved) the acetylated hydroxyl group was probably the one originally present in delpheline and the two new hydroxyl groups were probably both tertiary.



Attempts to isolate crystalline cleavage products from reaction of the demethylene compounds in the basic series with lead tetra-acetate or periodic acid under conditions indicated by titration were unsuccessful. But treatment of demethyleneoxodelpheline (I) with one mol. of periodic acid gave a crystalline *seco*-diketone (IV), showing bands in the infrared spectrum at 1754 and 1710 cm.$^{-1}$ but none in the region 2600—2800 cm.$^{-1}$ characteristic of the C–H of an aldehyde.[8] The *seco*-diketone therefore probably had one carbonyl group in a five-membered ring, and one in a six(or more)-membered ring: the more readily split glycol must have been ditertiary, and the original secondary hydroxyl group cannot have been involved. In agreement, the *seco*-diketone could be acetylated to a substance (V) identical with that got by oxidation of demethyleneoxodelpheline acetate (II) with lead tetra-acetate. Neither the *seco*-diketone nor its acetate formed an oxime or 2 : 4-dinitrophenylhydrazone; both were stable to permanganate in acetone. We can now write (*A*) for demethylenedelpheline, where the numbers indicate the probable sizes of the rings.

While the acetate of the *seco*-diketone was inert to lead tetra-acetate, the *seco*-diketone itself took up a second mol. to give an acidic product. By use of periodate in an alkaline buffer (in acid solution the rate of reaction was negligible[9]) a crystalline *diseco*-acid (VII) was isolated after one mol. of oxidant had been used up. The *diseco*-acid (VII) had maxima, amongst others, at 1710 cm.$^{-1}$ (aldehyde and *cyclo*hexanone) and at 2800 cm.$^{-1}$ (aldehyde),

[7] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[8] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 135.
[9] Cf. Buist and Bunton, *J.*, 1954, 1406.

confirming its formulation as (*B*), and establishing beyond doubt that the middle hydroxyl group in demethyleneoxodelpheline is tertiary and attached to the main nucleus rather than to a side chain. The strength of the *diseco*-acid (pK' 4·1 in 50% ethanol) indicated stabilisation of the anion by, amongst other possibilities, a strongly electron-attracting α-substituent, for which the only function available would be the amide (cf. *N*-acetylglycine with a pK' of 4·9 in the same solvent).

Oxidation of dehydrodemethyleneoxodelpheline (III) with lead tetra-acetate gave a red α-diketone (VI) with bands in the infrared spectrum at 1775 and 1755 cm.$^{-1}$ from the *cyclo*pentanedione and at 1712 cm.$^{-1}$ from the *cyclo*hexanone. The absence of a band at 2600—2800 cm.$^{-1}$ (compared with the *diseco*-acid) confirmed that the hydroxyl group remote from the known secondary hydroxyl group was tertiary, not secondary.

Dilute acid induced elimination of methanol from each of the *seco*-compounds with formation of substances that were recognised as αβ-unsaturated ketones by their spectroscopic properties. The *seco*-diketone (IV) formed the unsaturated *seco*-diketone (IX), the maximum in whose ultraviolet absorption at 225 mμ (ε 11,800) showed that the double bond must be conjugated with one of the carbonyl groups, and only lightly substituted. The bands in the infrared spectrum at 1768 and 1680 cm.$^{-1}$ proved that the double bond had been introduced into conjugation with the *cyclo*hexanone, not the *cyclo*pentanone, carbonyl group. By a parallel change the red α-diketone (VI) gave the red unsaturated analogue (X). This showed the same chromophore, $\lambda_{max.}$ 223 mμ (ε 10,000), as (IX) in the ultraviolet spectrum, and the same two infrared bands of very high frequency due to the *cyclo*pentanedione, as its precursor (VI), but instead of the band at 1712 cm.$^{-1}$ shown by the latter had a broad one at 1660 cm.$^{-1}$ from the conjugated ketone and amide unresolved.

Elimination of methanol from the *diseco*-acid (VII) led to the αβ-unsaturated keto-acid (XI), which had its ultraviolet maximum at a rather longer wavelength (233 mμ) and rather less intense (ε 6250) than its two pentacyclic analogues (IX) and (X). When treated with hydrochloric acid in methanol the acid (XI) was converted into a very high-melting *pseudo*-ester (VIII), showing the expected band at 1755 cm.$^{-1}$ from the δ-lactone, its frequency raised by about 20 cm.$^{-1}$ by the adjacent methoxy-group.[10]

Under mild alkaline conditions the *seco*-compounds underwent an interesting series of changes. The *seco*-diketone (IV) was converted by such mild reagents as alkaline alumina and potassium carbonate into a substance isomeric with the αβ-unsaturated *seco*-diketone (IX), which could be made also from (IX) itself in the same way. This isomer did not absorb intensely in the accessible ultraviolet region, and had lost the infrared band corresponding to either the unconjugated or the conjugated *cyclo*hexanone carbonyl group, but retained the high-frequency band. The isomer was stable to boiling dilute acid, and to chromic oxide in pyridine. It absorbed one equivalent of oxygen from chromic acid in acetic acid rapidly, and a second more slowly. It therefore contained two tertiary, but easily oxidised, hydroxyl groups in place of the secondary hydroxyl and six-ring carbonyl group of the precursor (IX). The change is most simply explained as an internal aldol addition of one of the two possible enolates of the ketol to the six-ring carbonyl group (c) in (IX). Whether it involved addition of $C_{(b)}$ to $C_{(c)}$, with regeneration of the original ring-system, or of $C_{(a)}$ to $C_{(c)}$ with formation of a rearranged ring-system, could not be decided; but that one of these alternatives had occurred was proved by oxidation of the isomer with lead tetra-acetate, one mol. being taken up to produce the red unsaturated α-diketone (X).

A pink solution of the α-diketone (VI) immediately became colourless on addition of alkali. The colour gradually reappeared, even at room temperature, and the unsaturated α-diketone (X) could then be isolated from the solution. By rapid extraction of the initially decolorised solution at low temperatures a colourless, crystalline isomer of the α-diketone (VI) was separated. It was also formed, in rather higher yield, by boiling the α-diketone (VI) in ethyl acetate containing a trace of acetic acid. Further treatment of the colourless isomer with alkali turned it into the unsaturated α-diketone (X). As well as having lost the long-wavelength band in the visible region due to the α-diketone, the

[10] Grove and Wallis, *J.*, 1951, 877.

colourless isomer lacked one of the two high-frequency bands in the CO stretching region, having maxima only at 1755 (*cyclo*pentanone) and 1720 cm.$^{-1}$ (*cyclo*hexanone). Evidently the colourless isomer results from another aldol cyclisation; here a carbon atom α to carbonyl-c in (VI) has become linked to $C_{(a)}$ or $C_{(b)}$, which then carries a tertiary hydroxyl group. Alkali promotes equilibrium between the hexacyclic aldol and the pentacyclic enolate, which loses methoxide to form the unsaturated ketone (X). Neither the α-diketone (VI) nor its unsaturated analogue (X) showed any sign of enolising, so that the carbon atoms attached to $C_{(a)}$ and $C_{(b)}$ may be fully substituted or at bridge-heads.[11] The failure of dehydrodelpheline and dehydro-oxodelpheline to absorb bromine in acetic acid containing hydrogen bromide can also be construed as showing that the carbon atom attached to $C_{(a)}$ is unable to enolise.

The reactions of the *seco*-diketone (IV) from demethyleneoxodelpheline that do not involve the secondary hydroxyl group are closely analogous to those of the *seco*-diketones from oxolycoctonine * and de(hydroxymethyl)oxolycoctonine.[12] The main difference is that in the lycoctonine series the dehydrodemethoxy-*seco*-diketone (as IX), which cannot rearrange like the ketol (IX), appears to be stable to base. The parallel in the optical properties of the *seco*-diketones is particularly striking (see Table, where values are given

	Demethyleneoxodelpheline				De(hydroxymethyl)oxolycoctonine			
	$\nu_{max.}$ [a] (cm.$^{-1}$)	$\lambda_{max.}$ [b] (mμ)	ε	$[M]_D$ [a]	$\nu_{max.}$ [a] (cm.$^{-1}$)	$\lambda_{max.}$ (mμ)	ε	$[M]_D$ [b]
Parent compound	1624	—	—	+170°	1630	—	—	+220°
seco-Diketone (IV)	1765, 1706, 1645	319	310	+410	1765, 1707, 1644	322	260	+380
Dehydrodemethoxy-*seco*-diketone (IX)	1768, 1680, 1645	225 320	11,000 320	+300	1765, 1679, 1642	223 321	11,000 320	+360

[a] In chloroform. [b] In ethanol.

for derivatives of lycoctonine in which the hydroxymethyl group is replaced by hydrogen, so as to avoid complications from the primary hydroxyl group), especially their unusual spectroscopic behaviour (which will be discussed in a separate paper). In addition, the acid-catalysed rearrangements of oxolycoctonine [14] and demethyleneoxodelpheline [15] are quite analogous, and leave no doubt that the environments of the ditertiary glycol groups are identical in the two series, and that the secondary hydroxyl group in demethylenedelpheline replaces a secondary methoxyl group in lycoctonine.

As the result of a remarkable feat of *X*-ray analysis [16] de(hydroxymethyl)lycoctonine has recently been found to have the structure (XII). From chemical evidence [17] the hydroxymethyl group in lycoctonine must be attached in the position indicated by the arrow. The resulting structure for lycoctonine does not immediately recall that of other plant products, but it can be rewritten as the enantiomorph (XIII), which looks more like a nor-diterpene and indicates the stereochemistry † established by Przybylska and Marion.[16]

* We use the name "oxolycoctonine," after discussion with the Editor, in preference to Edwards and Marion's [12] "lycoctonam" in order to agree with the name used here for the analogous oxidation product of delpheline; to accord with traditional usage in the literature on the aconite and larkspur alkaloids; [13] and, it so happens, to conform with current systematic nomenclature.

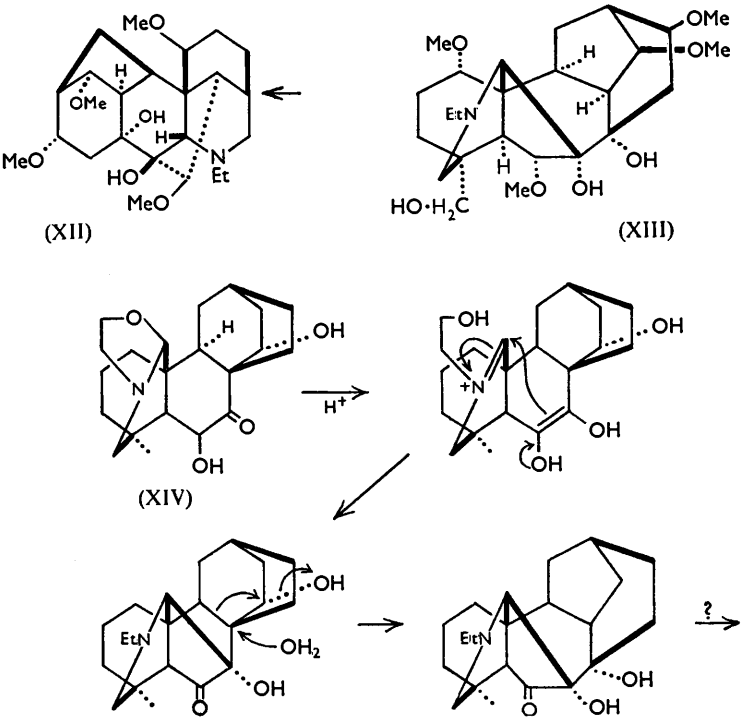
† As a means of showing configuration, the conventional flat projection formula is apt to be ambiguous when applied to bridged-ring systems. In formula (XIII) the carbocyclic system of 6-, 7-, and 5-membered rings, analogous—at least formally—to rings A, B, and C of the perhydrophenanthrene system of the tricyclic diterpenes, is taken for reference in the plane of the paper, and is shown by normal, thin bonds. The configuration of substituents on these rings is shown as usual by thick or broken bonds, according to whether the substituent is above or below the formally flattened ring-system. The configuration of substituents on carbon atoms in the bridges is indicated by writing the substituent on the appropriate side of the bridge.

[11] But see Büchi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 442; 1948, **31**, 139.
[12] O. E. Edwards and Marion, *Canad. J. Chem.*, 1954, **32**, 195.
[13] Henry, "The Plant Alkaloids," Churchill, London, 4th Edn., 1949, p. 673; Stern in "The Alkaloids," Ed. Manske and Holmes, Academic Press, New York, 1954, Vol. IV, p. 275.
[14] O. E. Edwards, Marion, and McIvor, *Canad. J. Chem.*, 1954, **32**, 708.
[15] Cookson and Trevett, *Chem. and Ind.*, 1954, 1391; Cookson, Klee, and Trevett, unpublished experiments.
[16] Przybylska and Marion, *Canad. J. Chem.*, 1956, **34**, 185.
[17] O. E. Edwards and Marion, *ibid.*, 1952, **30**, 627.

In passing, we note that lycoctonine (XIII) and its functional variants might arise in the plant from a precursor with the skeleton of atisine [18] or a stereoisomer, by loss of a methyl group or its equivalent,[19] a Wagner–Meerwein rearrangement, and cyclisation by a condensation such as a Mannich reaction. As usual the order and precise nature of the steps in the hypothetical series of reactions can be varied, but one possible scheme is illustrated in formulæ (XIV) * to (XIII).

Whereas lycoctonine contains only one *C*-methyl group, delpheline contains two,[4] so that the simplest way in which the two bases could be related would be that demethylenedelpheline should have structure (XVI). Indeed all the known chemistry of demethylenedelpheline and its derivatives can be reconciled with that structure.

The relation of demethylenedelpheline to delpheline still has to be discussed. We cannot devise a structure that would allow the carbon atom eliminated to correspond to either the hydroxymethyl group of lycoctonine or the missing carbon atom of a diterpenoid skeleton, and there is no alternative to Goodson's methylenedioxy-group. If demethylenedelpheline is (XVI), then delpheline is probably its formal (XVII).



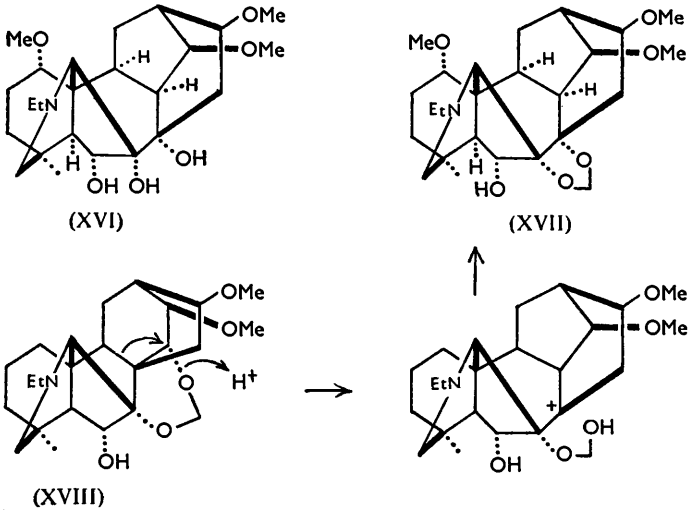
Under certain conditions oxodelpheline could be converted by acid into an isomer as well as demethyleneoxodelpheline. Further treatment of *iso*oxodelpheline with acid gave formaldehyde and the same demethylene compound. Since *iso*oxodelpheline was inert to chromic oxide in pyridine and contained a tertiary hydroxyl group instead of the original secondary one it can differ from oxodelpheline only in a migration of the formal group, which must bridge the secondary and one of the tertiary hydroxyl groups rather than the

* Since the position of the methylene group in atisine has not been rigidly proved, and the stage at which it might be lost in the genesis of lycoctonine is elastic, it is omitted in this scheme. The formation of the rather strained norcamphane unit in the intermediate (XV) could, of course, be avoided by reversing the order of the two essential reactions.

[18] Wiesner and J. A. Edwards, *Experientia*, 1955, **11**, 255; Pelletier and Jacobs, *J. Amer. Chem. Soc.*, 1954, **76**, 4496.

[19] Woodward and Bloch, *ibid.*, 1953, **75**, 2023; Eschenmoser, Ruzicka, Jeger, and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890.

two tertiary ones. The infrared spectra of oxodelpheline and its isomer were similar, but had a different distribution of the intense ether bands near 1100 cm.$^{-1}$. If, as is probable, the hydroxyl group in delpheline has the same configuration as the corresponding methoxyl group in lycoctonine, the six-membered methylenedioxy-ring in *iso*oxodelpheline is the more likely alternative.



A small amount of demethyleneoxodelpheline could be isolated by chromatography on alumina of the amorphous by-products formed during the oxidation of delpheline with permanganate. The uncrystallisable fractions from the chromatogram absorbed at 1758, 1720, 1676, and 1645 cm.$^{-1}$, suggesting that they consisted mainly of *seco*-compounds derived from demethyleneoxodelpheline by oxidation of the ditertiary glycol. The demethylene compound may arise by oxidation of the formal to the orthoformate group, followed by hydrolysis. Unless separation of formate provides sufficient driving force to promote rearrangement, the removal of the methylene group in the absence of strong acid tends to discount the possibility of skeletal rearrangement during formation of the demethylene compounds. But rearrangement is still conceivable. For example, the structure (XVIII) might conceivably rearrange as indicated to (XVII), which would then represent an unisolated intermediate on the way to the *iso*- and demethylene derivatives.

Experimental

Unless otherwise noted, physical constants were determined as follows : optical rotations were measured in $CHCl_3$ at about 1—2% concentration ; ultraviolet spectra in EtOH ; infrared spectra, kindly taken for us by Glaxo Laboratories Ltd., in $CHCl_3$; apparent dissociation constants in ethanol–water (1 : 1 v/v) by electrometric titration.

Demethylenedelpheline.—Delpheline (100 mg.) and 2 : 4-dinitrophenylhydrazine (44 mg.) in concentrated hydrochloric acid (3 ml.) were set aside at room temperature overnight. After recrystallisation from ethanol the formaldehyde 2 : 4-dinitrophenylhydrazone (6 mg.) had m. p. and mixed m. p. 166°.

A solution of delpheline (500 mg.) in concentrated hydrochloric acid (15 ml.) that had been at room temperature overnight was brought to pH 7·0 with ammonia, and dimedone (1·0 g.) in water (100 ml.) was added. After 10 days the formaldehyde–dimedone compound (96 mg.) was collected (m. p. and mixed m. p. 191—193°).

Delpheline (2·0 g.) in concentrated hydrochloric acid (30 ml.) was left overnight. The solution was diluted with water, made alkaline with ammonia, and repeatedly extracted with chloroform. Crystallisation from aqueous methanol afforded *demethylenedelpheline* (1·72 g.) as plates, m. p. 70—78° after sintering at 66°, $[\alpha]_D$ +24° (+14° in ethanol), pK' 8·3 (Found :

C, 57·1; H, 9·25; N, 2·85; loss at 100°/vac., 13·9. $C_{24}H_{39}O_6N,4H_2O$ requires C, 56·6; H, 9·3; N, 2·75; loss, 14·1%).

After recrystallisation from methanol–acetone the *hydriodide* had m. p. 193—194° (decomp.) (Found: C, 50·4; H, 7·4; N, 2·1; I, 21·7. $C_{24}H_{39}O_6N,HI,CH_3{\cdot}OH$ requires C, 50·3; H, 7·4; N, 2·3; I, 21·3%). When a solution of demethylenedelpheline in ethyl acetate was just acidified with perchloric acid in the same solvent the *perchlorate*, m. p. 200° (decomp.), separated (Found: C, 53·1; H, 7·6; Cl, 6·6. $C_{24}H_{39}O_6N,HClO_4$ requires C, 53·6; H, 7·5; Cl, 6·6%). The *nitrate* melted at 191—193° (decomp.), after recrystallisation from acetone–ether (Found: C, 57·7; H, 8·1; N, 5·4. $C_{24}H_{39}O_6N,HNO_3$ requires C, 57·6; H, 8·05; N, 5·6%).

Demethyleneoxodelpheline (I).—A solution of oxodelpheline (100 mg.) in concentrated hydrochloric acid was left overnight. Isolation with chloroform and crystallisation from aqueous ethanol gave *demethyleneoxodelpheline* (50 mg.), m. p. 108—110° after sintering at 101°, $[\alpha]_D$ +35° (34° in ethanol), $\nu_{max.}$ 1624 cm.$^{-1}$ (Found: C, 59·2; H, 8·5; N, 3·1; loss at 80°/vac., 7·3. $C_{24}H_{37}O_7N,2H_2O$ requires C, 59·1; H, 8·5; N, 3·0; $2H_2O$, 7·4%).

Demethyleneoxodelpheline was heated on a steam-bath for 1 hr. with acetic anhydride in pyridine. Elution of the product from active alumina with ethyl acetate–benzene (1 : 1 v/v) gave the *acetate* (II), which crystallised from aqueous ethanol in plates, m. p. 209—212°, $[\alpha]_D$ +13° (+18° in EtOH) (Found: C, 63·1; H, 7·8; N, 2·7. $C_{26}H_{39}O_8N$ requires C, 63·3; H, 8·0; N, 2·8%).

iso*Oxodelpheline*.—The residue from evaporation of the mother-liquors from crystallisation of demethyleneoxodelpheline crystallised from ethyl acetate–*cyclo*hexane. iso*Oxodelpheline* formed needles, m. p. 212—215°, $[\alpha]_D$ +20°, $\nu_{max.}$ 1642 cm.$^{-1}$ (1644 cm.$^{-1}$ in CS_2) (Found, anhydrous: C, 64·75; H, 8·1; N, 3·2. $C_{25}H_{37}O_7N$ requires C, 64·8; H, 8·05; N, 3·0. Loss on drying hydrate at 100° *in vacuo*, 3·8. $1H_2O$ requires 3·9%).

Dehydrodemethyleneoxodelpheline (III).—A solution of dehydro-oxodelpheline (83 mg.) in concentrated hydrochloric acid (10 ml.) was left overnight, and the product was crystallised from ethyl acetate–ether to yield cube-like crystals of *dehydrodemethyleneoxodelpheline* (55 mg.), m. p. 156—158°, $[\alpha]_D$ −115°, $\lambda_{max.}$ 315 mμ (ε 57), $\nu_{max.}$ 1752 and 1640 cm.$^{-1}$ (Found, anhydrous: C, 64·2; H, 7·7; N, 3·5. $C_{24}H_{35}O_7N$ requires C, 64·1; H, 7·85; N, 3·1%. Loss at 100° *in vacuo*, 10·35. $3H_2O$ requires 10·7%). The m. p. of this substance varied widely with the rate of heating and method of observation: values were noted in the range 110—115° (hydrate ?) as well as 150—160° (anhydrous ?).

In some later experiments a small amount (10%) of a by-product crystallised rapidly in needles, before the cubes of demethyleneoxodelpheline that separated more slowly. This *substance* had m. p. 184—194°, $[\alpha]_D$ −130°, $\lambda_{max.}$ 316—319 mμ (ε 46), $\nu_{max.}$ 1748 and 1663 cm.$^{-1}$ (Found: C, 63·5; H, 7·8; N, 3·1; no loss at 100° *in vacuo*. $C_{24}H_{35}O_7N$ requires C, 64·1; H, 7·85; N, 3·1%).

Reduction of Dehydrodemethyleneoxodelpheline.—The ketone (56 mg.) was boiled with lithium aluminium hydride (200 mg.) in ether (30 ml.) for 2 hr. The product, crystallised from ether, was demethyleneoxodelpheline (39 mg.), m. p. 98—115°, $[\alpha]_D$ +35°. The derived acetate, crystallised from ethyl acetate–*cyclo*hexane, had m. p. and mixed m. p. 210—212°, $[\alpha]_D$ +25°.

Estimation of Formaldehyde.—The reagent was made by dissolving chromotropic acid (50 mg.) in 50% sulphuric acid (25 ml.) and clarifying the solution by centrifugation. The compound (0·2—0·3 mg.) in 50% sulphuric acid (0·5 ml.) was heated with the reagent (0·8 ml.) on a steam-bath for ¾ hr. After cooling of the solution, the extinction at 570 mμ was compared with a blank. The spectrophotometer had been calibrated against solutions of accurately known formaldehyde content. The mols. of formaldehyde produced by various compounds were: delpheline 1·03, oxodelpheline 1·02, dehydrodelpheline 1·08, dehydro-oxodelpheline 1·02, demethyleneoxodelpheline 0·02, dehydrodemethyleneoxodepheline 0·00.

Titration with Chromic Acid.—The compound (20—25 mg.), and chromic oxide (about 10 mg., 4 mols.) in the minimum amount of water, were dissolved in acetic acid (to 10 ml.). At intervals 1 ml. samples were run into excess of acidified potassium iodide solution. After 10 min. the iodine was titrated against N/100-sodium thiosulphate solution. Appropriate blank experiments were run in parallel. The atom-equivs. of oxygen consumed by various compounds at room temperature after 5, 20, 60, and 120 min. respectively were: delpheline, 0·52, 0·86, 1·20, 1·37; demethylenedelpheline, 0·79, 1·84, 2·44, 2·70; dehydrodelpheline, 0·00, 0·21, 0·64, 0·85; oxodelpheline, 1·07, 1·34, 1·64, 1·90; demethyleneoxodelpheline, 1·81, 2·13, 2·36, 2·51; demethyleneoxodelpheline acetate, 1·04, 1·65, 2·31, 2·53; dehydrodemethyleneoxodelpheline, 2·06, 2·20, 2·93, —.

Titration with Lead Tetra-acetate.—The compound (about 25 mg.) and lead tetra-acetate

(about 2·5 mols.) in glacial acetic acid (to 10 ml.) were kept in the dark. At intervals 2 ml. samples were run into 3% potassium iodide in saturated sodium acetate solution. After 15 min. the iodine was titrated against N/100-sodium thiosulphate. The consumption of lead tetra-acetate in mols. compared with a blank solution (time in min.) was: delpheline, 0·0 (90), 0·4 (1200); demethylenedelpheline, 1·1 (2), 1·1 (5), 1·3 (15), 1·3 (20), 1·6 (60), 1·7 (90), 2·2 (180), 2·8 (1200); oxodelpheline, 0·0 (180); demethyleneoxodelpheline, 1·0 (2), 1·0 (5), 1·15 (10), 1·8 (30), 2·0 (90); demethyleneoxodelpheline acetate, 0·25 (2), 0·54 (5), 0·74 (10), 0·96 (30), 1·02 (90); dehydrodelpheline, 0·0 (180); dehydro-oxodelpheline, 0·0 (180); dehydrodemethyleneoxodelpheline, 0·56 (2), 0·77 (5), 0·91 (10), 0·99 (20), 1·09 (60).

Titration with Periodic Acid.—The compound (about 20 mg.) and periodic acid dihydrate (about 60 mg.) in water (5 ml.) and ethanol (to 10 ml.) were kept in the dark. At intervals 1 ml. samples were run into saturated sodium hydrogen carbonate solution (5 ml.). N/10-Sodium arsenite (1 ml.) was added at once, followed by excess of potassium iodide (50—100 mg.). Ten minutes later the excess of arsenite was titrated with N/50-iodine. The consumption of periodic acid in mols. compared with a blank solution (time in min.) was: oxodelpheline, dehydro-oxodelpheline, and demethylenedehydro-oxodelpheline, 0·0 (1080); demethyleneoxodelpheline, 0·94 (10), 0·96 (30), 1·07 (120), 1·23, *1·69* (1080); demethyleneoxodelpheline acetate, *0·3* (1080). Figures in italics denote up-take in the presence of sodium hydrogen carbonate.

Demethyleneoxodelpheline seco-*Diketone* (IV).—Demethyleneoxodelpheline (103 mg.) and periodic acid (57 mg., 1·1 mols.) in ethanol (5 ml.) and water (5 ml.) were kept at room temperature for 15 min. The resulting seco-*diketone* (IV), isolated with chloroform, crystallised from ethyl acetate–*cyclo*hexane in plates (60 mg.), m. p. 212—214°, $[\alpha]_D$ +92°, $\lambda_{max.}$ 319 mμ (ε 310), $\nu_{max.}$ 1765, 1706, and 1645 cm.$^{-1}$ (in Nujol 1754, 1710, and 1630 cm.$^{-1}$) (Found: C, 64·2; H, 7·7; N, 3·3. $C_{24}H_{35}O_7N$ requires C, 64·1; H, 7·85; N, 3·1%). In this preparation it is important to exclude added acid or base, and to work at low temperature.

Demethyleneoxodelpheline seco-*Diketone Acetate* (V).—(*a*) The *seco*-diketone (65 mg.) was treated with acetic anhydride (1 ml.) and pyridine (3 ml.) at room temperature overnight, to form the *acetate* (V) (58 mg.), which separated from ethyl acetate–*cyclo*hexane in sheaves of crystals, m. p. 177—179° (after sintering at 176°), $[\alpha]_D$ +97°, $\lambda_{max.}$ 317 (ε 344) (Found: C, 63·5; H, 7·7; N, 3·1. $C_{26}H_{37}O_8N$ requires C, 63·5; H, 7·6; N, 2·85%). (*b*) Demethyleneoxodelpheline acetate (51 mg.) in acetic acid (1·0 ml.) and a saturated solution of lead tetra-acetate in acetic acid (2·5 ml., 1·25 mols.) was left for 90 min. Saturated sodium acetate solution (3 ml.), potassium iodide (50 mg.), and excess of sodium thiosulphate were then added. Isolation with chloroform and crystallisation from ethyl acetate–*cyclo*hexane produced the *seco*-diketone acetate (V) (40 mg.), m. p. 175—178°, not depressed by sample *a*.

Demethyleneoxodelpheline diseco-*Acid* (VII).—Demethyleneoxodelpheline (310 mg.) and periodic acid (300 mg., 2·1 mols.) in ethanol (10 ml.) and water (10 ml.) were left for 15 min. The solution was then saturated with sodium hydrogen carbonate. Next day the acidic product was extracted with chloroform and crystallised from chloroform–ether. The resulting diseco-*acid* (VII) had m. p. 201—201·5° (after sintering at 198°), $[\alpha]_D$ −3°, $\lambda_{max.}$ 285 mμ (ε 57), $\nu_{max.}$ 1738, 1710, and 1642 cm.$^{-1}$, p*K*′ 4·06 (Found: C, 62·0; H, 7·6; N, 3·2. $C_{24}H_{35}O_8N$ requires C, 61·9; H, 7·6; N, 3·0%). In some experiments using crude demethyleneoxodelpheline a small amount of *iso*oxodelpheline was also isolated.

Alternatively, the *seco*-diketone (IV) (22 mg.) and periodic acid (23 mg.) in ethanol (2 ml.) and saturated sodium hydrogen carbonate solution (5 ml.) were kept overnight, to give the same *diseco*-acid (VII) (15 mg.), m. p. 198—201° not depressed by the first sample.

Diazomethane converted the acid into the *methyl ester*, plates (from methanol–*cyclo*hexane), m. p. 194—196° (Found: C, 62·6; H, 7·8; N 3·1. $C_{25}H_{37}O_8N$ requires C, 62·6; H, 7·8; N, 2·9%).

Dehydrodemethyleneoxodelpheline seco-*Diketone* (VI).—When a saturated solution of lead tetra-acetate in acetic acid (4 ml., 1 mol.) was added to a solution of dehydrodemethyleneoxodelpheline (100 mg.) in the same solvent a deep orange-pink colour gradually developed. After ½ hr. the reaction was stopped and the product isolated as in the oxidation of demethyleneoxodelpheline. The resulting α-*diketone* (VI) crystallised from ethyl acetate–*cyclo*hexane as orange-red rosettes (58 mg.), m. p. 161—163°, $[\alpha]_D$ −250°, $\lambda_{max.}$ 490 mμ (ε 163), $\nu_{max.}$ 1775, 1755, 1712, and 1670 cm.$^{-1}$ (Found: C, 64·0; H, 7·5; N, 2·7. $C_{24}H_{33}O_7N$ requires C, 64·4; H, 7·4; N, 3·1%).

Elimination of Methanol from the seco-*Compounds with Acid.*—A solution of the *seco*-diketone (IV) (125 mg.) in methanol (3 ml.) and N-hydrochloric acid (10 ml.) was boiled for ½ hr. The resulting unsaturated *ketone* (IX), isolated with chloroform (and kept away from base),

crystallised from ethyl acetate–*cyclo*hexane in plates (97 mg.), m. p. 213—215° (after sintering at 210°), $[\alpha]_D$ +72°, $\lambda_{max.}$ 225 and 320 mμ (ε 11,000 and 322), $\nu_{max.}$ 1768, 1680, and 1645 cm.$^{-1}$ (Found: C, 66·2; H, 7·7; N, 3·2; OMe, 15·0. $C_{23}H_{31}O_6N$ requires C, 66·2; H, 7·5; N, 3·4; 2OMe, 14·8%).

The *diseco*-acid (VII) (134 mg.) in methanol (4 ml.) and N-hydrochloric acid (6 ml.) was boiled for 15 min. Isolation with chloroform gave two products. The unsaturated *acid* (XI) crystallised from ether in rosettes (65 mg.), m. p. 233—234° (decomp.), $[\alpha]_D$ −52°, $\lambda_{max.}$ 233 mμ (ε 6250) (Found: C, 63·8; H, 7·2; OMe, 15·15. $C_{23}H_{31}O_7N$ requires C, 63·7; H, 7·2; 2OMe, 14·3%). The neutral pseudo-*ester* (VIII) formed prisms (35 mg.) (from chloroform–ether), m. p. 314° (decomp.), $[\alpha]_D$ −53°, $\lambda_{max.}$ 209—210 and 230—233 mμ (ε 8000 and 7000), $\nu_{max.}$ 1755, 1685, and 1646 cm.$^{-1}$ (Found: C, 64·1; H, 7·5; N, 3·2; OMe, 20·9. $C_{24}H_{33}O_7N$ requires C, 64·4; H, 7·4; N, 3·1; 3OMe, 20·8%). The *pseudo*-ester (VIII) was also made by treatment of the unsaturated acid (XI) with acid methanol.

The red α-diketone (VI) (35 mg.) in methanol (1 ml.) and N-hydrochloric acid (10 ml.) was boiled for 10 min. Isolation with chloroform and crystallisation from ethyl acetate–*cyclo*hexane yielded the unsaturated α-*diketone* (X) (25 mg.) as red leaflets, m. p. 176—179°, $[\alpha]_D$ −287°, $\lambda_{max.}$ 223 and 494 mμ (ε 10,000 and 184), $\nu_{max.}$ 1772, 1754, and 1658 cm.$^{-1}$ (last band broad and intense) (Found: C, 66·6; H, 7·0; OMe, 15·2. $C_{23}H_{29}O_6N$ requires C, 66·5; H, 7·0; 2OMe, 14·9%).

Action of Alkali on the seco-*Compounds*.—The *seco*-diketone (IV) (113 mg.) in ethanol (2 ml.) and N-sodium hydroxide (4 ml.) was boiled for 8 min. The *aldol* isomer of the unsaturated ketone (IX) (85 mg.), isolated with chloroform and crystallised from ethyl acetate–*cyclo*hexane, had m. p. 219—220°, $[\alpha]_D$ −164°, $\lambda_{max.}$ 319—322 mμ (ε 75), $\nu_{max.}$ 1752 and 1635 cm.$^{-1}$ (Found: C, 66·0; H, 7·6; N, 3·35; OMe, 14·7. $C_{23}H_{31}O_6N$ requires C, 66·2; H, 7·5; N, 3·4; 2OMe, 14·85%). Similar treatment of the *seco*-diketone acetate (V) led to the same product.

The unsaturated *seco*-diketone (IX) (100 mg.) in methanol (4 ml.) and N-sodium hydroxide (6 ml.) was boiled for 15 min. to produce the aldol isomer (76 mg.), $[\alpha]_D$ −160°, m. p. 221—224°, not depressed by the previous sample.

Addition of N-sodium hydroxide (1 ml.) to a solution of the α-diketone (VI) (100 mg.) in methanol (2 ml.) at 0° decolorised the solution, which was immediately extracted with chloroform. The red gum that remained on evaporation of the solvent was dissolved in ether; colourless needles of the aldol isomer (10 mg.) were then deposited. After recrystallisation from ethyl acetate–*cyclo*hexane they had m. p. 198—201° (decomp.), $[\alpha]_D$ −101°, $\lambda_{max.}$ 312 mμ (ε 59). The residue crystallised from ethyl acetate–*cyclo*hexane as the unsaturated α-diketone (X) (72 mg.), m. p. 166—168°, undepressed by the sample prepared with acid.

Alternatively, the α-diketone (VI) (531 mg.) in ethyl acetate (6 ml.) containing a trace of acetic acid was heated on a steam-bath for ½ hr. As the solution cooled it deposited colourless needles of the *aldol* isomer (50 mg.), m. p. 165—166° (decomp.), $[\alpha]_D$ −103°, $\lambda_{max.}$ 308 mμ (ε 56), $\nu_{max.}$ 1755, 1720, and 1642 cm.$^{-1}$ (Found: C, 64·2; H, 7·4; N, 3·65. $C_{24}H_{33}O_7N$ requires C, 64·4; H, 7·4; N, 3·1%). The m. p. could not be raised by repeated recrystallisation from ethyl acetate–*cyclo*hexane. A mixture of this sample with the one melting at 198—210° (above) melted at 175—185°. Lack of material prevented a closer investigation of the discrepancy.

Titration of Some seco-*Compounds with Lead Tetra-acetate*.—Under the conditions detailed before, the up-take of lead tetra-acetate in mols. (time in min.) was: *seco*-diketone (IV), 0·19 (2), 0·42 (5), 0·65 (12), 0·73 (15), 0·85 (30), 0·97 (60), 0·96 (120); *seco*-diketone acetate (V), 0·0 (120); aldol isomer of the unsaturated *seco*-diketone (IX), 0·71 (5), 0·88 (15), 0·93 (30), 0·99 (60).

Oxidation of the Aldol with Lead Tetra-acetate.—The aldol isomer of the unsaturated *seco*-diketone (IX) (22 mg.) in acetic acid (2 ml.) and saturated lead tetra-acetate solution (0·7 ml., 0·9 mol.) was left for 10 min. Crystallisation of the product from ethyl acetate–*cyclo*hexane produced the unsaturated α-diketone (X) (11 mg.), $[\alpha]_D$ −283°, m. p. and mixed m. p. 176—179°.

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