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Approaches to Total Synthesis of Adrenal Steroids. IV. The Stereochemistry of 5-Methyl-1,2,3,4,4aα,5,6,7,8,8aα-decahydronaphthalene-1β,4β-diol-6-one

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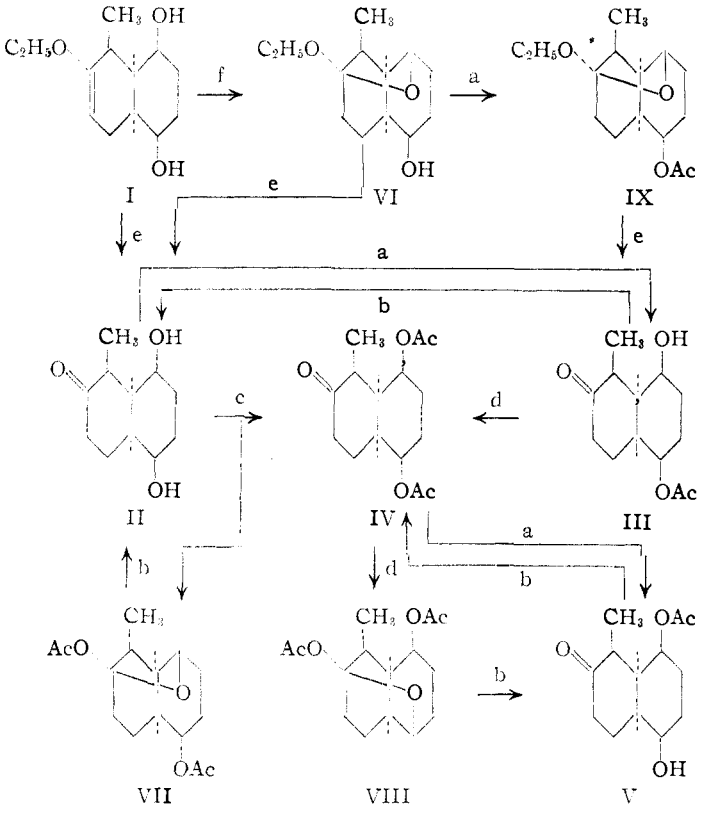
The product of the reduction of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione with lithium aluminum hydride is a dihydroxy enol ether which is capable of forming both γ- and δ-lactol derivatives. A comparison of the degree of hindrance of the C_4 hydroxyl group in the *normal* methyl series and in the *epi* methyl series is made. The data permit assignment of structure I to the dihydroxy enol ether. The stereospecificity of the lithium aluminum hydride reduction is in agreement with the high degree of steric hindrance implicit in the Bastiansen–Hassel formulation of *cis*-decalin.

The preparation of a single stereoisomer (I) of 5-methyl-6-ethoxy-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1,4-diol by consecutive reductions of the addition product of 3-ethoxy-1,3-pentadiene and *p*-benzoquinone has been described in Part I of this series.[1,2] Since a knowledge of the disposition of the functional groups in this molecule is important to the interpretation of its subsequent reactions, a study of its structure was undertaken.

A. Character of the Ring Fusion.—It has been demonstrated that the *cis*-decalin skeleton present in the Diels–Alder adduct of benzoquinone and 3-ethoxy-1,3-pentadiene is retained in its hydrogenation product, 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα - octahydronaphthalene-1,4-dione.[1] Noyce and Denny[3] have shown that the lithium aluminum hydride reduction of ketones containing an adjacent center which is both asymmetric and capable of racemization proceeds without steric alteration of that center. Finally, the isolation of γ- and δ-lactols derived from the enol ether (I) proves that no alteration of configuration at the bridgehead carbon atoms occurs in the transformation of the *cis*-decalin-1,4-dione to the decalin-1,4-diol.

B. Relation of the C_4-Hydroxyl to the Methyl Group.—Hydrolysis of the enol ether (I) in water containing a trace of acetic acid proceeded very rapidly at room temperature to give methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one (II). The C_5-carbon atom in this compound is asymmetric and susceptible of racemization. It was unaffected, however, by heating with 4 *N* hydrochloric acid or aqueous potassium carbonate. That the diolone (II) is capable of existing in a lactol form as well as in the open form was shown by formation of a hemimercaptal with methyl mercaptan-zinc chloride.

The diolone (II) on treatment with excess acetic anhydride–pyridine under standard conditions (95° for eight minutes) yielded a monoacetate (III), a result which could plausibly be ascribed either to steric hindrance of the C_4-hydroxyl group by the C_5-methyl or to the binding of one hydroxyl group in a lactol ring. Evidence that the former effect was the operative one could be obtained by acetylation of the diolone (II) or its 1-monoacetate (III) with acetyl chloride–pyridine or with acetic anhydride–perchloric acid. In each case the major product was a diacetate which on physical evidence had the open structure IV. The latter with dilute methanolic potassium carbonate, under conditions previously determined to be just sufficient for the hydrolysis of the monoacetate (III), yielded an isomeric monoacetate (V). Acetylation of the new monoacetate with acetic anhydride–pyridine regenerated the original diacetate. These results could be ascribed only to steric hindrance involving the C_4-hydroxyl group and the C_5-methyl. Since comparable reactions in the *epi* methyl series indicated a lesser degree of steric hindrance than in the *normal* series (*vide infra*), it followed that the C_4-hydroxyl group and the C_5-methyl were *cis*



a, excess acetic anhydride–pyridine at 95° for eight minutes; b, excess potassium carbonate in aqueous methanol at reflux for four minutes; c, acetyl chloride; d, acetic anhydride–perchloric acid; e, aqueous acetic acid; f, refluxing chloroform.

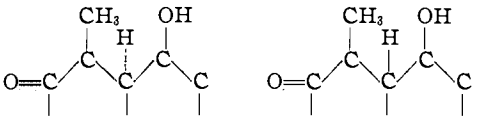
(1) L. H. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandegrift and G. E. Arth, THIS JOURNAL, **74**, 1393 (1952).

(2) The nomenclatural convention used in the present papers is described in Part I of this series.

(3) D. S. Noyce and D. B. Denny, THIS JOURNAL, **72**, 5743 (1950).

to each other in the *normal* series and that the structure of the isomeric monoacetate was that shown in formula V. Evidence for the retention of configuration of the C_5-carbon atom during the carbonate hydrolysis is presented in section D.

C. Relation of the C_4-Hydroxyl to the Bridgehead Hydrogen Atoms.—A choice between the alternative partial structures for the diolone (II) could be made by demonstrating that certain of its



IIa IIb

derivatives contained a γ-lactol ring. The first such derivative was an ethyl lactol ether (VI) isomeric with the enol ether (I) and prepared from the latter by brief refluxing in chloroform, by treatment with a trace of boron trifluoride or simply by permitting the enol ether to stand at room temperature for some time. The ethyl lactol ether was a distillable oil which like its precursor rapidly hydrolyzed in an acidulated aqueous medium to the diolone (II). Acetylation of VI yielded a monoacetate (IX) as an oil which was readily soluble in petroleum ether and which on mild acid hydrolysis yielded the same 1-monoacetate (III) that had been obtained by direct acetylation of the diolone (II). The position of the acetate group in III having been fixed by the argument above, it followed that the ethyl lactol ether had a γ-lactol structure (see Fig. 2). The second derivative was a diacetate isomeric with the open diacetate IV. It was obtained as a by-product of the acetylation of the diolone (II) with acetyl chloride. Physical evidence indicated that it had a closed structure. Hydrolysis with potassium carbonate under standard conditions regenerated the diolone (II), indicating the absence of an acetate group at C_4 and permitting formulation of the closed diacetate as the γ-lactol derivative VII. It is readily seen that the steric requirements of a γ-lactol are satisfied by partial structure (IIa) above but not by (IIb).

D. Configuration of the C_1-Hydroxyl.–Similarly it is evident that the existence of a δ-lactol derivative of the diolone (II) would imply that the C_1-hydroxyl group is *trans* to the bridgehead hydrogen atoms. The reactions of several derivatives of the diolone II provided inferential evidence that stable δ-lactols could be formed both in the series in which the C_5-methyl group is *normal* and that in which it is inverted. It has been noted above that the diolone (II) [or its 1-monoacetate (III)] gave the open diacetate IV with acetic anhydride–perchloric acid. Now when the reaction mixture was allowed to stand for a longer time, a third diacetate, isomeric with IV and VII, was the major product. This third diacetate, like VII, lacked a ketonic carbonyl group. Under the standard conditions of treatment with potassium carbonate it yielded the 4-monoacetate (V). The δ-lactol structure VIII can therefore be assigned to the precursory diacetate.

A reaction series which provided more direct

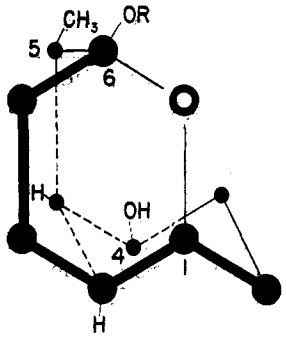


Fig. 1.—δ-Lactol structure.

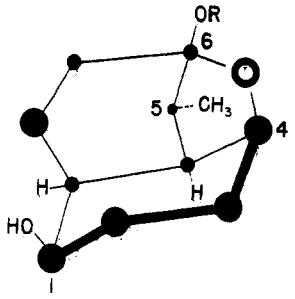


Fig. 2.—γ-Lactol structure.

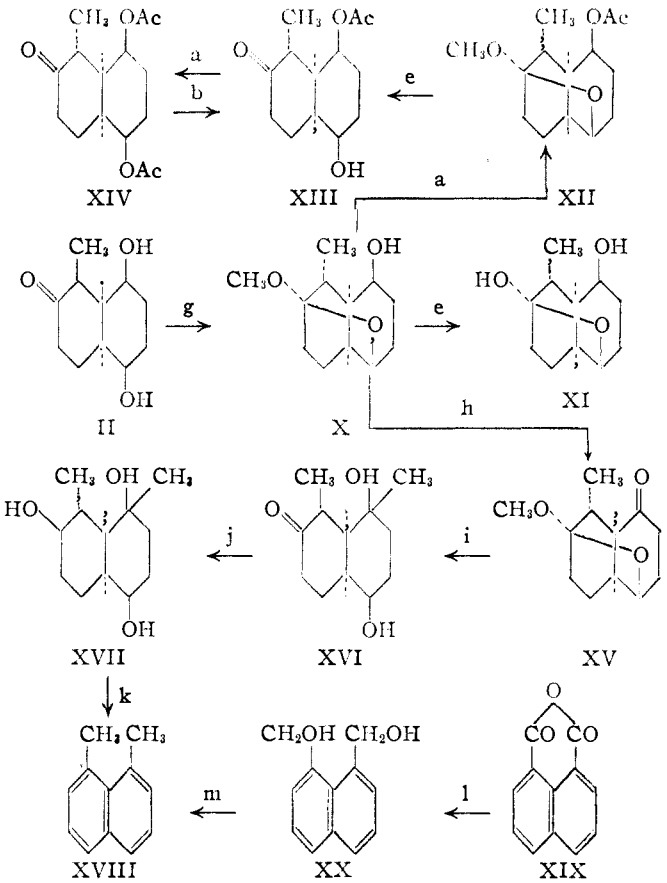
proof for the existence of a δ-lactol ring also lent support to the argument presented in paragraph B. When a solution of the diolone (II) in methanolic hydrogen chloride was allowed to stand, a crystalline methyl lactol ether (X) was formed in high yield. This substance could be hydrolyzed with aqueous acetic acid at room temperature. Its rate of hydrolysis, however, was less than a thousandth as fast as that of the ethyl lactol ether (VI).[4] The product (XI) obtained by hydrolysis was isomeric with the original diolone but lacked a carbonyl group (infrared data). Acetylation of the methyl lactol ether (X) under standard conditions, followed by hydrolysis with dilute acetic acid gave an open monoacetate (XIII) (infrared data) isomeric with III and V which in turn could be acetylated to an open diacetate isomeric with IV. There being only two plausible structures for the pair of open diacetates, *viz.*, those involving isomerization at C_5, the new diacetate must be assigned the structure XIV in which C_5 is inverted. It is evident from this reaction series that the C_5-methyl group in its inverted configuration offers appreciably less hindrance since acetic anhydride under standard conditions sufficed to acetylate both hydroxyl groups here but only one in the *normal* series.

The assignment of configuration to the C_5-methyl group in the various derivatives described above is based on the assumption that potassium carbonate under the prescribed conditions does not lead to epimerization at C_5. Since the *normal* configuration at C_5 is probably the preferred equilibrium form of the diolone (II) and its open derivatives, a conclusion concerning the effect of this reagent can be drawn only from experiments in the *epi*-methyl (less stable) steries. The hydrolysis of the open diacetate (XIV) with potassium carbonate provided this comparison. It was found that the major product was the same monoacetate (XIII) from which the diacetate (XIV) had been derived. Thus, in neither the *normal* nor the inverted series is the configuration at C_5 altered by potassium carbonate.

The formation of the monoacetate (XIII) from both the diacetate (XIV) and the methyl lactol ether (X) proves that X is a δ-lactol (see Fig. 1). Confirmation of the above formulations was obtained by correlation with a known dimethyl-

(4) It is interesting to note that the greater sensitivity of the furanosides to hydrolysis as compared with the pyranosides is paralleled in the present lactol series. See, for example, W. N. Haworth, *Ber.*, **65A**, 43 (1932).

naphthalene. The oxidation of X gave the corresponding keto ether (XV), the carbonyl position of which was tagged by treatment with methylmagnesium bromide. After hydrolysis of the lactol ring and catalytic hydrogenation of the keto group at C_6, a two-stage dehydration–dehydrogenation then yielded crystalline 1,8-dimethylnaphthalene (XVIII). A sample for comparison was prepared by reduction of naphthalic anhydride with lithium aluminum hydride, and hydrogenolysis of the resulting 1,8-naphthalenedimethanol (XX) with palladium–hydrogen.



a-f, as assigned above; g, CH_3OH-HCl; h, N-bromoacetamide–pyridine; i, CH_3MgBr; dilute HCl; j, H_2, Pt; k, C_6H_5COCl–pyridine; pyrolysis, Pd–C; l, $LiAlH_4$; m, H_2, Pd.

TABLE I

INFRARED SUMMARY OF MONO- AND DIACETATES

Compound	Hydroxyl (2.95 μ)	Ester carbonyl (5.75 μ)	Ketonic carbonyl (5.85 μ)
III	+	+	+
V	+	+	+
XIII	+	+	+
IV	−	+	+
XIV	−	+	+
VII	−	+	−
VIII	−	+	−

The symbol "+" denotes absorption at the approximate frequency indicated at the head of the column.

It has been pointed out by Noyce and Denny[3] that of the three methods for reducing ketones to alcohols, *viz.*, the Meerwein–Ponndorff procedure, catalytic hydrogenation and lithium aluminum hydride reduction, the last is least susceptible to steric influences. Conversely a highly stereospecific reduction with lithium aluminum hydride implies that one face of the carbonyl carbon is markedly less accessible than the other. The formation of the single isomer 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (I) from the corresponding diketone[1] demonstrates that the face of the *cis*-decalin molecule behind which the bridgehead hydrogen atoms lie (the rear face, as the formulas are drawn in the present series of papers) is unhindered and that the opposite face is decidedly hindered for *both* carbonyl groups.[5] This is in agreement with the Bastiansen–Hassel[6] formulation of *cis*-decalin as a boat-shaped structure derived from two cyclohexane rings each in the chair conformation.

Experimental[7]

5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one (II).—A suspension of 3.8 g. of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (I) in 10 cc. of water was treated with 0.3 cc. of acetic acid. The mixture became warm and rapidly precipitated crystals of 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one (II). The mixture was stirred for a few minutes to ensure completion of the hydrolysis, then concentrated to dryness *in vacuo*. The residue after recrystallization from acetone amounted to 2.95 g. (89%) and melted at 193–194°. The dihydroxy ketone was soluble in water (10 g. per 100 cc. at room temperature) and nearly insoluble in dry ether.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15. Found: C, 66.72; H, 9.03.

A solution of the dihydroxyketone in 4 *N* hydrochloric acid was heated on the steam-bath for 30 minutes. After removal of the acid *in vacuo*, recrystallization of the residue from acetone gave unchanged starting material. A similar experiment using 1 *N* potassium carbonate resulted in recovery of most of the starting material.

5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-Acetate (III).—A solution of 100 mg. of the dihydroxyketone (II) in 0.8 cc. of pyridine was treated with 0.5 cc. of acetic anhydride. The mixture was heated on the steam-bath for 8 minutes, the solvents then removed *in vacuo*[8] and the residue recrystallized from alcohol. The monoacetate melted at 187–188°. A transition occurred at 164°.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39; CH_3CO, 17.91. Found: C, 64.90; H, 8.41; CH_3CO, 18.00.

The monoacetate in ether–benzene was not isomerized by passage over a column of alumina.

Hemimercaptal Derived from 5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one.—A suspension of 200 mg. of finely powdered dihydroxyketone (II) in 5 cc. of absolute ether was treated with a solution of 800 mg. of anhydrous zinc chloride in 5 cc. of absolute ether and then with an additional 2 cc. of ether containing 400 mg. of methyl mercaptan. The resulting gummy precipitate was triturated for 20 minutes then poured into excess aqueous potassium hydroxide solution and the mixture thoroughly extracted with additional portions of ether. Concentration of the dried extract gave a yellow oil which crystallized from a small volume of ether, m.p. 101–102°.

(5) That the steric course of reductions with lithium aluminum hydride entails inversion has been shown by L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949).

(6) O. Bastiansen and O. Hassel, *Nature*, **157**, 765 (1946). See also D. H. R. Barton, *J. Chem. Soc.*, 340 (1948).

(7) Melting points were taken on the Kofler micro hotstage.

(8) These steps are subsequently referred to as "standard acetylation procedure."

Anal. Calcd. for $C_{12}H_{20}O_2S$: C, 63.12; H, 8.83; S, 14.04. Found: C, 63.50; H, 8.80; S, 13.74.

The infrared spectrum in chloroform solution showed the presence of COH (2.95 μ) and the absence of C=O and C=C.

Thioenol Ether Derived from 5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-Acetate.—A solution of 240 mg. of 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-acetate (III) in 12 cc. of benzene was treated with 12 cc. of 20% methyl mercaptan in ether. Dry hydrogen chloride was passed into the solution until saturated, 3 cc. more of the 20% methyl mercaptan added and the mixture allowed to stand for 2.5 days at room temperature. Excess aqueous potassium hydroxide was added and the resulting ether extract washed until the water washes were neutral. After ether removal, there remained 285 mg. of oil from which 30 mg. of starting material was crystallized. Chromatography of the remainder yielded crystals in the 9:1 and 8:2 petroleum ether–ether eluates. Recrystallization from ether–petroleum ether gave prisms, m.p. 85–86°.

Anal. Calcd. for $C_{14}H_{22}O_3S$: C, 62.19; H, 8.20; S, 11.86. Found: C, 61.87; H, 8.12; S, 12.20.

The infrared absorption showed the presence of C=C (6.10 μ) and of CH_3COO (5.78 μ and 8.03 μ) and COH (2.73 μ).

Acetylation of 5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-Acetate (III) with Acetyl Chloride.—To a solution of 500 mg. of the dihydroxyketone 1-acetate in 3.0 cc. of pyridine was added 0.5 cc. of acetyl chloride. The mixture was heated on the steam-bath for 2 minutes, then diluted with water and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, with dilute sodium carbonate solution and with water, then concentrated to dryness. Chromatography of the residue over acid-washed alumina separated the mixture into two diacetates. The first was 5-methyl 4β,6β-epoxyperhydro-(4aα,8aα)-naphthalene-1β,6-diol diacetate (VII), eluted with 9:1 petroleum ether–ether, 150 mg., m.p. 108–109°, after recrystallization from cold methanol, soluble in warm petroleum ether.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 64.16; H, 8.20.

The second was 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one diacetate (IV), 208 mg., eluted with 6:4 petroleum ether–ether, m.p. after recrystallization from aqueous methanol 104–105°, sparingly soluble in warm petroleum ether.

Anal. Found: C, 63.57; H, 7.97.

A mixed melting point of the isomeric diacetates showed a depression of 30°. Refluxing the free dihydroxyketone (II) or its 1-monoacetate in excess acetyl chloride in the absence of pyridine gave comparable results.

Saponification of 5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-Acetate (III).—To a refluxing solution of 20 cc. of 75% aqueous methanol containing 800 mg. of potassium carbonate was added 845 mg. of the monoacetate III. After 4 minutes, the solution was quickly cooled, concentrated to a small volume *in vacuo* at 10–20°, the residue converted to a watery paste by addition of solid sodium sulfate and extracted several times with chloroform.[9] The combined chloroform extracts were concentrated to dryness *in vacuo* and the residual crude dihydroxyketone (820 mg.) crystallized from acetone. The product, 292 mg. (42%) melted at 188–190°; a mixed melting point with 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one (II) melted at 189–192°. The mother liquors yielded 30 mg. of unsaponified acetate. The yield on this saponification varied from 40–55%.

Acetylation of 5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-Acetate (III) with Acetic Anhydride–Perchloric Acid.—The reagent used for acetylation was prepared by adding 1.0 cc. of 70% perchloric acid to 1.0 cc. of glacial acetic acid, cooling the mixture and then adding 7.5 cc. of acetic anhydride. To a portion (0.5 cc.) of this mixture was added 100 mg. of the monoacetate (III). After standing at room temperature for 1.5 hours, the solution was cooled in an ice-bath and diluted with water to turbidity. After crystallization the product, 5-methyl-1β,6β-epoxyperhydro-(4aα,8aα)-naphthalene-4β,6-diol diacetate (VIII), was filtered and recrystallized from dilute methanol; yield 60 mg., m.p. 95–96°, depressed to *ca.* 70° on admixture with the isomeric diacetates IV and VII. It was soluble in warm petroleum ether and eluable from alumina with 9:1 petroleum ether–ether.

Anal. Found: C, 63.79; H, 7.64.

Acetylation of the dihydroxyketone (II) or its 1-monoacetate (III) with the perchloric acid–acetic acid–acetic anhydride solution for 15 minutes at room temperature yielded the open diacetate (IV) as the major product by direct crystallization.

Saponification of Isomeric Diacetates. A. Saponification of 5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one Diacetate (IV).—Saponification of 1.40 g. of the diacetate (IV) with potassium carbonate under standard conditions gave 500 mg. of 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 4-acetate (V) after recrystallization from cold ether, m.p. 112°.

Anal. Found: C, 65.41, 65.15; H, 8.27, 8.51.

B. Saponification of 5-Methyl-4β,6β-epoxyperhydro-(4aα,8aα)-naphthalene-1β,6-diol Diacetate (VII).—Saponification of 84 mg. of the diacetate (VII) with potassium carbonate under standard conditions gave 35 mg. of water-soluble crystals which melted constantly at 184–188° after recrystallization from acetone. A mixture with a sample of dihydroxyketone (II) melted at 184–189°.

C. Saponification of 5-Methyl-1β,6β-epoxyperhydro-(4aα,8aα)-naphthalene-4β,6-diol Diacetate (VIII).—Saponification of 150 mg. of the diacetate (VIII) with potassium carbonate under standard conditions yielded 75 mg. of 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 4-acetate (V), m.p. 110–111°, not depressed on admixture with the sample prepared as in A above.

A sample (3 mg.) of the monoacetate (V) with pyridine and acetic anhydride under standard conditions gave 3 mg. of 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one diacetate (IV), m.p. 103–105°, not depressed on admixture with an authentic sample.

5-Methyl-4β,6β-epoxy-6-ethoxyperhydro-(4aα,8aα)-napthalene-1β-ol (VI).—A sample of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (I) (1.10 g.) was permitted to stand in a stoppered flask at room temperature for three weeks. The crystalline starting material at the end of this time had been largely converted to a viscous liquid. The latter was chromatographed over alkaline alumina and the fractions eluted with 1:1 petroleum ether–ether (930 mg.) distilled. The lactol ether (VI) boiled at 103–104° (0.2 mm.), was soluble in petroleum ether and showed a strong COH band but no C=O or C=C absorption in the infrared.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.98; H, 9.85. Found: C, 68.52; H, 9.54.

In spite of several attempts to prepare a sample with satisfactory analytical values, the carbon and hydrogen values were invariably low. The lactol ether could also be prepared in 70% yield by refluxing the enol ether (I) in 5% chloroform solution for 10 minutes or by suspending a sample of the enol ether in petroleum ether containing 0.02% of boron trifluoride–ether complex and stirring until the mixture was homogeneous.

The lactol ether was sensitive to moisture and a sample on exposure to air hydrolyzed rapidly to the dihydroxyketone (II). A second type of decomposition led to a polymeric substance by intermolecular elimination of ethanol. Upon attempting to distil relatively large quantities, one frequently observed a sudden evolution of ethanol vapor and concomitant formation of a glassy, non-volatile residue. The latter material also yielded the dihydroxyketone (II) on hydrolysis with 0.05 *N* hydrochloric acid.

Hydrolysis of 5-Methyl-4β,6β-epoxy-6-ethoxyperhydro-(4aα,8aα)-naphthalene-1β-ol (VI).—A sample (25 mg.) of the ethyl lactol ether was stirred with 2 drops of a 4% solution of acetic acid in water. The mixture became warm and solidified to a crystalline mass in less than a minute. The water was removed *in vacuo* and the crystalline residue washed with ether. It melted at 188–190°; mixed m.p. with the dihydroxyketone (II) 189–191°.

5-Methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one 1-Acetate (III) from 5-Methyl-4β,6β-epoxy-6-ethoxyperhydro-(4aα,8aα)-naphthalene-1β-ol (VI).—A solution of 143 mg. of the ethyl lactol ether (VI) in 0.30 cc. of pyridine

(9) This procedure is the standard potassium carbonate saponification referred to elsewhere in the Experimental Section.

was treated with 0.20 cc. of purified acetic anhydride. The mixture was heated for 8 minutes on the steam-bath, then cooled and dissolved in petroleum ether. The petroleum ether solution was washed with aqueous potassium carbonate, dried over sodium sulfate and concentrated to dryness. The residue (150 mg.) was chromatographed over 3.0 g. of (alkaline) alumina and the material eluted with 9:1 petroleum ether–ether collected, giving 131 mg. of colorless, rather mobile oil, 5-methyl-4β,6β-epoxy-6-ethoxyperhydro-(4aα,8aα)-naphthalene-1β-ol 1-acetate (IX). The latter was freely soluble in petroleum ether. It was stirred with 0.5 cc. of a 10% solution of acetic acid in water. As the oily lactol ether dissolved, crystals of the dihydroxyketone 1-monoacetate (III) separated; 110 mg., m.p. and mixed m.p. 186–187°.

5-Methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4α-ol (X).—A suspension of 10.0 g. of 5-methylperhydro-(4aα,8aα)-naphthalene-1β,4β-diol-6-one (II) in 75 cc. of toluene was freed from moisture by removal of nearly all of the toluene *in vacuo*. The residue was dissolved in 200 cc. of absolute methanol containing 2.0 g. of hydrogen chloride. After the mixture had stood at room temperature for 20 hours, it was neutralized with 4 *N* methanolic sodium methoxide and concentrated nearly to dryness *in vacuo*. Traces of methanol were removed by addition of 50 cc. of benzene and concentration to dryness *in vacuo*. The residue was taken up in 300 cc. of benzene, and the benzene solution shaken with 5.0 g. of sodium sulfate in order to adsorb the finely divided inorganic salts. The filtered benzene solution was concentrated to a small volume and the product precipitated as a crystalline mat by addition of petroleum ether; yield 9.0 g. The methyl lactol ether was sparingly soluble in water and in ether. For analysis a sample was recrystallized from acetonitrile and melted at 122–123°.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.63; H, 9.55.

The infrared spectrum in chloroform indicated the presence of COH (2.95 μ) and the absence of C=O.

5-Methyl-1α,6α-epoxyperhydro-(4aβ,8aβ)-naphthalene-4α,6-diol (XI).—A suspension of 50 mg. of 5-methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4α-ol (X) in 1.0 cc. of water containing 3 drops of glacial acetic acid was shaken for 5 minutes at room temperature without visible evidence of reaction. Therefore, the mixture was heated 5 minutes and concentrated (aided by an air jet) on the steam-bath. Trituration of the residual oil with acetone gave 36 mg. of crystals, m.p. 122–125°. Several recrystallizations from acetone did not significantly raise the melting point of the analytical sample (m.p. 123–125°). A mixed melting point with the methyl lactol ether (X) was 100–120°.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.65; H, 9.04.

Infrared measurements showed no significant absorption in the carbonyl region.

5-Methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4α-ol-4-acetate (XII).—A solution of 150 mg. of the methyl lactol ether (X) in 6 cc. of pyridine and 6 cc. of purified acetic anhydride was heated on the steam-bath for 8 minutes. The volatile components were removed *in vacuo* leaving 183 mg. of petroleum ether-soluble oil. This was chromatographed over 3.5 g. of (alkaline) alumina. The acetate (XII) was eluted as a colorless oil in nearly quantitative yield with petroleum ether and 9:1 petroleum ether–ether. A sample for analysis was distilled under high vacuum in a short-path still.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72; CH_3CO, 16.92. Found: C, 65.83; H, 8.53; CH_3CO, 16.09.

Infrared data showed the presence of CH_3CO_2 (5.75 μ) but no C=O (5.85 μ) or COH (2.95 μ).

5-Methylperhydro-(4aβ,8aβ)-naphthalene-1α,4α-diol-6-one 4-Acetate (XIII).—A solution of 1150 mg. of chromatographically purified 5-methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4α-ol 4-acetate in 1.0 cc. of 68% aqueous acetic acid was heated on the steam-bath for 20 minutes. The solvents were then removed *in vacuo* and the residue crystallized from ether–petroleum ether giving 1073 mg. of the monoacetate XIII, m.p. 110–113°. Recrystallization from ether–petroleum ether gave 832 mg. of the pure product, m.p. 115°.

Anal. Found: C, 64.96; H, 8.10.

It was found that hydrolysis at room temperature was only 15% complete after 20 hours; at steam-bath temperatures it was 50% complete after 7 minutes.

5-Methylperhydro-(4aβ,8aβ)-naphthalene-1α,4α-diol-6-one Diacetate (XIV).—A solution of 32 mg. of the monoacetate (XIII) in a mixture of 2.5 cc. of pyridine and 2.5 cc. of acetic anhydride was heated on the steam-bath for 8 minutes. The pyridine and acetic anhydride were removed *in vacuo*. The residual oil crystallized readily and was recrystallized several times from ether–petroleum ether, giving 20 mg. of needles, m.p. 120°.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.60; H, 8.04.

The diacetate was unaffected by chromatography over alumina.

Saponification of 5-Methylperhydro-(4aβ,8aβ)-naphthalene-1α,4α-diol-6-one Diacetate (XIV).—A sample (500 mg.) of the diacetate, m.p. 120°, was treated with potassium carbonate under standard conditions. The crude product (460 mg.) was chromatographed and gave a trace of unsaponified diacetate followed by the monoacetate XIII, m.p. and mixed m.p. 115°. The yield of the latter was 220 mg.

5-Methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4-one (XV).—To 3.94 g. of 5-methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4α-ol (X) in 10 cc. of pyridine and 40 cc. of *t*-butanol was added 3.85 g. of N-bromoacetamide (freshly recrystallized from ethyl acetate). This mixture was allowed to stand at room temperature for 3 hours, then taken up in 300 cc. of petroleum ether, washed with aqueous sodium sulfite–sodium carbonate solution, then with water, dried and the solvent removed *in vacuo*. The residual amber oil (3.95 g.), which partially crystallized after standing overnight, was chromatographed over 80 g. of (alkaline) alumina. The crystalline ketone (XV), m.p. 68–72°, was eluted with 9:1 petroleum ether–ether (2.92 g., 75%) followed by 384 mg. of starting material in the 1:1 petroleum ether–ether fraction. Several recrystallizations from petroleum ether gave analytically pure 5-methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4-one (XV), m.p. 74.0–74.5°.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.31; H, 8.43.

A solution of 90 mg. of the ketone (XV), 0.5 cc. of methanol, 0.55 cc. of water and 6 drops of glacial acetic acid was allowed to stand at room temperature overnight. The mixture was concentrated *in vacuo* to a crystalline residue, which yielded 72 mg. (85%) of crystals, m.p. 151–155°, in two crops from ethyl acetate. Several recrystallizations from ethyl acetate gave pure **5-methylperhydro-(4aβ,8aβ)-naphthalene-1β-ol-4,6-dione**, m.p. 155–156°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.52; H, 8.08.

The acetate of this diketone was prepared in good yield using the standard acetic anhydride–pyridine method, m.p. 113–114°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.52; H, 7.62. Found: C, 65.26; H, 7.23.

Structure Proof of 5-Methyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4-one (XV) A. 4,5-Dimethyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4-ol.—An ethereal solution of methylmagnesium bromide was prepared using 8.0 g. of methyl bromide, 1.94 g. of magnesium and 90 cc. of ether. To this was added 4.31 g. of the keto lactol ether (XV) in 40 cc. of ether during 15 minutes. The resulting suspension was stirred at room temperature for 1.5 hours and then decomposed by the addition (with stirring and cooling) of 13 cc. of saturated aqueous ammonium chloride. The resulting precipitate was filtered, thoroughly washed with ether and the filtrate concentrated to give 4.31 g. of residual oil. Chromatography of 3.60 g. of this crude product yielded 3.27 g. of noncrystalline 4,5-dimethyl-1α,6α-epoxy-6-methoxyperhydro-(4aβ,8aβ)-naphthalene-4-ol in the 8:2 to 1:1 petroleum ether–ether fractions. The early eluates (9:1 petroleum ether–ether) contained 240 mg. of the starting ketone (XV).

B. 4,5-Dimethylperhydro-(4aβ,8aβ)-naphthalene-1α,4-diol-6-one (XVI).—To 3.24 g. of the Grignard product was added 25 cc. of 1 *N* hydrochloric acid. The resulting cloudy solution was allowed to stand at room temperature for 41 hours (weaker acids or shorter time gave incomplete hy-

drolysis). After the addition of potassium carbonate (until alkaline) to the clear reaction mixture it was extracted thoroughly with chloroform. The chloroform extract was dried and concentrated to give 3.40 g. of viscous oil which was induced to crystallize by trituration with ether. After washing with cold ether 2.35 g. (77%) of crystalline 4,5-dimethylperhydro-(4aβ,8aβ)-naphthalene-1α,4-diol-6-one (XVI) was obtained, m.p. 120–135°. This material appeared to be a mixture of stereoisomers and so was recrystallized only twice from acetone for analysis, m.p. 145–155°.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.92; H, 9.65.

C. 4,5-Dimethylperhydro-(4aβ,8aβ)-naphthalene-1α,-4,6-triol (XVII).—The diolone (XVI) was hydrogenated at low pressure with platinum oxide in ethanol to give a 94% yield of 4,5-dimethylperhydro-(4aβ,8aβ)-naphthalene-1α,-4,6-triol (XVII) as a mixture of crystalline stereoisomers, m.p. 160–180°. Two recrystallizations from acetone yielded micro needles, m.p. 175–181°.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.51; H, 10.32.

D. Benzoylation and Benzoate Pyrolysis.—The crude triol (1.44 g.) was heated for 2 hours on the steam-bath with 6.0 cc. of benzoyl chloride and 6.0 cc. of pyridine. The solution was then treated with 5.0 cc. of water and 1.0 cc. of pyridine and heated an additional 20 minutes. The resultant heterogeneous reaction mixture was dissolved in 100 cc. of ether and washed with dilute hydrochloric acid, aqueous potassium carbonate, and with water. The ether extract was dried and after removal of the ether the crude tribenzoate was obtained as a viscous amber oil. The latter was pyrolyzed at 300–320° in a small retort, giving a mixture of yellow oil and crystalline benzoic acid as the distillate. This was dissolved in ether and washed with aqueous sodium carbonate and water. After drying and removal of solvent, 1.78 g. of viscous amber oil was obtained. Fractional distillation gave 410 mg. of the dimethyltetralin, b.p. 38–45° (0.03 mm.) as a mobile oil with a penetrating odor. The higher boiling fraction, b.p. 100–110° (0.03 mm.), an odorless viscous oil, was again pyrolyzed. In this way an additional 60 mg. of the dimethyltetralin was obtained after distillation (44% yield from the triol).

E. 1,8-Dimethylnaphthalene via Palladium Dehydrogenation.—The dimethyltetralin (470 mg.) was heated with 100 mg. of 10% palladium-on-charcoal for 2 hours in a metal-bath maintained at 220–240° and for 1.5 hours at 250–260° under a slow stream of nitrogen. After cooling, the mixture was thoroughly extracted with ether from which 356 mg. of yellow oil was obtained after evaporation of the ether. This oil gave crystals when cooled to −70° and scratched. The crystals were washed several times with ethanol (−70°) giving 107 mg. of crude dimethylnaphthalene, m.p. 48–60°. After five recrystallizations from 75% ethanol the melting point was 61–63° and was not depressed upon admixture with authentic 1,8-dimethylnaphthalene (*vide infra*). Infrared comparison confirmed the identity of the two samples.

1,8-Naphthalenedimethanol (XX).—A stirred suspension of 3.8 g. of lithium aluminum hydride in 400 cc. of tetrahydrofuran was refluxed in an apparatus arranged so that the hot tetrahydrofuran percolated through a porous paper thimble containing 8.57 g. of technical naphthalic anhydride, m.p. 255–265°. The naphthalic anhydride was completely dissolved after about 3 hours and the reaction mixture was allowed to cool and stand overnight at room temperature. It was decomposed with dilute hydrochloric acid, saturated with sodium sulfate, and extracted thoroughly with ether. After drying and removal of the ether there was obtained 8.81 g. of crude crystalline residue. Recrystallization from acetone yielded 4.95 g. (61%) of 1,8-naphthalenedimethanol (XX) in three crops. After several recrystallizations from acetone, needles, m.p. 158°, were obtained.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.67; H, 6.34.

1,8-Dimethylnaphthalene (XVIII).—The 1,8-naphthalenedimethanol (XX) (4.12 g.) was dissolved in 175 cc. of methanol, 2 drops of concentrated hydrochloric acid was added and the hydrogenation carried out using palladium oxide at room temperature and low pressure (140% of the theoretical amount of hydrogen consumed). Filtration from catalyst and concentration of the filtrate yielded 4.30 g. of the semi-crystalline residue. The residue was thoroughly extracted with petroleum ether and concentrated, yielding 2.16 g. of crude 1,8-dimethylnaphthalene (XVII), m.p. 50–60°. Recrystallization from 75% ethanol gave the pure hydrocarbon, m.p. 62.0–63.5°.[10]

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(10) R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937), give m. p. 63°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND RESEARCH CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF WYOMING]

The Alkaloids of *Delphinium Barbeyi* H.

BY WILLIAM BOYD COOK[1] AND O. A. BEATH

Delphinium barbeyi Huth has been found to contain two crystalline alkaloids, lycoctonine and anthranoyllycoctonine plus smaller amounts of amorphous bases. New empirical formulas have been assigned to these alkaloids on the basis of elementary analyses of the bases and their salts and peripheral group studies. The X-ray diffraction patterns and ultraviolet absorption spectra of lycoctonine, anthranoyllycoctonine and ajacine have been determined. The basic dissociation constant of lycoctonine shows it to be a moderately strong base. Nine derivatives of each of these alkaloids have been prepared and their physical constants determined.

The first larkspur alkaloid was isolated from *D. staphisagria* L. by Brandes in 1819. Since that time about twenty different crystalline bases have been isolated from larkspurs and reported in the literature. The source of these alkaloids has been, with few exceptions, the seed of European species of delphiniums. Of the seventy-nine species of delphiniums native to North America only *D. brownii* has been the object of any intensive study to determine the nature of the alkaloid content. *D. menziesii, D. bicolor, D. nelsonii, D. glaucum, D. glaucescens, D. barbeyi, D. geyeri* and perhaps others have been subjected to superficial chemical examination to determine the total alkaloid content and toxicity.

In the present investigation *D. barbeyi*, the most abundant of the so-called tall larkspurs and a major cause of cattle poisoning in the Rocky Mountain region, was the species studied. The object of the investigation was to learn whether or not the alkaloids of this plant were crystalline and, if so, how

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