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The Aconite Alkaloids. XXXV. Structural Studies with Delphinine Derivatives*

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The investigations reported do not permit the derivation of a ring structure for delphinine and aconitine. Renewed studies on the exhaustive methylation of delphonine confirm our previous findings. This could not be brought beyond the stage of the first methine base. The formation of the latter with the nitrogen attached to a diterpenoid geminal methyl would require rearrangement of the other methoxyl-bearing geminal group. The oxidation of oxodelphonine, dihydropyrooxodelphonine, and dihydroisopyrooxodelphonine has in each case been intercepted at the stage of a cyclopentanone (infrared data) which can be oxidized further to a keto acid in which the new keto group is in a six-membered or larger ring. The cyclopentanones, in contrast to the original hydroxy compounds, are all readily isomerized to strongly levorotatory stereoisomers. This is apparently due to enolization. On vacuum sublimation the keto acid from dihydroisopyrooxodelphonine readily cyclizes to yield the previously described neutral diketone in contrast to the acids from α-oxodelphonine and dihydropyrooxodelphonine which distil unchanged. A number of these derivatives have been crystallized. Attempts to reconcile all of our data with a lycoctonine or napelline structure have not been successful and our previous proposal for delphinine has been withdrawn.

The aconite alkaloids which have been grouped provisionally into the very poisonous highly oxygenated aconitine type of ester bases and the less toxic atisine type[1] have been long suspected to be chemically related, and recent work has given data from a number of them which strengthen this suspicion. The first clue to the relationship of these substances to the diterpenes was found in the dehydrogenation studies of this laboratory.[2] More recent work has led to the practically complete structural elucidation of veatchine,[3,4] atisine,[4,8] and garryfoline and cuauchichicine.[9] The dehydrogenation procedure unfortunately proved much less satisfactory with the aconitine type of base but the accumulated data made quite certain that a saturated hexacyclic structure is involved in the case of aconitine and delphinine in which a ring nitrogen carries an ethyl or a methyl group. Extensive studies have shown the nature and probable interrelationships of the substituting groups of delphinine.[10,11] The first derivation of the actual skeletal structure of a hexacyclic aconitine base, however, was shown by the outstanding x-ray studies of a lycoctonine derivative by Przybylska and Marion.[12] This was shown to be related in part to a phyllocladene structure in which ring B has been enlarged to a cycloheptane at the expense of ring C, and the latter reduced to a cyclopentane with other changes. Such a ring structure has been satisfactorily adopted by Cookson and Trevett[13] for their experimental data with delpheline and by Anet, Clayton and Marion for delcosine.[14] Very recently Wiesner *et al.* have adopted a more normal diterpenoid core to explain their data with napelline and napellonine.[15]

In this laboratory the attempt was once made to correlate the data accumulated for delphinine with the lycoctonine structure, but a number of facts persist which appear inconsistent with this interpretation unless unusual rearrangements are assumed to occur. There is the authors' early and now recently repeated experience in an attempted exhaustive methylation of delphonine.[16,17] At the

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) E. S. Stern, "The Aconitum and Delphinium Alkaloids" in *The Alkaloids, Chemistry and Physiology*, Vol. IV, edited by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1954, pp. 275–333.

(2) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **152**, 645 (1944).

(3) K. Wiesner *et al.*, *J. Am. Chem. Soc.*, **76**, 6068 (1954).

(4) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

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(8) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, **78**, 4139, 4144 (1956).

(9) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor, and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801, 6633 (1955).

(10) W. A. Jacobs and S. W. Pelletier, *J. Am. Chem. Soc.*, **76**, 161 (1954).

(11) W. A. Jacobs and S. W. Pelletier, *Chemistry and Industry*, 948 (1955).

(12) M. Przybylska and L. Marion, *Can. J. Chem.*, **34**, 185 (1956).

(13) R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 3121 (1956).

(14) R. Anet, D. W. Clayton, and L. Marion, *Can. J. Chem.*, **35**, 397 (1957).

(15) K. Wiesner, Z. Valenta, J. F. King, R. K. Mandgal, L. G. Humber, and Shô Iho, *Chemistry and Industry*, 173 (1957).

(16) L. C. Craig, L. Michaelis, S. Granick, and W. A. Jacobs, *J. Biol. Chem.*, **154**, 293 (1944).

(17) In earlier work in this laboratory all attempts to carry such degradation beyond this first stage to nitrogen-free material proved unsuccessful. In view of the recent papers of Schneider [*Arch. d. Pharm.* **283**, 86, 281 (1950)] who reported carrying the procedure to nitrogen-free material which was then oxidized to an acid $C_{20}H_{24}O_{12}$, the authors have repeated this study. After the first step, attempted methylation of the methine base with subsequent distillation of the "ammonium base" always gave negligible amounts of nitrogen-free material. The recovered base gave *N*-methyl analyses incompatible with further methylation. By following the experimental conditions reported

first stage the methyl ammonium base yields without difficulty what appears to be an *N*-dimethyl methine base. Barring rearrangement perhaps involving the methoxyl bearing geminal methyl group such a product would not be expected to arise from a lycoctonine type of skeleton. A second point is the formation from dihydroisopyrooxodelphonine[18] of a keto acid, $C_{24}H_{35}NO_8$[19] which readily cyclizes on vacuum sublimation to give the diketone, $C_{24}H_{33}NO_7$. This was shown more recently to contain both a cyclohexanone and a cyclopentanone ring.[20] An attempt was made in the authors' last communication[20] to reconcile the data at hand with a new structural proposal for delphinine.[21] However, more recent work has now shown such a structure to be untenable, and inconsistencies also persist with a lycotonine or napelline type of skeleton for it.

Unless no change in ring structure can be shown to occur in the steps leading to the formation of isopyrooxodelphonine, the data obtained with the latter could give rise to false conclusions. The authors have therefore studied other delphinine derivatives beginning with delphonine. In a recent study of the latter it has been found that when allowed to stand exposed it gradually becomes contaminated, probably by oxidation, and shows infrared peaks of varying intensity at 1710 and 1653 cm.$^{-1}$. However, when chromatographed through alumina, such contaminating material can be readily removed and the purified delphonine shows no significant band in this region. Schneider[22] has attributed the absorption of crude delphonine at 5.87 μ to an –NCHOH– group which opens to give an amino aldehyde. The authors' experience does not substantiate this conclusion.

On turning to α-oxodelphonine it was recently obtained crystalline for the first time, separating from methanol with one mole of solvent. On oxidation with chromic oxide it passes through the stage of a beautifully crystalline α-oxodelphonone, $C_{24}H_{35}NO_8$, which shows the absorption of a cyclopentanone (1751 cm.$^{-1}$ in Nujol). On further oxidation the amorphous keto acid was obtained showing a band at 1736 cm.$^{-1}$ (Nujol) 1728 (chf.). The position of this absorption does not permit a decision between a cyclopentanone and a larger ring ketone. Because of the infrared data found with the amorphous methyl ester (1706 cm.$^{-1}$, cyclohexanone; 1730 cm.$^{-1}$, methyl ester) it is probable that the keto acid contains a cyclohexanone or larger ring.

A return was then made to the study of the pyro series. Dihydropyro-α-oxodelphonine[19] has recently been obtained crystalline from methanol. On oxidation with chromic acid it yields the previously reported keto acid, $C_{24}H_{35}NO_8$[19]. The latter has been found to crystallize also from methanol but in a solvated form (m.p. 183–190°) different from that previously described. The infrared absorption (1724 cm.$^{-1}$) in Nujol of the latter indicates a cyclohexanone or larger ring. After sublimation this remained the same.

The formation of the ketoacid was intercepted at the stage of the neutral intermediate crystalline ketone, dihydropyro-α-oxodelphonone, $[\alpha]_D$+9.4°. The infrared absorption (1749 cm.$^{-1}$ in Nujol; 1766 in CCl_4) of the latter again indicates a cyclopentanone. This on further oxidation gave the keto acid. The keto acid yields a crystalline methyl ester with absorption indicating a cyclohexanone (or higher) acid. (1706, 1734 cm.$^{-1}$ in CCl_4; 1711, 1727 in $CHCl_3$). Contrary to the experience with the keto acid from dihydroisopyro-α-oxodelphonine which forms a neutral diketone on sublimation, this keto acid is distilled as such in mercury pump vacuum without loss of water; infrared absorption (1724 cm.$^{-1}$ in Nujol). The fact that the keto acid from dihydropyrooxodelphonine can be distilled unchanged in contrast to the previously recorded behavior of the keto acid from dihydroisopyrooxodelphonine, which yielded a neutral diketone containing a new cyclopentanone ring, suggested the possibility of a change in ring size during the isomerization of pyrooxodelphonine to the isoderivative.[23] To check such a possibility the oxidation of dihydropyroisooxodelphonine was again studied. Under conditions analogous to those used with its isomer, chromic oxide was found to oxidize it through an intermediate neutral ketone to the previously recorded keto acid.[19] Unfortunately, this neutral ketone was not obtained in pure crystalline form. It was found to separate as mixed crystals with its precursor. From the rotation of this mixture, $[\alpha]_D$ −25°, the ketone must be less levorotatory, if not actually dextrorotatory, than its precursor of $[\alpha]_D$ −36°. Preliminary infrared study of such mixtures showed a small fractional peak at 1754 cm.$^{-1}$ ($CHCl_3$) as required by a cyclopentanone and resembling the data from the

by Schneider similar results were obtained. In the available communications of the author, no nitrogen analysis on the "nitrogen-free" material is reported. His statement that the product gave a negative Lassaigne nitrogen test is hardly convincing.

It can be reported in this connection that reaction of the methine base with methyliodide has given in small yield a beautifully crystalline iodide of lower methoxyl content and of no greater *N*-methyl content. This suggests possible loss of the methoxyl-bearing geminal methyl group. This is being studied further.

(18) W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, **170**, 209 (1947).

(19) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **180**, 479 (1949).

(20) W. A. Jacobs and S. W. Pelletier, *J. Am. Chem. Soc.*, **78**, 3542 (1956).

(21) In several formulas given in this paper an error has come to the authors' attention in which the position at 9,14 assigned to the double bond violates Bredt's rule. However, this can be overcome by placing the double bond at 8,14 or the acetoxyl group at 8 and the former at 7,8.

(22) W. Schneider, *Chem. Ber.*, **89**, 768 (1956).

(23) Such a proposal, but without any experimental data, was also made by K. Wiesner in a personal communication to us.

isomeric dihydropyrooxodelphonone. The attempt to separate this mixture through acid-washed alumina (*p*H 4.5) led to a most unusual result. More than a third of the material was eluted as a ketone before the appearance of the original unoxidized dihydroisopyrooxodelphonine. But the ketonic material was now strongly levorotating, $[\alpha]_D$ −127°. Its infrared absorption showed a strong cyclopentanone peak at 1747 cm.$^{-1}$ (CCl_4) which approximated that of the original mixture. Its analysis confirmed it to be an isomer of the intermediate neutral ketone, $C_{24}H_{35}NO_7$. On further oxidation with chromic acid it yielded an amorphous keto acid, $C_{24}H_{35}NO_8$, $[\alpha]_D$ −3°, isomeric with the crystalline oxidation product from dihydroisopyro-oxodelphonine.

Dihydropyrooxodelphonone was also found to isomerize when passed through acid-washed alumina to yield an amorphous strongly levo rotating isomer, $[\alpha]_D$−107°.[24] This isomerization was shown to be rather general, since α-oxodelphonone was similarly isomerized by alumina to a strongly levorotating amorphous iso-α-oxodelphonone, $[\alpha]_D$ −80°. Since the preparation of these intermediate ketones was carried out under acid conditions it appeared probable that such alumina-induced (*ca. p*H 4 to 5) isomerizations were not due to acid. This was substantiated in the case of α-oxodelphonone by its rapid change with sodium hydroxide to the same substance obtained with alumina. It was not affected in a similar way by acid and was in part recovered unchanged. Since the precursors of the intermediate ketones are obtained by alkali saponification, the isomerizations must involve the carbonyl group of the ketones, and are presumably effected by enolization with a vicinal hydrogen-bearing carbon atom, with change of configuration and formation of the epimeric ketone.

Since attempts to accommodate our data to a specific ring system have not been satisfying as yet, the authors shall not attempt, at the present time, to propose a structure for delphinine or its derivatives. This will be left to a later opportunity when work which is still in progress has been completed. But it can be concluded that the data here reported are inconsistent with the previously proposed structure for delphinine.[20] There are only two positions in ring C in such a structure available for a benzoylated secondary hydroxyl group which after saponification followed by oxidation would yield an intermediate cyclopentanone. Although the latter, on further oxidative ring cleavage could give a ketoacid containing a cyclohexanone or larger ring ketone, in neither case, barring unusual rearrangements, would cyclization occur to give a new cyclopentanone ring such as is present in the neutral diketone obtained from dihydroisopyro-α-oxodelphonine.

(24) Unfortunately infrared data for all of these isomerized substances were not available at the time of the writing of this paper.

EXPERIMENTAL

Delphonine. A solution of 20 g. of delphinine in a mixture of 200 ml. of ethanol and 200 ml. of 10% sodium hydroxide was heated under reflux for 2 hr. After removal of most of the alcohol *in vacuo* the delphonine was extracted with ether. The extract was dried over potassium carbonate. After removal of solvent 15 g. of resin remained. A solution of 11.5 g. of this material in 100 ml. of benzene was chromatographed through 550 g. of Merck alumina and first eluted with benzene (1 l.) then with 0.5% methanol in benzene (1 l.) without result. On changing to 1% methanol no solid emerged until 1800 ml. was used and then elution began in very small fractions of about 30 mg./25 ml. which gradually rose to about 90 mg. After 80 such fractions, the eluted material had diminished to about 60 mg. in 25 ml., and a change to 2% methanol was made. Since this did not quickly affect the result after another 600 ml. was used, a change to 3% methanol was made. The eluted material gradually reached a peak of 0.2 g. per 25 ml. After about 900 ml. was used this quickly diminished to very small amounts of solid. However, only in this final material which totaled only about 0.48 g. was a large peak shown in the infrared at 1652 cm.$^{-1}$ The fractions from the beginning of elution through the greatest part which totaled about 9.2 g. showed no appreciable infrared absorption in the 6-μ region. $[\alpha]_D^{27}$ +36° (*c*, 0.6 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{39}NO_7$: C, 63.55; H, 8.67. Found: C, 63.52; H, 8.64.

α-Oxodelphonine. A suspension of 10 g. of α-oxodelphinine in 250 ml. of 95% alcohol was brought to a boil and after addition of 50 ml. of 4% aqueous sodium hydroxide was refluxed for 7 min. during which solution rapidly occurred. Sufficient 50% acetic acid was added to acidify the mixture which was then concentrated *in vacuo* to remove the alcohol. The residue was dissolved in water and treated with sodium bicarbonate solution and the solution was extracted 10 times with chloroform. The cleared extract yielded 8.55 g. of resin. Contrary to earlier experience this was finally crystallized from methanol forming four-sided, pointed platelets which contained 1 mole of solvent and melted at 118–120°; $[\alpha]_D^{25}$ −7.5° (*c*, 0.80 in chloroform). It is readily soluble in acetone.

Anal. Calcd. for $C_{24}H_{37}NO_8 \cdot CH_3OH$: CH_3OH, 6.22. Found: 6.28.

For analysis it was dried at 100° at 0.2 mm.

Anal. Calcd. for $C_{24}H_{37}NO_8$: C, 61.65; H, 7.98. Found: C, 61.38; H, 7.99.

α-Oxodelphonone and the keto acid $C_{24}H_{35}NO_9$. A solution of 3 g. of α-oxodelphonine in 75 ml. of redistilled acetic acid[25] was stirred at room temperature and treated during 10 min. with 5.6 ml. (4.3 ml. represents about one equivalent of oxygen) of a fresh 10% aqueous chromium trioxide solution. After an hour the mixture was diluted with 100 ml. of water and extracted 10 times with chloroform. At this point and at the following steps of the procedure, the addition of small amounts of NaCl solution to the aqueous phases aided an otherwise somewhat slow phase separation. The extract was washed four times with 20-ml. portions of water and then with water containing sufficient sodium carbonate to remain alkaline to phenolphthalein. This was followed by repeated washings with small portions of water until the washings were no longer alkaline. The chloroform layer, after clearing with sodium sulfate, concentrating *in vacuo* to dryness, and flashing off with benzene yielded 2.28 g. of resin. When dissolved in a small volume of acetone α-oxodelphonone soon crystallized as well-formed hexagonal or rhombic platelets

(25) The acetic acid used in all of the oxidations reported was twice distilled over CrO_3.

of varying width and length. Because of persistent contamination with starting material it was necessary to recrystallize it repeatedly; m.p. 198–208°; $[\alpha]_D^{29}$ +33° (*c*, 0.52 in chloroform) ν^{Nujol} 1751.cm^{-1} It contained solvent and for analysis was dried at 110° and 0.2 mm. It also crystallized readily from methanol.

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.90; H, 7.51.

As described later, this substance is changed on standing with alkali or on attempted chromatographing through alumina.

Following the separation of additional less pure fractions from the acetone mother liquors, a resinous solid remained which crystallized readily from methanol on seeding and proved to be starting material.

The sodium carbonate extract with subsequent aqueous washings was repeatedly extracted with chloroform to remove retained dissolved neutral material, then acidified with sulfuric acid and repeatedly extracted with chloroform. The latter on concentration yielded 277 mg. of the keto acid, $C_{24}H_{35}NO_9$. All attempts to crystallize this acid were unsuccessful and it was therefore analyzed directly after drying at 110° and 0.2 mm. $[\alpha]_D^{29}$ +9.6° (*c*, 0.52 in chloroform). ν^{Nujol} 1736, ν^{CHCl_3} 1728 $cm.^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_9$: C, 59.86; H, 7.33. Found: C, C, 59.91; H, 7.20.

The same keto acid was obtained by similar oxidation of the previous intermediate ketone. 0.1 g. of the latter gave 47 mg. of the keto acid; $[\alpha]_D^{29}$ +10° (*c*, 0.50 in chloroform). ν^{Nujol} 1736 $cm.^{-1}$

Anal. Found: C, 59.97; H, 7.21.

The methyl ester which was obtained with diazomethane could not be crystallized. $[\alpha]_D^{31}$ −24.5° (*c*, 0.49 in $CHCl_3$) ν^{Nujol} 1706, 1730 $cm.^{-1}$ For analysis it was dried at 100° and 0.2 mm.

Anal. Calcd. for $C_{25}H_{37}NO_9$: C, 60.59; H, 7.53. Found: C, 60.13; C, 7.48.

Dihydropyro-α-oxodelphonine. Two grams of octahydropyro-α-oxodelphinine in 25 ml. of methanol was treated with 25 ml. of 10% sodium hydroxide and allowed to stand at room temperature for 1 hr. The solution was diluted with 20 ml. of saturated sodium chloride solution to aid separation and extracted ten times with chloroform. The latter was washed with sodium chloride solution and the solvent was removed *in vacuo* followed by flashing with benzene. The resin crystallized from methanol as nearly rectangular platelets. When recrystallized from methanol, it contained one mole of solvent and melted at 103–104°. $[\alpha]_D^{29}$ −24°. (*c*, 0.50 in chloroform).

Anal. Calcd. for $C_{24}H_{37}NO_7 \cdot CH_3OH$: CH_3OH, 6.65. Found: CH_3OH, 6.40. For analysis it was dried at 0.2 mm. and 100°.

Anal. Calcd. for $C_{24}H_{37}NO_7$: C, 63.81; H, 8.26. Found: C, 63.74; H, 8.13.

Oxidation of dihydropyro-α-oxodelphonine. Different conditions than previously reported were used in this oxidation. A stirred solution of 1.49 g. of solvent-free dihydropyro-α-oxodelphonine in 50 ml. of acetic acid was carefully treated during 10 min. with 7.0 ml. of a fresh 10% aqueous chromium trioxide solution which was approximately 50% in excess of the amount required for conversion to the keto acid. However, even after an additional 5 min., when the reaction was interrupted, oxidation was found to be incomplete as shown by the isolation of some of the intermediate ketone in the neutral fraction. The diluted solution, after addition of sodium chloride to aid separation, was thoroughly extracted with a good volume of chloroform. The dried extract was concentrated *in vacuo*, finally flashing off the residue with benzene to remove acetic acid. The residue was dissolved in acetone, filtered from a small amount of inorganic material, and concentrated to a small volume. On careful addition of water and seeding, the acid gradually separated as micro leaflets and was collected with 25% acetone. It possessed the properties previously reported and contained water of crystallization; m.p. 132–136° after preliminary sintering. Additional succeeding fractions were gradually obtained by concentration and seeding of the filtrates. The yield of crude keto acid was about 0.64 g. These fractions were found to be contaminated increasingly with neutral material and were therefore purified by extraction of their chloroform solution with dilute sodium carbonate solution followed by washing with water. It was found necessary to rextract these combined aqueous phases repeatedly with chloroform before acidification to remove some neutral material which was carried into the aqueous phase. The reacidified carbonate solution was then further extracted with chloroform to obtain the keto acid. This has been found to crystallize from methanol as well-formed four-sided plates or prisms which contained solvent and gradually melted at 183–190°; $[\alpha]_D^{28}$ −5.7° (*c*, 0.47 in $CHCl_3$); ν^{Nujol} 1724 $cm.^{-1}$ The analysis of this material was found difficult since even when dried at 130° and 0.2 mm. it retained solvent and gave low carbon figures.

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.35; H, 7.80.

When such material was dissolved in acetone and the solvent was flashed off *in vacuo* it gave correct figures when dried at 110°.

Anal. Found: C, 61.82; H, 7.68.

Contrary to the isomeric keto acid from dihydroiso-pyro-α-oxodelphonine this keto acid sublimed largely unchanged. It (0.2 g.) was introduced into the sublimation apparatus with acetone and after removal of solvent it was gradually heated in an oil bath under a mercury pump vacuum of 0.01 to 0.001 mm. Condensation occurred especially from 170–190°. After reaching 220° practically all had sublimed during a total of 33 minutes' heating. The condensate was dissolved in chloroform and extracted with dilute sodium carbonate solution. The latter with the washings, after reacidification, was reextracted with chloroform. It yielded 0.15 g. of unchanged keto acid, ν^{Nujol} 1724 $cm.^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.85; H, 7.38. It recrystallized readily from methanol; m.p. 183–190°; $[\alpha]_D^{27}$ −4° (*c*, 0.56 in $CHCl_3$).

Dihydropyro-α-oxodelphonone. The filtrate from the keto acid in the previous oxidation was dissolved in chloroform and extracted with sodium carbonate solution followed by several washings with water. The chloroform containing the neutral fraction, after drying and concentration *in vacuo*, yielded 0.43 g. In a small volume of methanol the ketone crystallized gradually as microneedles or four-sided and six-sided, long platelets which contained 1 mole of solvent; m.p. 169–177°; $[\alpha]_D^{29}$ +9.4° (*c*, 0.48 in $CHCl_3$). ν^{Nujol} 1749 $cm.^{-1}$; ν^{CCl_4}1766 $cm.^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_7 \cdot CH_3OH$: CH_3OH, 6.65. Found: CH_3OH, 6.80. For analysis it was dried at 0.2 mm. and 125–130°.

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85. Found: C, 64.08, H, 8.02.

The solvent-free ketone (36 mg.) was further oxidized in acetic acid with excess chromium trioxide. After dilution and exhaustive extraction with chloroform, the keto acid was extracted with dilute sodium carbonate and aqueous washings. After reacidification and reextraction 22 mg. of the above keto acid was obtained which crystallized readily from methanol on seeding; m.p. 180–185°. $[\alpha]_D^{31}$ −13.5° (*c*, 0.52 in $CHCl_3$). The somewhat different rotation obtained with the material isolated above in the direct oxidation will require further study. The substance as obtained from methanol again showed the difficulty in removing solvent for analysis.

Anal. Found: C, 61.16; H, 7.64.

The methyl ester. The keto acid (45 mg.) in acetone readily yielded the ester with diazomethane. It crystallized without solvent from methanol mostly as four-sided prisms or from methanol-ether as needles; m.p. 177–180°; $[\alpha]_D^{28}$ −25° (*c*, 0.48 in $CHCl_3$). ν^{CHCl_3} 1725, 1712 $cm.^{-1}$; ν^{CCl_4} 1733, 1706 $cm.^{-1}$

Anal. Calcd. for $C_{25}H_{37}NO_8$: C, 62.61; H, 7.78. Found: C, 62.71; H, 7.65.

The oxidation of dihydroisopyrooxodelphonine. A solution of 0.4 g. of dihydroisopyrooxodelphonine [$[\alpha]_D^{30}$ −36° (*c*, 0.5 in $CHCl_3$)] in 13.6 ml. of acetic acid was gradually treated with stirring with 1.2 ml. of fresh 5% aqueous chromium trioxide solution (1 mole). The reagent was used up quite rapidly and after 35 min. the solution was diluted, treated with 1 ml. of saturated sodium chloride solution to aid separation, and extracted 13 times with chloroform. The extract was washed once with 5 ml. of water, cleared with sodium sulfate, and concentrated *in vacuo* to dryness with final flashing off with benzene to remove acetic acid. The solution in chloroform was extracted with a solution of 0.15 g. of sodium carbonate dissolved in 2 ml. of water, followed by three 1-ml. washings with water. After standing about an hour the combined sodium carbonate and water washings were extracted 7 times with chloroform. The latter yielded only 8 mg. of neutral material. The acidified aqueous phase after extraction with chloroform gave 0.112 g. of the previously described keto acid[19] which crystallized readily from acetone-ether as needles, m.p. 169–173°. The melting point varies considerably with the conditions of crystallization but this and the rotation of $[\alpha]_D^{31}$ −13.5° (*c*, 0.52 in $CHCl_3$) are somewhat different from the values obtained with the keto acid previously described.[19] The rotation of the latter has now been found to be $[\alpha]_D^{28}$ −3.6° (*c*, 0.56 in $CHCl_3$). This suggests isomerization at some stage which will require further study.

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.66; H, 7.61.

The chloroform solution containing the main neutral fraction yielded 0.295 g. of residue after flashing off with acetone. When dissolved in a small volume of acetone crystallization started, especially after addition of ether and partial concentration; after several hours a first fraction of 0.15 g. was collected, $[\alpha]_D^{28}$ −25°. (*c*, 0.48 in $CHCl_3$); m.p. 166–175°.

The mother liquor when similarly manipulated gave a second crystalline fraction of 55 mg; after sintering at 154° it gradually melted at 162 to 182°; $[\alpha]_D^{28}$ −28° (*c*, 0.54 in $CHCl_3$). Preliminary attempts to resolve this material into its components were not promising although from certain observations which will be left to a later communication it is probable that this can be done by the proper use of solvents. The attempt was made to do this with alumina washed to a *p*H of 4.5.

A solution of 0.21 g. of this mixture was chromatographed in benzene through 8.5 g. of alumina. Following preliminary unsuccessful elution with 100 ml. of benzene, 0.5% methanol in benzene was used. After 50 ml. it gradually yielded continuously very small fractions the nature of which was followed by rotations. The rotation of the initial fraction $[\alpha]_D^{30}$ −127° (*c*, 0.7 in $CHCl_3$) and succeeding fractions gave about the same value until elution had become very small. After the use of about 600 cc. solvent about 65 mg. were eluted, ν^{CCl_4} 1747 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85. Found: C, 64.38; H, 7.87.

The later elution with 1% methanol in benzene gradually yielded a total of 0.124 g. of unoxidized dihydroisopyrooxodelphonine which showed no ketonic band in the infrared.

A solution of 49 mg. of the ketone in 1.7 ml. of acetic acid was treated with 0.3 ml. of 5% chromium trioxide. Reaction quickly occurred. After 40 min. the mixture was diluted and extracted with chloroform. After removal of solvent and acetic acid the chloroform solution was extracted with sodium carbonate solution. The latter, after acidification and reextraction, yielded 35 mg. of amorphous keto acid which could not be crystallized. $[\alpha]_D^{31}$ −3° (*c*, 0.34 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 62.12; H, 7.34.

Dihydropyro-α-oxodelphonone and alumina. Dihydropyro-α-oxodelphonone (66 mg.) was chromatographed through 3.5 g. of acid-washed alumina as described in the case of its isomer. The material which was eluted with 0.5 methanol in benzene showed $[\alpha]_D^{28}$ −107° (*c*, 0.67 in $CHCl_3$). It formed a low-melting resin which could not be crystallized.

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85. Found: C, 64.20; H, 8.06.

Treatment of α-oxodelphonone with alumina. A solution of 0.24 g. of the ketone was chromatographed through 10 g. of acid-washed alumina. After benzene, 1% methanol in benzene was finally required for elution. Material appeared in successive fractions. The material could not be crystallized and showed a rotation of $[\alpha]_D^{28}$ −80°. (*c*, 0.625 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.94; H, 7.68.

A suspension of 25 mg. of α-oxodelphonone in 4 ml. of water and 1 ml. of methanol was warmed to effect solution. The cooled solution was treated with 0.5 cc. of 0.1*N* NaOH. The rotation taken within 11 minutes showed $[\alpha]_D$ −66°. No significant change of rotation was found after 24 hr. The diluted solution when extracted with chloroform yielded amorphous material which showed $[\alpha]_D^{30}$ −79.5° (*c*, 0.44 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 62.12; H, 7.69.

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Note added in proof: Since sending in this manuscript a paper on delphonine by N. K. Abubakurov and S. Yu. Unusov [*J. Gen. Chem. URSS*, **26**, 2011 (1956)] has come to our attention. From data obtained with a substance which they considered to be delphonine and which was obtained from saponified mother liquors of a mixture of alkaloids isolated from *Delphinium rotundifolium* Afan. they concluded that delphonine is not an *N*-methyl base but an *N*-ethyl base and that its formula is $C_{25}H_{41}NO_9$. This and other data which they report are so incompatible with the wealth of analytical data which we have obtained along with our other findings that we cannot accept their conclusions. There is the possibility that their "delphonine" is not identical with the delphonine from *Delphinium staphisagria*.

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