Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67. Found: C, 65.32; H, 8.77.

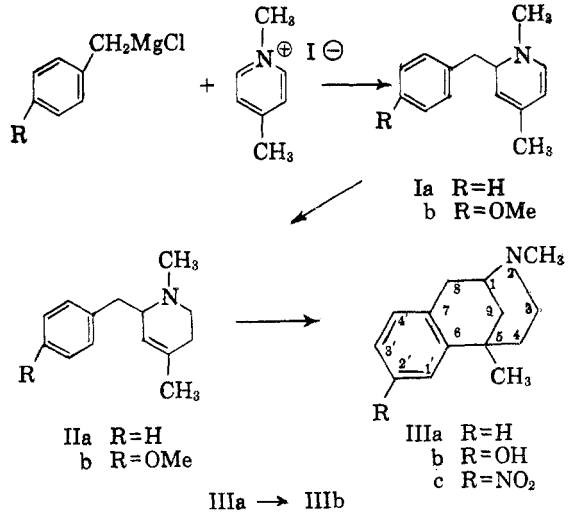
The corresponding *base* crystallized from methanol in prisms, m.p. 196–197.5°. It was dried *in vacuo* at 77° for analysis.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.64. Found: C, 76.46; H, 9.63.

2,5-Dimethyl-2'-nitro-6:7-benzomorphan (IIIc) *picrate.* To 11 ml. of nitric acid (sp. gr. 1.49–1.50) and 6 ml. of acetic acid, stirred and kept at 3–7°, was added during 2 hr. 2.3 g. of IIIa in 5 ml. of acetic acid. The solution was left for 20 hr. at *ca.* 25°, freed of acetic acid *in vacuo* at a bath temperature below 60°, and basified with ice–ammonium hydroxide. The liberated oil was dried in ether. Evaporation of the ether left 2.8 g. of base which, in 10 ml. of acetone, was added to 3.0 g. of picric acid in 30 ml. of acetone. Left at room temperature for 2 hr. and at 0° for 2 hr. the solution deposited 3.9 g. (72%) of IIIc picrate, m.p. 227–229°. The analytical sample (prisms from acetone) melted at 233–234.5° (dec.).

Anal. Calcd. for $C_{20}H_{21}N_5O_9$: C, 50.53; H, 4.45. Found: C, 50.69; H, 4.47.

Conversion of IIIc to IIIb. A mixture of 1.3 g. of IIIc (from 2.9 g. of picrate), 5 ml. of methanol, and 0.5 g. of 5% palladium–barium sulfate absorbed three molecular equivalents of hydrogen during 15 min. The filtered solution was evaporated to dryness. To the residue in 8 ml. of 3*N* sulfuric acid was added (0°, stirring) during 30 min., 0.3 g. of sodium nitrite in 2.5 ml. of water. The solution was then treated at 60–70° with a solution of 6 ml. of water and 6 ml. of water and 6 ml. of sulfuric acid, warmed to 80° during 15–20 min., poured into ice–ammonium hydroxide, and extracted with 40 ml. of chloroform in 4 portions. The dried extract was evaporated to give 0.8 g. of residue which crystallized from 8 ml. of acetone in a yield of 0.3 g. (25% from IIIc) m.p. 210–215°. A recrystallization from methanol (Norit) gave material identical with the IIIb described above. It was converted to the hydrochloride, m.p. 240–243° (dec.) whose infrared spectrum was identical with that of the IIIb hydrochloride prepared from γ-picoline methiodide.



Acknowledgment. We are indebted to Wendy Ness of this institute for statistical analysis of the pharmacological data.

BETHESDA, MD.

[CONTRIBUTION FROM THE DIVISION OF PURE CHEMISTRY, NATIONAL RESEARCH COUNCIL OF CANADA]

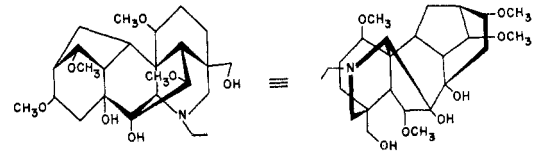
Lycoctonine: The "α-iso" and "Anhydro-α-iso" Compounds*[1]

O. E. EDWARDS, LÉO MARION, AND K. H. PALMER[2]

Received June 27, 1957

The lactam II from the *Delphinium* alkaloid lycoctonine can be oxidized by lead tetraacetate to a diketone III. This underwent internal aldol condensation to a compound IV which on heating with acid gave an isomer V. Further action of acid on V produced a pinacolic dehydration to VII. By hydrolysis of a methoxyl and lead tetraacetate cleavage, VII was converted to the γ-lactone acid IX. The properties and reactions of these compounds lend strong support to the currently accepted structure I for lycoctonine.

Structure I for lycoctonine[3] follows unambiguously[4] from the structure for des(oxymethylene)-lycoctonine determined by x-ray crystallography.[5] Most of the published chemistry of lycoctonine has been interpreted on the basis of this formula.[4]



I

The structures tentatively assigned to the transformation products of the *seco*diketone III derived from lycoctonam (II) seemed capable of chemical

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

(1) Issued as N.R.C. No. 4516.

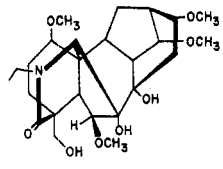
(2) National Research Council of Canada Postdoctoral Fellow.

(3) The representation showing the diterpenoid character of the structure (I) will be used in this communication.

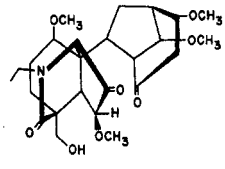
(4) O. E. Edwards, L. Marion, and D. K. R. Stewart, *Can. J. Chem.*, **34**, 1315 (1956).

(5) M. Przybylska and L. Marion, *Can. J. Chem.*, **34**, 1555 (1956).

verification. We wish now to report on the results of a study of these products.

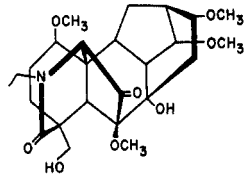


II



III

Treatment of III with bicarbonate or activated alumina[6] converted it to an isomer which was considered to be the internal aldol condensation product IV since the cyclopentanone carbonyl remained.[4,6] The correctness of this assignment of

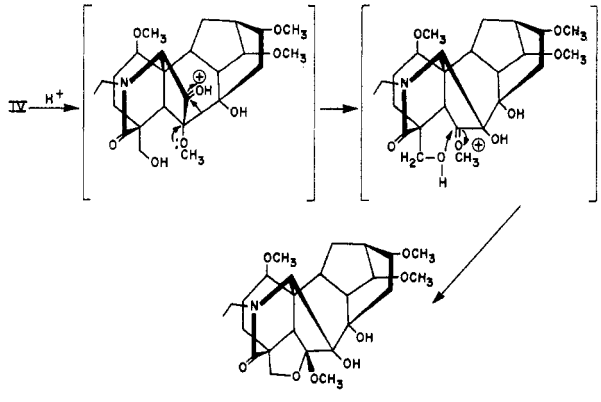


IV

iso COMPOUND

structure to the *iso* compound has now been established by tests of the structures of its acid-catalyzed transformation products, the *α-iso* and *anhydroiso* compounds.[6]

It was suggested[4] that the action of hot mineral acid on the *iso* compound IV brought about an interesting analog of the acid-catalyzed rearrangement of *tert*-α-ketols, giving rise to a second isomer, the *α-iso* compound. The probable mechanism for this transformation is illustrated below:



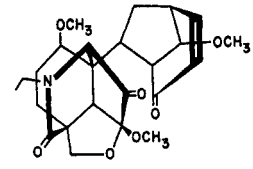
V

α-iso COMPOUND

A fully concerted mechanism is unlikely because of the difficulty of bringing the hydroxyl into bonding distance with the carbon holding the methoxyl, as long as this is tetrahedral (methoxyl interferes). Furthermore, such a mechanism ignores the role of the methoxyl in the reaction. We consider it very unlikely that a retropinacol-type reaction would take place with facility if no methoxyl were present.

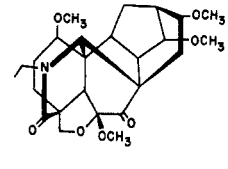
(6) O. E. Edwards and L. Marion, *Can. J. Chem.*, **32**, 195 (1954).

In structure V the original carbon skeleton of lycoctonine has been regenerated, and the vicinal glycol system is present in a very similar environment to that in lycoctonam (II). The obvious way to test this possibility was to try to cleave the molecule to a *seco*diketone, which should have unusual absorption spectra similar to those of III.[6] The *α-iso* compound was indeed cleaved by lead tetraacetate to a diketone having the characteristic carbonyl absorption in the infrared at 1716 and 1759 cm.$^{-1}$, and an ultraviolet spectrum (λ_{max} 3358 Å, log ε 2.13) similar to that of *seco*lycoctonam diketone (III). In addition, on treatment with acid the new *seco*diketone lost the elements of methanol under the same conditions[6] as *seco*lycoctonam diketone (III). The product had ultraviolet (λ_{max} 3460 Å, log ε 2.18; λ_{max} 2230 Å, log ε 3.96) and infrared absorption (max. 1765 cm.$^{-1}$, shoulder at 1670 cm.$^{-1}$) similar to that of desmethanol*seco*lycoctonam diketone,[6] hence can be formulated as VI. Thus strong support is provided for structure V for the *α-iso* compound.

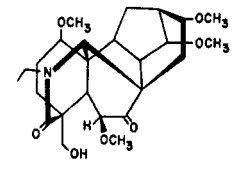


VI

Even more striking evidence for the correctness of the above assignments came however from a consideration of the structure of the *anhydroiso* compound. It was soon demonstrated that this product was not produced directly from IV, as we had originally assumed,[4] but was the product of further action of acid on V. (We shall, therefore, designate this substance as the *anhydro-α-iso* instead of *anhydroiso* compound.) Since the action of mineral acid on the glycol system of lycoctonam produces first a pinacolic dehydration,[7] a very reasonable postulate for the structure of the *anhydro-α-iso* compound was VIIa, the analog of the structure assigned to anhydrolycoctonam VIIb.



VII a



VII b

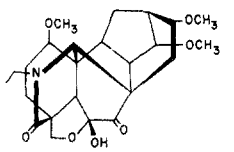
anhydro-α-iso COMPOUND

As would be expected from the fact that the *anhydro-α-iso* compound is the product of reaction in hot aqueous acid, the methoxyl of the postulated masked α-diketone of this compound proved difficult to hydrolyze. However, refluxing 6*N* acid

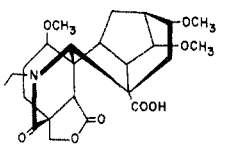
(7) O. E. Edwards and L. Marion, *Can. J. Chem.*, **30**, 627 (1952).

slowly hydrolyzed one methoxyl of the *anhydro-α-iso* compound producing a compound which should be the hemiketal VIII.

The correctness of all the assigned structures was demonstrated by the cleavage of VIII to the acid IX containing a γ-lactone (IR max. 1783 cm.$^{-1}$ in the acid, 1785 cm.$^{-1}$ in the methyl ester).



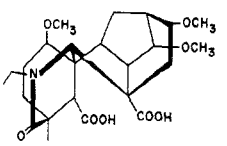
VIII



IX

The above reaction sequences confirm: (*1*) The nature of the *iso*, *α-iso* and *anhydro-α-iso* compounds. (*2*) The correctness of the direction of migration assigned to the pinacolic dehydration.[4] (*3*) The presence of a methoxyl alpha to the vicinal glycol system. A methoxyl had been located in this position earlier on the basis of much weaker chemical evidence.[6]

Finally, the extensive correspondence of the chemistry of lycoctonine with the x-ray crystallographic structure lends strong support to that structure.



X

The lactone acid IX can possibly be converted to the dicarboxylic acid X. This structure has been assigned to a lactam dicarboxylic acid from delpheline.[8] If the two proved identical this would firmly establish the assumed relationship between lycoctonine and delpheline.[9]

EXPERIMENTAL

The physical constants, unless otherwise stated, were determined as follows. Melting points, uncorrected, were made on a Kofler microscope hot stage; optical rotations were measured in absolute ethanol at the cited room temperature; ultraviolet spectra in 95% ethanol using a Carey 11M recording spectrophotometer; the infrared spectra using the nujol mull technique were recorded on the Perkin-Elmer DB 21 instrument. The neutral reaction alumina[10] used for adsorption chromatography was standardized according to Brockman.[11]

Secolycoctonam diketone (III). In a trial experiment lycoctonam hydrate (10.0 mg.) was dissolved in a saturated solution of lead tetraacetate in glacial acetic acid (10 ml.). The molar ratio of the lead tetraacetate consumed after 2 hr. was 1.02; after 20 hr., 1.08.[12]

Lycoctonam hydrate (4.9 g.) was dissolved in acetic acid (100 ml.) and was added to a solution of lead tetraacetate (5.4 g.) in acetic acid (180 ml.). After 2.5 hr. sodium metabisulfite was added followed by a saturated solution of sodium sulfate, and the precipitated lead sulfate was removed by centrifugation. The supernatant liquid together with the precipitate washings were evaporated to a small volume under reduced pressure, neutralized and extracted with chloroform. Evaporation of this extract gave the *seco*diketone III as a white froth (4.8 g.).

Iso Compound (IV). Activity 2 alumina (48 g.) was added to a solution of *seco*lycoctonam diketone (4.8 g.) in benzene (60 ml.). The resultant slurry was shaken for 2.5 hr., then poured on to the top of a column of alumina (96 g.) of activity 2. Elution of the column 24 hr. later with a benzene-chloroform mixture (1:1) gave after two recrystallizations from acetone the "iso" compound (3.09 g.), m.p. 217–218°.

α-Iso and anhydro-α-iso compound. To a solution of the *iso* compound (3.0 g.) in methanol (10 ml.) was added 6*N* sulfuric acid (100 ml.) at 95°C.; the resulting initially opalescent solution was heated on a boiling water bath for 0.5 hr. The neutral product (2.96 g.) extracted by chloroform from the cold reaction mixture was adsorbed from benzene (25 ml.) on to a chromatographic column made with activity 2 alumina (79 g.).

Eluate Fractions (50 Ml.)		Weight Eluted (Mg.)
1–3	Benzene	12.5
4–9	Benzene-chloroform (1:1)	1025
10	Chloroform	199
11–15	Chloroform-ethanol (400:3)	838
16–21	Methanol	616

Fractions 4–9 when crystallized from ether gave transparent square plates (0.98 g.) m.p. 204° alone or in admixture with the *anhydro-α-iso* compound (VIIa). After crystallization from acetone-ether, fractions 10–15 gave colorless prisms (0.99 g.), m.p. 175–176° alone or in admixture with the *α-iso* compound (V).

Seco-diketone from V. A solution of 14.9 mg. of *α-iso* compound V in a saturated solution of lead tetraacetate in acetic acid (10 ml.) showed a molar uptake of reagent of 0.93 mole in 1 hr., and 0.99 in 2 hr.

To a solution of *α-iso* compound (154 mg.) in acetic acid (2.0 ml.) was added a saturated solution of lead tetraacetate in acetic acid (10 ml.). After 4 hr. the oxidation was stopped and the cleavage product extracted as for *seco*lycoctonam diketone. The resultant white froth (151 mg.) when crystallized twice from acetone-ether gave long colorless needles (110 mg.) which melted at 202–203° $[\alpha]_D^{27}$ +1.9° (c, 1.03), $[M]_D^{27}$ +9°.

Anal. Found: C, 62.77; H, 7.28; OCH_3, 27.34. Calcd. for $C_{25}H_{35}O_8N$: C, 62.87; H, 7.39; $4OCH_3$, 27.77.

Ultraviolet spectrum, λ_{max} 3358 Å., log ε 2.13. Infrared spectrum (nujol mull) 1759 cm.$^{-1}$ and 1716 cm.$^{-1}$ (carbonyls), 1655 cm.$^{-1}$ (lactam).

Desmethanol-seco-diketone (VI). Sulfuric acid (2.5 ml. 6*N*) was added to a solution of *seco*-diketone (from V) (50 mg.) in methanol (0.2 ml.), the turbid solution was heated on a steam bath for 45 min., cooled and extracted with chloroform. The neutral product (47 mg.) from the extraction after two crystallizations from acetone-ether gave colorless prisms (35 mg.), m.p. 230°, $[\alpha]_D^{29}$ −10° (c, 1.04), $[M]_D^{29}$ −43°.

Anal. Found: C, 64.54; H, 6.92; OCH_3, 20.69. Calcd. for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; $3OCH_3$, 20.90.

(8) R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 3864 (1956).

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

(10) "Woelm" brand neutral alumina.

(11) H. Brockman and H. Schodder, *Ber.*, **74**, 73 (1941).

(12) These determinations were kindly made by Dr. D. K. R. Stewart.

Ultraviolet spectrum, λ_{max} 2230 Å., log ϵ 3.96; λ_{max} 3460 Å., log ϵ 2.18. Infrared spectrum (nujol mull) 1765 cm.$^{-1}$, shoulder at 1670 cm.$^{-1}$ (carbonyls), 1660 cm.$^{-1}$ (lactam).

Anhydro-α-iso compound from the α-iso compound. Sulfuric acid (3 ml., 6*N*) was added to a solution of *α-iso* compound (20 mg.) in methanol (0.1 ml.). The initially cloudy solution was heated on a steam bath for 3 hr., cooled and extracted with chloroform. Evaporation of the extract under reduced pressure gave a white froth (20 mg.) which was dissolved in benzene (0.5 ml.) and chromatographed on an activity 2 alumina (1.5 g.) column.

	Eluate Fractions (25 Ml.)	Weight in Mg.
1–2	Benzene	1.6
3–5	Benzene-chloroform (1:1)	13.7
6–7	Chloroform-methanol (200:1)	6.0

Fractions 3–5 crystallized from ether in square plates (10 mg.), m.p. 204° alone or in admixture with *anhydro-α-iso* compound. Comparison of the infrared spectra confirmed the identity. Unchanged starting material (5 mg.) was recovered from fractions 6–7.

Des(O-methyl)anhydro-α-iso compound (VIII). *Anhydro-α-iso* compound (1 g.) was dissolved in a small amount of methanol (2 ml.), 6*N* sulfuric acid was added (50 ml.), and the resultant mixture was heated under reflux for 5 hr. The cold solution was extracted with chloroform, and the extract after evaporation under reduced pressure gave a faintly yellow froth (0.962 g.). This was dissolved in benzene (8 ml.) and chromatographed on an activity 2 alumina (20 g.) column.

	Eluate Fractions (50 Ml.)	Weight in Mg.
1–3	Benzene	12
4–8	Benzene-chloroform (1:1)	300
9–13	Chloroform	270
14–17	Chloroform-methanol (9:1)	340

Fractions 4–8 when crystallized from ether gave unchanged starting material, m.p. 204°. Depending upon the solvent system used, crystallization of the products from fractions 9–13 and 14–17 gave two distinctly different crystallographic forms, benzene-hexane (1:1) gave colorless needles, m.p. 238–240°, ether gave square plates, m.p. 237–240°, while acetone gave needles m.p. 224–225°. All these forms are interconvertible and their infrared spectra (solution in chloroform) are identical. $[\alpha]_D^{29}$ +57° (c, 1.23), $[M]_D^{29}$ +261°.

Anal. Found: C, 64.57; H, 7.52; N, 3.27; OCH_3, 20.50. Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; N, 3.13; $3OCH_3$, 20.78.

Ultraviolet spectrum, λ_{max} 2980 Å., log ϵ 1.66. Infrared spectrum (nujol mull) 3500 cm.$^{-1}$ (—OH), 1742 cm.$^{-1}$ (>C=O), 1652 cm.$^{-1}$ (lactam) and 1100 cm.$^{-1}$ (—OCH_3).

Lead tetraacetate oxidation of des(O-methyl) anhydro-α-iso compound (VIII). The compound (34.6 mg.) in 23 ml. of lead tetraacetate solution (a saturated solution in glacial acetic acid diluted with 10% of its volume of water) consumed 0.27 (1 hr.), 0.33 (2 hr.), 0.80 (7 hr.), 1.02 (24 hr.) moles of reagent.

A solution of des(*O*-methyl)anhydro-α-iso compound (203 mg.) in 90% aqueous acetic acid (5 ml.) was added to 25 ml. of the above lead tetraacetate solution. After 28 hr. the excess lead tetraacetate was decomposed with sodium metabisulfite. The solution treated as previously described gave a white froth (204 mg.) from the chloroform extract, which after two recrystallizations from anhydrous methanol yielded colorless needles (83 mg.), m.p. 239–240° (immersion at 200°). $[\alpha]_D^{30}$ +34° (c, 1.01) $[M]_D^{30}$ +156°.

Anal. Found: C, 62.06; H, 7.07; N, 2.92; OCH_3, 19.98. Calcd. for $C_{24}H_{33}O_8N$: C, 62.25; H, 7.18; N, 3.02; 3 OCH_3, 20.04.

Ultraviolet spectrum, featureless. Infrared spectrum (nujol mull) 2580 cm.$^{-1}$ (—OH, acid), 1783 cm.$^{-1}$ (γ-lactone), 1716 cm.$^{-1}$ (>C=O acid), 1615 cm.$^{-1}$ (lactam).

Methyl ester of the γ-lactone acid. A saturated solution of diazomethane in ether (5 ml.) was added to a solution of the γ-lactone acid (35 mg.) in methanol (4 ml.); after 5 min. the solution was evaporated to dryness under reduced pressure. The residue (35 mg.) after two recrystallizations from acetone-ether gave colorless prisms (23 mg.), m.p. 222–224°, $[\alpha]_D^{29.5}$ +42° (c, 1.05) $[M]_D^{29.5}$ +200°.

Anal. Found: C, 62.30; H, 7.33. Calcd. for $C_{25}H_{35}O_8N$: C, 62.87; H, 7.39.

Ultraviolet spectrum, featureless. Infrared spectrum (nujol mull) 1785 cm.$^{-1}$ (γ-lactone), 1736 cm.$^{-1}$ (>C=O, ester), 1645 cm.$^{-1}$ (lactam).

Acknowledgments. We wish to thank Dr. R. N. Jones and Mr. R. Lauzon for obtaining the infrared spectra and Mr. H. Seguin for the microanalysis.

OTTAWA, CANADA