

From a comparable reaction employing 3.99 g. (0.041 mole) of 2-methylcyclopentanone, 1.61 g. (0.054 mole of formaldehyde) of paraformaldehyde, 5.00 g. (0.040 mole) of dimethylamine hydrobromide, and 5 ml. of ethanol, distillation of the crude basic product separated 4.5 g. (73%) of the Mannich base 15, b.p. 43–45° (0.3 mm.),  $n_D^{25}$  1.4562. The mass spectrum of the product exhibits a molecular ion peak at  $m/e$  155; the sample has infrared absorption<sup>11</sup> at 1730  $\text{cm}^{-1}$  (cyclopentanone C=O). The n.m.r. spectrum<sup>11</sup> of this sample has a singlet at  $\delta$  2.13 (NCH<sub>3</sub>) superimposed on a complex series of peaks in the region  $\delta$  1.5–2.5 and a singlet at  $\delta$  0.83 (CH<sub>3</sub>C). A broadening at the base of the last mentioned singlet and several very small peaks in the region of  $\delta$  0.9–1.2 suggests that the major product 15 may be contaminated by a small amount (less than 20%) of one or both of the stereoisomeric Mannich bases 3, containing a CH<sub>3</sub>CH< function, whose n.m.r. C-methyl signals could appear as a pair of doublets. A solution of the Mannich base 15 in deuterium oxide containing 20% deuterium chloride exhibited n.m.r. peaks at  $\delta$  3.39 (2H singlet, CCH<sub>2</sub>N<sup>+</sup>D<) and 1.22 (3H singlet, CH<sub>3</sub>C) with complex absorption in the region  $\delta$  1.6–2.8 and two peaks at  $\delta$  2.92 and 2.98 (6H, CH<sub>3</sub>N<sup>+</sup>D<). The presence of two peaks for the N-methyl signal in the salt suggests that the dimethylammonium grouping exists in a preferred conformation with respect to the asymmetric C-2 position of the cyclopentanone ring. As was the case for the n.m.r. spectrum of free base 15, the n.m.r. singlet at  $\delta$  1.22 attributable to the C-methyl group has a slight broadening at the base suggesting the presence of a small amount of the salt of either one or both of the amino ketones 3.

**Mannich Reaction of 2-Methylcyclohexanone (2).** A. With Dimethylamine Hydrochloride.—A mixture of 9.0 g. (0.080 mole) of 2-methylcyclohexanone, 3.42 g. of an aqueous solution containing 37% (0.040 mole) of formaldehyde, and 3.26 g. (0.040 mole) of dimethylamine hydrochloride was refluxed for 15 min. and then diluted with water and saturated with sodium chloride. After the resulting mixture had been extracted with ether, it was made basic with potassium hydroxide and extracted with ether. The resulting basic extract was dried, concentrated, and distilled to separate 3.95 g. (59%) of the Mannich base (a mixture of 5 and 16), b.p. 48–50° (0.15 mm.),  $n_D^{25}$  1.4638 [lit. 71° (1.3 mm.),<sup>2a</sup> 62–63° (0.7 mm.),<sup>2b</sup>  $n_D^{20}$  1.4650,<sup>2a</sup>  $n_D^{25}$  1.4639<sup>2b</sup>]. The mass spectrum of the product exhibits a molecular ion peak at  $m/e$  169; the material has infrared absorption<sup>11</sup> at 1710  $\text{cm}^{-1}$  (C=O). The n.m.r. spectrum of a solution of this Mannich base in deuterium oxide containing 20% deuterium chloride exhibits, apart from complex absorption in the region  $\delta$  1.7–2.7, a singlet at  $\delta$  3.33 (CCH<sub>2</sub>N<sup>+</sup>D), a singlet at  $\delta$  2.98 (CH<sub>3</sub>N<sup>+</sup>D), and a singlet at  $\delta$  1.39 (CH<sub>3</sub>C) attributable to the salt of the amino ketone 16. In addition there is a small peak at  $\delta$  2.87 (CH<sub>3</sub>N<sup>+</sup>D<) and two

(11) Determined as a solution in carbon tetrachloride.

doublets centered at  $\delta$  0.98 ( $J = 6.5$  c.p.s.) and 1.22 ( $J = 7$  c.p.s.) corresponding to the C-methyl signal from the CH<sub>3</sub>CH< grouping in the two stereoisomeric salts derived from the amino ketones 5. From the relative areas under these C-methyl peaks, we estimate the Mannich base to contain approximately 70% of the amino ketone 16 and 30% of the amino ketones 5. The n.m.r. spectrum<sup>11</sup> of the free base has single peaks at  $\delta$  2.36 (CCH<sub>2</sub>N<), 2.13 (CH<sub>3</sub>N<), and 0.97 (CH<sub>3</sub>C). In the n.m.r. spectrum of the free base, the singlet C-methyl peak at  $\delta$  0.97 partially obscures the small C-methyl doublets in the region  $\delta$  0.85–1.0.

B. With Dimethylamine.—Into a mixture of 6.0 g. (0.053 mole) of 2-methylcyclohexanone and 2.16 g. of an aqueous solution containing 37% (0.027 mole) of formaldehyde was distilled 1.22 g. (0.027 mole) of dimethylamine. An exothermic reaction occurred as the amine was added. The resulting mixture was refluxed for 10 min. and then cooled, poured into dilute aqueous hydrochloric acid, and extracted with ether. The aqueous layer was made basic with potassium hydroxide and again extracted with ether. After the basic, ethereal extract had been dried and concentrated, distillation of the residue separated 2.7 g. (59%) of the Mannich base (a mixture of 5 and 16), b.p. 50–52° (0.2 mm.),  $n_D^{25}$  1.4645. This sample, which has infrared absorption practically identical with the infrared absorption of the previous sample, has comparable n.m.r. absorption except that the C-methyl doublets are slightly more intense. From the areas under the C-methyl peaks we estimate that the sample contains about 35% of 5 and 65% of 16.

**N.m.r. Spectra of the Quaternary Salts Derived from the Mannich Base of 2-Methylcyclohexanone.**—The previously described<sup>2</sup> methiodide, m.p. 190–192°<sup>2b</sup> exhibits three n.m.r.<sup>12</sup> singlets at  $\delta$  3.81 (2H, CCH<sub>2</sub>N<sup>+</sup>), 3.22 (9H, CH<sub>3</sub>N<sup>+</sup>), and 1.42 (3H, CH<sub>3</sub>C) as well as complex absorption in the region  $\delta$  1.7–2.9 and should be assigned structure 18 rather than the previously<sup>2</sup> assigned structure 9. The methiodide sample, m.p. 160–163°<sup>2b</sup> is apparently a mixture of approximately equal amounts of 18 and one of the diastereoisomers of structure 9, since the n.m.r.<sup>12</sup> C-methyl absorption consists of a singlet at  $\delta$  1.42 and a doublet ( $J = 6.5$  c.p.s.) centered  $\delta$  0.99. The previously described<sup>2b</sup> crude methotosylate, m.p. 120–145°, has C-methyl peaks in the n.m.r.<sup>12</sup> indicating the presence of 19 (about 65%, singlet at  $\delta$  1.32) and one of the diastereoisomers of 10 (about 35%, doublet,  $J = 6.5$  c.p.s., centered at  $\delta$  0.97). The one pure isomer, m.p. 141–142°<sup>2b</sup> isolated from the mixture has the structure 19 rather than the previously assigned structure 10. The n.m.r. spectrum<sup>12</sup> has two doublets ( $J = 9$  c.p.s. for each) centered at  $\delta$  7.37 and 7.74 (4H, aryl CH) as well as singlets at  $\delta$  3.69 (2H, CCH<sub>2</sub>N<sup>+</sup>), 3.12 (9H, CH<sub>3</sub>N<sup>+</sup>), 2.38 (3H, aryl CH<sub>3</sub>), and 1.32 (3H, CH<sub>3</sub>C), and complex absorption in the region  $\delta$  1.5–2.8.

(12) Determined as a solution in deuterium oxide.

## Preparation of Perhydronaphthalene-1,8-dione from 1,4,4a $\beta$ ,5,8,8a $\beta$ -Hexahydronaphthalen-5 $\alpha$ -ol-1,4-dione Acetate

IRVING ALLAN KAYE AND RICHARD S. MATTHEWS<sup>1</sup>

Department of Chemistry, Brooklyn College, The City University of New York, Brooklyn 10, New York

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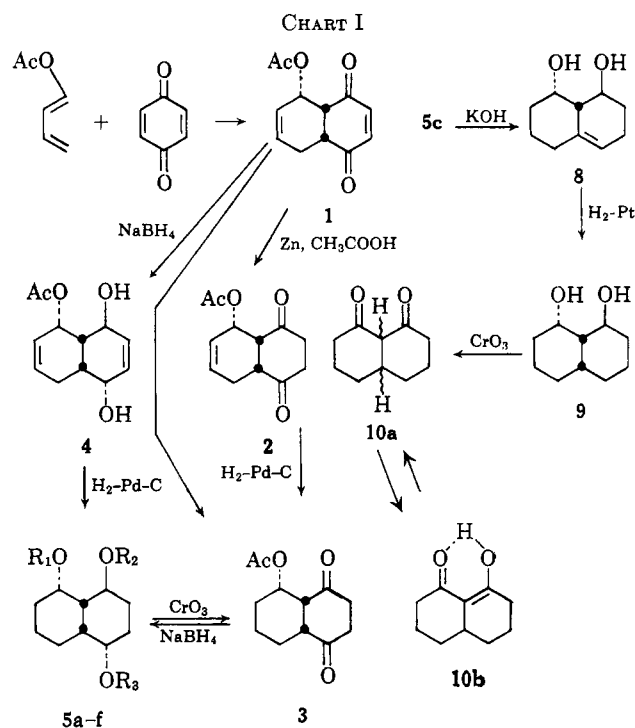
Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-acetate (5a) was prepared by a two-step reduction from 1,4,4a $\beta$ ,5,8,8a $\beta$ -hexahydronaphthalen-5 $\alpha$ -ol-1,4-dione acetate (1). The triol monoacetate (5a) was selectively tosylated in the 1-position and the tosyl group was eliminated with base. The 1,2,3,5,6,7,8,8a $\beta$ -octahydronaphthalene-1 $\beta$ ,8 $\alpha$ -diol (8) formed was hydrogenated and then oxidized to perhydronaphthalene-1,8-dione (10a). A new synthesis of 2-*n*-butyrylcyclohexanone (14a) is described wherein the diketone was prepared from 2-(1-hydroxy-*n*-butyl)cyclohexanone (11a). The n.m.r. spectra of these 1,3-diketones indicate that the decalindione (10a) is completely enolized in chloroform solution at room temperature, while its flexible monocyclic analog (14a) is only 77% enolized. Intermediate between these two values is the enolization (87%) of the bicyclic analog, perhydroindane-1,7-dione (15a).

Interest in this laboratory has been focused recently on the preparation of  $\beta$ -diketones which can give rise only to *cis* enols and in which the distance between the

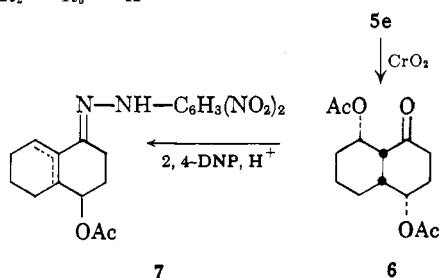
carbonyl groups is fixed and determined by the geometry of the molecule. In a previous communication<sup>2</sup> two methods were described for the preparation of a

(1) National Science Foundation Undergraduate Research Participant, 1961–1962.

(2) I. A. Kaye and R. S. Matthews, *J. Org. Chem.*, **28**, 325 (1963).



- 5a, R<sub>1</sub> = Ac; R<sub>2</sub> = R<sub>3</sub> = H  
 b, R<sub>1</sub> = Ac; R<sub>2</sub> = R<sub>3</sub> = SO<sub>2</sub>CH<sub>3</sub>  
 c, R<sub>1</sub> = Ac; R<sub>2</sub> = H; R<sub>3</sub> = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>  
 d, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = Ac  
 e, R<sub>1</sub> = R<sub>3</sub> = Ac; R<sub>2</sub> = H  
 f, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H



compound of this type, perhydronaphthalene-1,8-dione (decalin-1,8-dione, 10a). The diketone was prepared by a modification of the procedure of Stetter and Milbers<sup>3</sup> and also by the Jones oxidation<sup>4</sup> of a mixture of perhydronaphthalene-1,8-diols formed by hydrogenating 8-hydroxy-1-tetralone in the presence of a supported rhodium catalyst. At the time of the publication of Stetter and Milbers' preparation of this compound,<sup>3</sup> we had made considerable progress in synthesizing the diketone by an entirely different route. This procedure is outlined in Chart I and forms the subject of this report.

1,4,4aβ,5,8,8aβ-Hexahydronaphthalen-5α-ol-1,4-dione acetate<sup>5</sup> (1) was formed on heating a mixture of 1-acetoxy-1,3-butadiene<sup>6</sup> and *p*-benzoquinone. This stereochemistry is consistent with assigned products obtained in reactions of dienophiles with 1-substituted

1,3-butadienes<sup>7</sup> and is supported by the fact that only one product was obtained in high yield, that relatively mild conditions were employed in the condensation, and that the reaction proceeded at a rate rapid enough to afford little opportunity for the kinetically favored *cis* ring-fused adduct to isomerize to the *trans* form.

The tetrahydro derivative, perhydro(4aβ,8aβ)naphthalen-5α-ol-1,4-dione acetate (3), was obtained by hydrogenating the Diels-Alder adduct (1) in the presence of palladium-carbon. Alternatively it could be prepared by catalytic reduction of 1,2,3,4,4aβ,5,8,8aβ-octahydronaphthalen-5α-ol-1,4-dione acetate (2), which was formed in excellent yield by reducing 1 with zinc in acetic acid solution.<sup>8</sup> From the combined mother liquors of several preparations of the dihydro compound (2), which had been subjected to prolonged heating, there was obtained a small amount of a higher melting isomer. Since Sarett, *et al.*,<sup>9</sup> have shown that *cis*-1,4-diketodecalins are readily transposed to the *trans* isomers in the presence of alkaline alumina, and Hückel<sup>10</sup> has found that *cis*-α-decalone isomerizes slowly to the *trans* form at room temperature, it seems probable that the by-product is one of the *trans*-decalin isomers.<sup>11</sup>

With sodium borohydride at 0° the tetrahydro compound (3) was converted in good yield to the triol monoacetate (5a). That no change in the stereochemistry of the ring fusion had occurred was demonstrated by the formation of the starting diketone (3) on oxidation of the product (5a) with chromium trioxide-pyridine.<sup>12</sup> The nonequivalence of the two hydroxyl groups in the reduction product was revealed by the isolation of a monotosylate derivative from a reaction with *p*-toluenesulfonyl chloride at 0°. The hindrance to esterification is in large measure due to the bulk of the reagent, since, under the same conditions, reaction with methanesulfonyl chloride afforded the dimesylate. A scale model of the product (5a) suggested that, if both hydroxyl groups were equatorial, the 4-hydroxyl should be hindered by the equatorially oriented 5-acetate. An alternate possibility was an axial orientation for only one of these two substituents. In view of the hindrance at the equatorial 4-position and the fact that reduction with sodium borohydride follows "steric control" to give axial epimer<sup>13</sup> in proportion to the amount of hindrance at the carbonyl site, the possibility existed

(7) (a) D. Craig, *J. Am. Chem. Soc.*, **72**, 1678 (1950); (b) D. Craig, J. J. Shipman, and R. B. Fowler, *ibid.*, **83**, 2885 (1961); (c) K. Alder and M. Schumacher, *Ann.*, **565**, 148 (1949); (d) P. A. Robbins and J. Walker, *J. Chem. Soc.*, 3249 (1956); (e) A. Alberola, M. Lora-Tamayo, J. L. Soto, and M. Soto, *ibid.*, 3941 (1962); (f) M. F. Ansell and G. C. Culling, *ibid.*, 2908 (1961); (g) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(8) W. Albrecht, *Ann.*, **348**, 31 (1906).

(9) L. H. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandegriff, and G. E. Arth [*J. Am. Chem. Soc.*, **74**, 1393 (1952)] obtained both of the two possible *trans* forms from 5α-methyl-6-ethoxy-1,2,3,4,4aβ,5,8,8aβ-octahydronaphthalen-1,4-dione.

(10) W. Hückel, *Ann.*, **441**, 1 (1925).

(11) Since only one product was obtained under presumably equilibrium conditions, it seems likely that this is 1,2,3,4,4aα,5,8,8aβ-octahydronaphthalen-5α-ol-1,4-dione acetate, in which the acetoxy group is equatorially oriented. P. A. Robbins and J. Walker [*J. Chem. Soc.*, 642 (1952)] also obtained a small amount of a higher melting compound on reducing an acetic acid solution of their Diels-Alder adduct with zinc dust. They, too, assumed that their by-product had been formed by an isomerization at one of the ring junction hydrogens.

(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(13) (a) H. J. Loewenthal, *Tetrahedron*, **6**, 269 (1959); (b) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

(3) H. Stetter and U. Milbers [*Chem. Ber.*, **91**, 977 (1958)] found, by ultraviolet spectroscopic measurements, that perhydronaphthalen-1,8-dione in ethanol at room temperature is completely enolized.

(4) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(5) W. Flaig [*Ann.*, **568**, 1 (1950)] obtained this product, m.p. 64°, in unstated yield by heating the reactants in acetic acid solution. The stereochemistry of the compound was not described.

(6) W. J. Bailey and R. Barclay, Jr., *J. Org. Chem.*, **21**, 328 (1956).

that the less reactive hydroxyl was at the 4 $\alpha$  (axial) position.

Evidence that the 4-hydroxyl group was indeed the hindered group was obtained in the following manner. When heated with excess acetic anhydride-pyridine at 95° for eight minutes,<sup>14</sup> the triol monoacetate (**5a**) afforded a diacetate (**5e**) in good yield. Oxidation of the triol diacetate (**5e**) with chromium trioxide-pyridine<sup>12</sup> yielded the keto diacetate (**6**). On heating this compound with 2,4-dinitrophenylhydrazine in methanol containing acid, there was obtained a red dinitrophenylhydrazone whose ultraviolet spectrum and elementary analysis indicated that it was the derivative of an  $\alpha,\beta$ -unsaturated ketone (**7**).<sup>15</sup> This ready loss of the elements of water is characteristic of  $\beta$ -ketols and their esters.

If the hindered 4-hydroxyl were axially oriented, then removal of the 5-acetyl group should not alter its chemical reactivity. The opposite should be true in the case of an equatorial 4-hydroxyl. This hypothesis was tested using the saponification and acetylation techniques of Beyler and Sarett.<sup>14</sup> On heating the triacetate (**5d**) prepared from the triol monoacetate (**5a**) and acetyl chloride, in refluxing aqueous methanolic potassium carbonate for exactly ten minutes, the triol (**5f**) was obtained. A hindered acetate group would have been expected to resist hydrolysis under these conditions.<sup>14</sup> Presumably the equatorial ester groups at the 1- and 5-positions were quickly saponified and, with removal of the hindering 5-acetyl moiety, the equatorial 4-acetate was then also cleaved rapidly. The ready triacetylation of the triol (**5f**), by heating with excess acetic anhydride-pyridine at 95° for eight minutes,<sup>14</sup> contrasts with the behavior of the triol monoacetate (**5a**) and supports the contention that the 4-hydroxyl is equatorially oriented and hindered by the nearby 5-acetate group.

Two other procedures for the synthesis of the triol monoacetate, perhydro(4 $\alpha,\beta,8\alpha,\beta$ )naphthalene-1 $\alpha,4\beta,5\alpha$ -triol 5-acetate (**5a**), were explored, but neither was so satisfactory as the palladium-catalyzed hydrogenation of the Diels-Alder adduct (**1**). The product could be obtained in low yield by hydrogenating the diketone acetate (**3**), in the presence of ruthenium-carbon,<sup>16</sup> or by palladium-catalyzed hydrogenation of 1,4,4 $\alpha,\beta,5,8,8\alpha,\beta$ -hexahydronaphthalene-1 $\alpha,4\beta,5\alpha$ -triol 5-acetate (**4**). The latter was prepared in low yield by reducing the adduct (**1**) with sodium borohydride at 0°; at a higher reaction temperature an isomer of **4** was obtained.<sup>17</sup>

(14) R. Beyler and L. Sarett, *J. Am. Chem. Soc.*, **74**, 1406 (1952). With a compound of structure very similar to **5a**, but with a methyl at the 5-position instead of an acetate group, the 4-hydroxyl, under these conditions, resisted acetylation while the 1-hydroxyl was easily esterified. When subjected to their standard potassium carbonate saponification conditions, their diacetate (analogous to **5d**, but with a methyl at the 5-position), unlike our triacetate (**5d**), was selectively saponified only at the 1-position.

(15) Migration of the initially formed double bond at the 8,8 $\alpha$ -position to the 4 $\alpha,8\alpha$ -position would be expected. M. I. Bowman, C. C. Ketterer, and A. U. Chamberlain [*J. Org. Chem.*, **18**, 905 (1953)] report an absorption maximum of 381 m $\mu$  (log  $\epsilon$  4.4) for an ethanolic solution of  $\Delta^1$ -1-octalone.

(16) Hydrogenations in the presence of ruthenium-carbon are reputed to effect reduction of carbonyl groups without hydrogenating olefinic bonds. This was apparently confirmed in one of our experiments wherein the dihydro adduct **2** was found to absorb exactly 2 moles of hydrogen in methanol in the presence of this catalyst. Similar reduction of the Diels-Alder adduct **1** resulted in the uptake of 3 moles of hydrogen indicating that the olefinic bond in the enedione system was reduced under these conditions.

(17) This isomer may be 1,4,4 $\alpha,\beta,5,8,8\alpha\alpha$ -hexahydronaphthalene-1 $\alpha,4\beta,5\alpha$ -triol 5-acetate; *cf.* ref. 11.

Advantage was taken of the ease with which the tosyl grouping is eliminated, when the tosylate (**5c**) is treated with nucleophilic reagents, to remove the 1-substituent. Accordingly, the unsaturated diol (**8**), 1,2,3,5,6,7,8-,8 $\alpha,\beta$ -octahydronaphthalene-1 $\beta,8\alpha$ -diol, was prepared by dissolving the tosylate (**5c**) in methanol containing potassium hydroxide. When **8**, in the form of its diacetate, was hydrogenated in acetic acid in the presence of platinum, a saturated diol was obtained in moderate yield. This method of reduction has been shown to be highly stereoselective in introducing both hydrogens from the same side of the molecule and to cause little, if any, isomerization of the unhydrogenated cycloalkene.<sup>18</sup> Consideration of a molecular model of the unsaturated diol (**8**) indicates that the introduction of hydrogen can best be accommodated from the less hindered side of the molecule containing the 8 $\alpha,\beta$ -hydrogen to give perhydro(4 $\alpha,\beta,8\alpha,\beta$ )naphthalene-1 $\beta,8\alpha$ -diol (**9**). The two hydroxyl groups in this configuration should both be equatorial and, indeed, the lack of hindrance at these functions was demonstrated by the ease with which they were both acetylated under the conditions of the "standard acetylation procedure" of Beyler and Sarett.<sup>14</sup> By contrast, the unsaturated diol (**8**), one of whose hydroxyls is axially oriented, was incompletely acetylated under these conditions<sup>14</sup> and yielded a mixture of the diacetate and the two isomeric monoacetates.

The diol (**9**) was oxidized by the method of Jones<sup>4</sup> to perhydronaphthalene-1,8-dione (**10a**), whose infrared spectrum was identical with that of a sample prepared by the method of Stetter and Milbers.<sup>3</sup> 2-*n*-Butyrylcyclohexanone (**14a**), a flexible monocyclic analog of this bicyclic diketone (**10a**),<sup>19</sup> was prepared similarly from 2-(1-hydroxy-*n*-butyl)cyclohexanol (**13**), whose method of preparation is outlined in Chart II. The latter was synthesized to provide a model for investigating the conditions necessary for effecting the oxidation of the 1,3-diol (**9**) to the 1,3-diketone (**10a**).<sup>20</sup>

In preparing the precursor (**11a**) of **13** by the mixed aldol condensation reaction, a small amount of a keto-diol by-product was isolated.<sup>21</sup> A distinction among the three likely structures for this compound, 2-(1,3-dihydroxy-2-ethyl-*n*-hexyl)cyclohexanone (**12a**), 2,2-bis(1-hydroxy-*n*-butyl)cyclohexanone (**12b**), and 2,6-bis(1-hydroxy-*n*-butyl)cyclohexanone (**12c**), was made by observing that the product formed by acid-catalyzed dehydration absorbed at 254 m $\mu$ . This absorption is in good agreement with the latter formula (**12c**), since the cross-conjugated ketone thus formed would be expected to have an absorption peak in the vicinity of that (245

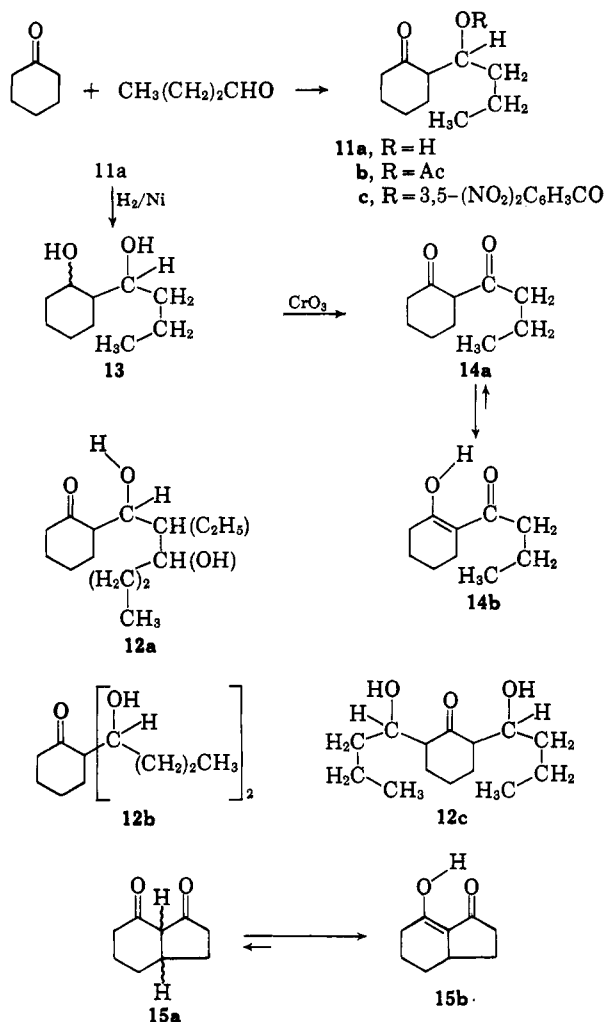
(18) (a) S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6082 (1960); (b) J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961).

(19) Some of the physical properties of **10**, **14**, and **15** are under investigation by Dr. L. Magnusson, Dr. C. Postmus, Jr., and Dr. C. Craig at the Argonne National Laboratory.

(20) The diol **12**, as well as 2-ethyl-1,3-hexanediol, was also used in trial reactions which explored the conditions necessary for the preparation of benzylidene acetals of 1,3-diols. These experiments are described in the Experimental section. A sample of 2-ethyl-1,3-hexanediol was generously contributed by the Union Carbide Chemicals Co.

(21) Since the ketodiol was apparently formed under equilibrating conditions, the product presumably has the *cis* configuration; *cf.* B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962). F. A. Fries and F. Broich [German Patent 956,948 (January 24, 1957); *Chem. Abstr.*, **53**, 7056 (1959)] prepared the ketol **11a** and some of its congeners by a similar process. They also found that a higher boiling product, which they did not investigate, was formed.

CHART II



$\mu$ ) shown by the  $\alpha,\beta$ -unsaturated ketone obtained from 2-(1-hydroxy-*n*-butyl)cyclohexanone (11a).<sup>22</sup> The monosubstituted product (12a) would have given rise to a conjugated dienone absorbing at about 296  $\mu$ <sup>22</sup>; from the unsymmetrically disubstituted cyclohexanone (12b) water would not have been eliminated readily nor would a product absorbing strongly in the ultraviolet have been formed.

Intercomparison of the intensities of the hydroxylic proton (at 16.37 p.p.m.) and combined ring proton signals, in the nuclear magnetic resonance<sup>23</sup> spectrum of perhydronaphthalene-1,8-dione (10a), indicates that, in chloroform solution at room temperature, the compound is completely enolized.<sup>3</sup> A similar comparison, in the case of the n.m.r. spectrum of perhydroindane-1,7-dione (15a) in the same solvent (the hydroxylic proton signal was also observed at 16.37 p.p.m.), leads to an enolization value of 86.9%. In the spectrum of the monocyclic analog of perhydronaphthalene-1,8-dione (10a), 2-*n*-butyrylcyclohexanone (14a), a comparison of its hydroxylic proton signal (at 16.28 p.p.m.)

with that of its methyl protons indicates that the compound is 76.7% enolized. The exchange of the hydrogen-bonded proton from one oxygen to the other in the  $\beta$ -dicarbonyl system has been considered as a factor contributing to the stabilization of the enol.<sup>24</sup> Such stabilization would apparently be greatest in the case of 1,2,3,4,4a,5,6,7-octahydronaphthalen-8-ol-1-one (10b) because of the equivalence of the two enolic forms, whereas in each of the other two diketones (14a and 15a) one of the two enolic structures possible in each case (14b and 15b) would be expected to be more stable.<sup>25</sup>

### Experimental<sup>26</sup>

**Materials.**—Redistilled cyclohexanone, b.p. 154–155°, *n*-butyraldehyde, b.p. 73–76°, and benzaldehyde, b.p. 179°, which had been distilled and stored under nitrogen, were used in the aldol condensation and acetal preparations. Pyridine and benzene were dried for several days over calcium hydride before use in reactions requiring anhydrous solvents. The Raney nickel catalyst, employed in the preparation of the diol (13), was obtained commercially,<sup>27</sup> as was the 10% palladium-carbon catalyst.<sup>28</sup> The nickel was washed with distilled water, isopropyl alcohol, and ethyl acetate in succession and then stored for several days under ethyl acetate until used. The acetone employed as solvent in the Jones oxidation had been refluxed for several hours over, and then distilled from, potassium permanganate. 1-Acetoxy-1,3-butadiene was prepared in 57% yield, b.p. 56.0–57.5° (37 mm.), by the procedure of Bailey and Barclay.<sup>6</sup>

**1,4,4a,5,8,8a,8b-Hexahydronaphthalen-5 $\alpha$ -ol-1,4-dione Acetate (1).**—The preparation of this compound was studied rather extensively and our optimum conditions are described. A vigorous exothermic reaction resulted on heating to reflux a solution of 86.3 g. of 1-acetoxy-1,3-butadiene<sup>6</sup> and 75.7 g. (0.70 mole) of *p*-benzoquinone in 70 ml. of carbon tetrachloride and 250 ml. of isopropyl ether. This was moderated by occasional immersion in an ice bath and then left at room temperature until spontaneous ebullition ceased. The reaction mixture was next heated under reflux for 1 hr. and then diluted to a volume of 1400 ml. with hot isopropyl ether. The clear yellow solution was decanted from a small amount of black tar, which seemed to have been formed by the decomposition of the *p*-benzoquinone, and left to cool slowly. It was seeded when its temperature had dropped to 37°. After standing at room temperature for several hours longer, it was left overnight at 0°. The large pale yellow hexagonal crystals were separated by filtration and washed three times with ice-cold isopropyl ether. In addition to this first crop of 1, which weighed 125.8 g. (80.4%) and melted at 64.5–66.5°, a second crop, weighing 14.8 g. (9.5%) and melting at 62–64°, was obtained by concentrating the filtrate to a volume of 250 ml. A solution of 2.4 g. of the higher melting product in 100 ml. of refluxing isopropyl ether deposited 1.49 g. of almost white rhombohedra on cooling to 0°; m.p. 66–66.5°;  $\lambda_{\text{max}}$  221 and 335.5  $\mu$  ( $\log \epsilon$  4.01 and 2.86, respectively),  $\lambda_{\text{min}}$  269  $\mu$  ( $\log \epsilon$  2.11);  $\lambda_{\text{max}}^{\text{CCl}_4}$  5.76 (s, acetate C=O), 5.83 (s), 5.89 (s), 5.95 (s), 6.06 (w, sh, unconjugated C=C), 7.34 (m, CH<sub>3</sub>), and 8.20  $\mu$  (s, acetate C–O st.).

The instability of the adduct to heat, acids, bases, and alumina is not unprecedented.<sup>11,12</sup>

(24) L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

(25) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(26) Cf. footnote 26 of ref. 2 for information relative to the determination and reporting of melting and boiling points, infrared and ultraviolet absorption spectra, and calculated and experimental elementary analyses. Ultraviolet spectra were measured in 95% ethyl alcohol. The n.m.r. spectra were determined with a Varian A-60 spectrometer operating at 60 Mc. on solutions of the samples in deuteriochloroform. The spectra were calibrated in p.p.m. downfield from internal tetramethylsilane. Alcoa F-20 alumina, activity I, was used in the chromatographic separations. Thin layer chromatograms were conducted on Merck Kieselgel G; ether was used as the developing solvent. The spots were visualized either by exposure to iodine vapor or by spraying with potassium permanganate solution.

(27) A sample of No. 28 Raney active nickel catalyst in water was generously supplied by the Raney Catalyst Co., Inc., Chattanooga, 2, Tenn.

(28) Purchased from Englehard Industries, Inc., Newark, 2, N. J.

(22) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 18–21.

(23) For a discussion on the application of n.m.r. to the determination of the position of equilibrium in systems capable of exhibiting keto-enol tautomerism, cf. F. C. Nachod and W. D. Phillips, "Determination of Organic Structures by Physical Methods," Vol. 2, Academic Press, New York, N. Y., 1962, p. 454. Difficulties in accurate area intercomparisons give rise to some uncertainty regarding the absolute accuracy of results obtained by this method.

**1,2,3,4,4a $\beta$ ,5,8,8a $\beta$ -Octahydronaphthalen-5 $\alpha$ -ol-1,4-dione Acetate (2).**—The reduction of the conjugated olefinic bond in 1 was carried out by a modification of the procedure of Albrecht<sup>8</sup> which exposed the starting material and product to a minimum amount of heating. The product (2) was stable at room temperature for long periods of time, but was stored at 4° since it had been noted that 3 decomposed after several months at room temperature.

Zinc dust was added in about 5-g. portions to a stirred solution of 76.5 g. (0.344 mole) of 1,4,4a $\beta$ ,5,8,8a $\beta$ -hexahydronaphthalen-5 $\alpha$ -ol-1,4-dione acetate (1) in 300 ml. of glacial acetic acid. The reaction flask was immersed in an ice bath during the addition, which was controlled so as to maintain a reaction temperature of 21–27°. After 96 g. of zinc dust had been added, further addition produced no immediate rise in temperature; a total of 101 g. of the metal was added over a 20-min. period. The mixture was stirred at room temperature (26–32°) for 18 hr. longer, then diluted with 1800 ml. of acetone and filtered through a layer of a diatomaceous earth. The filtrate was evaporated to dryness *in vacuo* below 30°. The tan solid which remained was dissolved, for the most part, in 150 ml. of boiling acetone. A small amount of zinc acetate was removed by filtering the mixture through a layer of a diatomaceous earth. The filtrate was evaporated to dryness at room temperature in a current of air and the residue was dissolved in 100 ml. of hot isopropyl alcohol. The hot solution was chilled immediately in an ice bath and left at 0° overnight after seeding. The colorless product which precipitated was separated by filtration, washed with cold isopropyl alcohol, air-dried at room temperature, and then dried *in vacuo*. The dihydro compound (2) weighed 63.9 g. (83.6%), m.p. 112.5–114.5°. Another recrystallization from the same solvent raised the melting point to 113.5–114.5°. A second crop of crystalline product was obtained by concentrating the mother liquors to a volume of about 25 ml. After recrystallization from isopropyl alcohol, an additional 2.89 g. (3.7%), m.p. 104–106.5°, was obtained. The infrared spectrum of a Nujol mull showed absorption at 5.78 (s, ester C=O st.), 5.84 (s, C=O st.), 7.67 (m, C=O), and 8.03–8.13  $\mu$  (s, acetate C–O st.).

*Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>4</sub>: C, 64.85; H, 6.35; O, 28.80. Found: C, 65.24; H, 6.49; O, 28.69.

From the combined filtrates of several previous preparations, in which the product had been subjected to prolonged heating in carbon tetrachloride and acetone, there was obtained a small amount of an isomeric product. This was much more insoluble in isopropyl alcohol than 2 and, after crystallization from this solvent, melted (evac.)<sup>26</sup> at 176–177°. Its infrared absorption spectrum in Nujol was similar to, but not identical with, that of 2; strong absorption was evident at 5.76, 5.84, and 8.10–8.27  $\mu$  and weak absorption was apparent at 6.05  $\mu$  (shoulder). No absorption was visible in the 2.0–3.4- $\mu$  region.

*Anal.* Found for C<sub>12</sub>H<sub>14</sub>O<sub>4</sub>: C, 64.69; H, 6.13; O, 28.93.

On hydrogenation in ethyl acetate over 10% palladium-carbon,<sup>28</sup> a reduction product was obtained in low yield which melted (evac.) at 177.0–179.5°, after crystallization from isopropyl alcohol.

*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.32.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalen-5 $\alpha$ -ol-1,4-dione Acetate (3).**—A mixture of 110.1 g. (0.50 mole) of 1,4,4a $\beta$ ,5,8,8a $\beta$ -hexahydronaphthalen-5 $\alpha$ -ol-1,4-dione acetate (1), 2.0 g. of 10% palladium-carbon,<sup>28</sup> and 150 ml. of ethyl acetate was hydrogenated at room temperature and an initial pressure of 40 p.s.i. After 3.5 hr., hydrogen was no longer absorbed. The mixture was filtered through a layer of a diatomaceous earth, and the yellow filtrate was evaporated to dryness at room temperature in a current of air. A solution of the residue in 185 ml. of boiling isopropyl ether was left overnight at 0°. The crude product, weighing 75.5 g. and melting at 85–95°, was recrystallized from the same solvent. The clusters of white needles which precipitated were air-dried to constant weight and then dried further at 0.1 mm. for several hours, yielding 65.7 g. (58.5%), m.p. 97.5–99.5°. Recrystallized again from isopropyl ether, the product melted at 99.5–100°;  $\lambda_{\max}^{Nujol}$  285–286.5  $\mu$  ( $\epsilon$  40);  $\lambda_{\max}^{CHCl_3}$  5.75 (ester C=O st.), 5.84 (C=O st.), 8.15 and 8.19  $\mu$  (ester C–O st.), all with strong bands.

*Anal.* Found for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>: C, 64.34; H, 7.27.

The tetrahydro compound (3), m.p. 95–96°, could also be obtained in lower yield by catalytic hydrogenation of 1,2,3,4,4a $\beta$ ,5,8,8a $\beta$ -octahydronaphthalen-5 $\alpha$ -ol-1,4-dione acetate (2) over

palladium-carbon or by oxidation of perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-acetate (5a) with chromic anhydride-pyridine,<sup>12</sup> m.p. 97.5–99.5°. Each of these products gave no depression in melting point on admixture, and gave an infrared spectrum identical with that of 3.

**1,4,4a $\beta$ ,5,8,8a $\beta$ -Hexahydronaphthalen-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-Acetate (4).**—A solution of 3.80 g. of sodium borohydride in 40 ml. of methanol was added dropwise to a stirred chilled suspension of 11.0 g. (0.05 mole) of the Diels-Alder adduct (1) in 45 ml. of methanol at a rate such that the reaction temperature was maintained below +5°. This required 45 min. when the reaction vessel was chilled in an ice-salt mixture. Stirring was continued for 1 hr. longer, during which period the reaction flask was chilled in an ice bath. An ice-cold solution of 12 ml. of acetic acid in 650 ml. of ice-water was added, and the mixture was extracted several times with methylene chloride. The extracts were decolorized with charcoal and the solvent then was removed; the oil which remained was triturated with isopropyl ether. The white powder, which was thus formed, weighed 1.37 g. Three recrystallizations from isopropyl ether gave 4 as clusters of needles whose melting point was constant at 106–108.5°;  $\lambda_{\max}^{CHCl_3}$  2.84 (m, shoulder), 2.91 (m), 5.78 (s), 6.06 (w, shoulder), and 8.01–8.31  $\mu$  (s).

*Anal.* Found for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>: C, 64.25; H, 7.36.

When the sodium borohydride reduction of the adduct 1 was conducted at reflux temperature, a very small amount of an isomeric product<sup>17</sup> was obtained which melted at 146–147°, after five recrystallizations from isopropyl ether;  $\lambda_{\max}^{CHCl_3}$  2.82 (w, shoulder), 2.96 (m), 5.80 (s), 6.05 (w), and 8.10  $\mu$  (s).

*Anal.* Found for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>: C, 64.06; H, 7.26.

On hydrogenating the lower melting isomer (4) at atmospheric pressure in the presence of palladium-carbon, 2 moles of hydrogen were absorbed. A crystalline product was isolated which melted at 130–137° and gave an infrared spectrum identical with that of perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-acetate (5a). The higher melting isomer also absorbed 2 moles of hydrogen but formed a colorless oil whose infrared spectrum differed from that of 5a mainly in the fingerprint region.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-Acetate (5a).**—A solution of 9.5 g. (0.25 mole) of sodium borohydride in 100 ml. of methanol was added dropwise over a period of 40 min. to a mixture of 57.1 g. (0.255 mole) of perhydro(4a $\beta$ ,8a $\beta$ )naphthalen-5 $\alpha$ -ol-4-dione acetate (3) in 400 ml. of methanol, immersed in a bath at –20°, at a rate such that a reaction temperature below 4° was maintained. A clear colorless solution was formed after a portion of the hydride solution had been added. After all the sodium borohydride solution had been added, the solution was left in an ice bath for 75 min. A considerable volume of hydrogen was evolved during this period. While maintaining the reaction temperature at 2 to 4°, a mixture of 30 ml. of glacial acetic acid and 70 ml. of water was added over a 15-min. period. The solution was evaporated *in vacuo* and a small amount of water which remained was removed by azeotropic distillation with ethylene chloride. The ethylene chloride solution was concentrated to a volume of 100 ml., after which 200 ml. of boiling isopropyl ether was added, and the mixture was left overnight at 0°. The hard crust which precipitated was broken up, separated by filtration, and washed well with cold isopropyl ether. The white powder, after drying in air and then at 0.1 mm. for several hours, weighed 44.1 g. (76%), m.p. 138–143.5°. After two recrystallizations from isopropyl ether, compound 5a melted at 145–146°;  $\lambda_{\max}^{Nujol}$  2.94 (s), 5.78 (s), and 8.03  $\mu$  (s).

*Anal.* Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>: C, 63.13; H, 8.83. Found: C, 63.11; H, 8.95.

From a mixture of 673 mg. (3 mmoles) of (3), 200 mg. of 5% ruthenium-carbon,<sup>28</sup> and 25 ml. of methanol, which had been hydrogenated at 765 mm. and 28°, there was obtained, after recrystallization from ethyl acetate, 140 mg. of the triol monoacetate (5a), m.p. 139–144°. On admixture with pure product obtained by sodium borohydride reduction, a melting point of 141–144° was observed. The infrared spectra of the two samples were identical.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol (5f).**—A solution containing 8.76 g. of potassium hydroxide and 11.41 g. (0.05 mole) of the triol monoacetate (5a) dissolved in a mixture of 25 ml. of distilled water and 250 ml. of methanol was heated under reflux for 1 hr. After adding a mixture of 6.5 ml. of glacial acetic acid and 100 ml. of benzene, the solution was evaporated on a steam bath in a current of air, and the last traces of water were removed by azeotropic distillation with benzene. The residue

remaining after removing the benzene was suspended in refluxing chloroform, and the mixture was filtered through a layer of a diatomaceous earth. The solvent was removed and the residue was crystallized from acetone-isopropyl ether. The air-dried triol (5f) weighed 7.96 g. (86%), m.p. 139–144.5°. After two recrystallizations from acetone, the product melted at 144.5–146°. No absorption was apparent in the carbonyl region of its infrared spectrum; a Nujol mull showed strong broad absorption at 3.14  $\mu$  (H-bonded OH) and strong bands at 9.39, 9.56, and 9.63  $\mu$ .<sup>29</sup>

*Anal.* Calcd. for C<sub>10</sub>H<sub>18</sub>O<sub>3</sub>: C, 64.49; H, 9.74. Found: C, 64.49; H, 9.49.

The triol (5f), m.p. 137–142°, was also obtained from the triacetate (5d) by the controlled saponification procedure of Beyler and Sarett.<sup>14</sup> No depression in melting point was observed on admixture with product obtained by the potassium hydroxide saponification of the triol monoacetate. Both samples in Nujol gave identical infrared absorption spectra.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol Triacetate (5d).**—A solution of 500 mg. (2.19 mmoles) of perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-acetate (5a) in 7 ml. of acetyl chloride was heated under reflux for 3 hr. and the solution then was evaporated on a steam bath in a current of air. On crystallization from methanol there was obtained 430 mg. (63%) of the triacetate, m.p. 120–122°. One recrystallization from isopropyl ether narrowed the melting point range to 121–122°;  $\lambda_{\text{max}}^{\text{Nujol}}$  5.77 (s) and 8.07  $\mu$  (s, broad); there was no absorption in the 2.00–3.40- $\mu$  region.

*Anal.* Calcd. for C<sub>18</sub>H<sub>26</sub>O<sub>6</sub>: C, 61.52; H, 7.75. Found: C, 61.44; H, 7.69.

The triacetate, m.p. 120.5–122°, was also prepared from the triol (5f), in 72% yield, by the method of Beyler and Sarett.<sup>14</sup>

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 1,5-Diacetate (5e).**—The diacetate was obtained in 61% yield, m.p. 161–162.5°, from the triol monoacetate (5a) by the acetylation procedure of Beyler and Sarett.<sup>14</sup> On recrystallization from isopropyl ether, the product melted at 162–163°;  $\lambda_{\text{max}}^{\text{Nujol}}$  2.91 (s), 5.78 (s, shoulder), 5.84 (s), and 8.06  $\mu$  (s).

*Anal.* Calcd. for C<sub>14</sub>H<sub>22</sub>O<sub>5</sub>: C, 62.20; H, 8.20. Found: C, 62.24; H, 8.32.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,5 $\alpha$ -diol-4-one Diacetate (6).**—From 1.00 g. (3.70 mmoles) of perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 1,5-diacetate (5e) and 1.09 g. of chromic oxide in 15 ml. of pyridine, there was obtained<sup>12</sup> 905 mg. (91%) of the ketone 6 after crystallization from isopropyl ether, m.p. 144.5–146°. After another crystallization from this solvent, the product melted at 145–146.5°;  $\lambda_{\text{max}}^{\text{Nujol}}$  5.74 (s, shoulder) and 5.82  $\mu$  (s). In one preparation a higher melting form was isolated, m.p. (evac.) 179–180°, m.m.p. 147–154.5°. The infrared spectra of the two forms were identical.

*Anal.* Calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>5</sub>: C, 62.67; H, 7.51. Found: C, 62.44; H, 7.44.

The 2,4-dinitrophenylhydrazone melted (evac.) at 193–194°,  $\lambda_{\text{max}}$  384  $\mu$  (log  $\epsilon$  4.34),<sup>15</sup> after crystallization from methanol.

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.83; H, 5.00; N, 14.44.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-Acetate Dimesylate (5b).**—From the reaction of 3.66 g. (0.016 mole) of the triol monoacetate (5a) with 5.3 ml. of methanesulfonyl chloride in 12 ml. of pyridine at 0° for 96 hr., there was obtained 4.88 g. (79%) of the dimesylate, m.p. 119–120°, after crystallization from acetone-isopropyl ether. The melting point depended on the rate of heating, on the temperature at which the capillary tube was inserted into the bath, and the length of time in the bath. In its infrared spectrum, no absorption was apparent in the 2.0–3.3- $\mu$  region;  $\lambda_{\text{max}}^{\text{KBr}}$  7.46 (s) and 8.50  $\mu$  (s, -OSO<sub>2</sub>-).

*Anal.* Calcd. for C<sub>14</sub>H<sub>24</sub>O<sub>8</sub>S<sub>2</sub>: C, 43.73; H, 6.29; S, 16.68. Found: C, 44.18; H, 5.93; S, 16.52.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-Acetate 1-Tosylate (5c).**—The tosylate was prepared by treating 1.37 g. (0.006 mole) of perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\alpha$ ,4 $\beta$ ,5 $\alpha$ -triol 5-acetate (5a) with 3.45 g. of *p*-toluenesulfonyl chloride in 7 ml. of pyridine at 0° for 19 hr. The product, crystallized from isopropyl ether, weighed 2.02 g. (88%) and melted at 113–114°;  $\lambda_{\text{max}}$  2.82 (m, OH), 7.30 (s, CH<sub>3</sub>), 7.44 (s), and 8.57  $\mu$  (s, -OSO<sub>2</sub>-),

(as a mull in hexachlorobutadiene). The melting point, like that of the dimesylate, varied with the manner in which it was determined.

*Anal.* Calcd. for C<sub>19</sub>H<sub>26</sub>O<sub>8</sub>S: C, 59.67; H, 6.85; S, 8.38. Found: C, 59.89; H, 7.06; S, 8.52.

**1,2,3,5,6,7,8,8a $\beta$ -Octahydronaphthalene-1 $\beta$ ,8 $\alpha$ -diol (8).**—The crude tosylate (5c), from the reaction of 2.74 g. (0.012 mole) of (5a) with 6.90 g. of *p*-toluenesulfonyl chloride in 14 ml. of pyridine, was dissolved in 150 ml. of hot methanol. A solution of 7.2 g. of potassium hydroxide in 15 ml. of hot water was added to the hot yellow solution which was then left at room temperature for 7 hr. The solution was concentrated *in vacuo* to a small volume and extracted with benzene. Evaporation of the dried (over sodium sulfate), decolorized (with charcoal) benzene extract left a white solid which was crystallized from isopropyl ether-hexane, weighing 1.27 g. (63%), m.p. 112–113°. After two further recrystallizations from isopropyl ether, the compound melted at 114–114.5°;  $\lambda_{\text{max}}^{\text{Nujol}}$  3.14 (s, H-bonded OH) and 9.89  $\mu$  (s). The n.m.r. spectrum exhibited multiplets centered at 5.77 p.p.m. (1H, vinyl C-H) and at 4.45 p.p.m. (2H, carbinol C-H), a broad peak centered at 3.30 p.p.m. (2H, OH) which was shifted on acidification with trifluoroacetic acid, and a complex series of peaks in the region 1.50–2.50 p.p.m. (11H, saturated C-H). The compound gave a yellow color with tetranitromethane. Its thin layer chromatogram showed only one spot.

*Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.54.

The thin layer chromatogram of the crude product, obtained by heating 63.0 mg. of the unsaturated diol 8, 0.8 ml. of pyridine, and 0.5 ml. of acetic anhydride in a boiling water bath for exactly 8 min.,<sup>14</sup> showed a spot whose *R<sub>f</sub>* was identical with that of the diol 8, another spot whose high *R<sub>f</sub>* was the same as that of the diacetate, and two more intense spots of intermediate *R<sub>f</sub>*.

**Perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\beta$ ,8 $\alpha$ -diol (9).**—The diacetate of the unsaturated diol 8 was prepared by heating under reflux a mixture of 900 mg. of 8 and 13 ml. of acetyl chloride for 3 hr. The solution was then evaporated *in vacuo*. The residue showed no absorption in the infrared in the 2.0–3.4- $\mu$  region, but absorbed strongly at 5.79 and 8.13  $\mu$ . To a solution of this viscous, slightly colored oil in 25 ml. of acetic acid was added 121 mg. of platinum oxide,<sup>28</sup> and the mixture hydrogenated at room temperature and at atmospheric pressure. In about 1 hr., 110% of the theoretical amount of hydrogen was absorbed; thereafter no further absorption was apparent. After removing the catalyst and acetic acid, the pleasant smelling oil which remained was saponified by heating under reflux for 2 hr. a solution in 75 ml. of methanol with 3 g. of potassium hydroxide dissolved in 5 ml. of water. Most of the methanol was removed on a steam bath in a current of air, and the product was extracted with copious amounts of hot benzene. The oil which remained, after evaporating the dried and decolorized benzene solution, crystallized quickly and was recrystallized from hexane. The clusters of small white needles weighed 555 mg. (61%) and melted at 115–116.5°. On recrystallization from the same solvent, the diol melted at 115.5–117°;  $\lambda_{\text{max}}^{\text{Nujol}}$  2.95 (s, broad), 9.60 (s, broad), and 9.72  $\mu$  (s). No vinylic proton absorption was apparent in the n.m.r. spectrum. It gave no color with tetranitromethane and only one spot on thin layer chromatography.

*Anal.* Calcd. for C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>: C, 70.54; H, 10.66. Found: C, 70.24; H, 10.58.

The compound had the correct analysis when dried *in vacuo* at 80° and 2 mm. just prior to analysis. The diol apparently hydrates readily, for a dried sample, which had been exposed to air for some time, gave a low carbon analysis.

The thin layer chromatogram of the crude product, obtained from the reaction of a solution of 65.1 mg. of the saturated diol (9) in 0.8 ml. of pyridine with 0.5 ml. of acetic anhydride at 100° for exactly 8 min.,<sup>14</sup> showed the absence of any starting material, a strong spot whose *R<sub>f</sub>* was identical with that of 1,2,3,5,6,7,8,8a $\beta$ -octahydronaphthalene-1 $\beta$ ,8 $\alpha$ -diol diacetate (diacetate of 8), and a faint spot whose *R<sub>f</sub>* was intermediate between those of the two monoacetates of the unsaturated diol 8.

**Perhydronaphthalene-1,8-dione (10a) [1,2,3,4,4a,5,6,7-Octahydronaphthalen-8-ol-1-one (10)].**—This product was prepared from perhydro(4a $\beta$ ,8a $\beta$ )naphthalene-1 $\beta$ ,8 $\alpha$ -diol (9) by the Jones oxidation,<sup>4</sup> as described in a previous publication,<sup>2</sup> and was isolated in 67% yield as its copper chelate. The infrared spectrum of a Nujol mull of the salt was superimposable on that of a sample prepared by the method of Stetter and Milbers.<sup>2,3</sup> It was decomposed by stirring a suspension in 4 *N* sulfuric acid-pentane

(29) E. L. Eliel and C. A. Lukach, [*J. Am. Chem. Soc.*, **79**, 5986 (1957)] reported that the equatorial hydroxyl in *trans*-2-methylcyclohexanol absorbed at 9.39, 9.50, and 9.63  $\mu$  in contrast with an axial hydroxyl which absorbed at 9.83, 10.23, and 10.60  $\mu$ .

mixture until two clear layers were formed. After crystallization from pentane at  $-70^{\circ}$ , the white crystals melted at  $54-55.5^{\circ}$ . On admixture with the authentic diketone,<sup>2</sup> no depression in melting point was observed; the infrared spectra of Nujol mulls of the two samples were identical. In the n.m.r. spectrum, the enolic hydroxylic signal was observed as a sharp singlet at 16.37 p.p.m. (1H). The absorption of the hydrogens on the carbon adjacent to the carbonyl group overlapped that of the allylic protons; these were observed as a series of peaks in the region 2.17-2.66 p.p.m. (5H). When the intensity of this absorption was compared with that of the hydroxylic proton, an enolization value of 98% was obtained. The remaining cyclic protons were evident as a complex series of peaks in the region of 0.88-2.12 p.p.m. (8H). A comparison of the intensity of the hydroxylic proton absorption with that of the combined ring protons leads to a value of 100% enolization.

The n.m.r. spectrum of perhydroindane-1,7-dione<sup>2</sup> exhibited an enolic hydroxyl signal, also as a sharp singlet at 16.37 p.p.m., and a complex series of peaks in the region 0.83-2.93, due to the cyclic protons. Comparison of the intensities of these signals indicated that the compound is 86.9% enolized in chloroform solution.

**2-(1-Hydroxy-*n*-butyl)cyclohexanone (11a).**<sup>21</sup>—A solution of 36.1 g. (0.50 mole) of *n*-butyraldehyde in 115 ml. of cyclohexanone was added dropwise over a period of 3 hr. to a stirred mixture of 300 ml. of cyclohexanone (total amount employed was about 3.40 moles) and 6.7 ml. of 10% aqueous sodium hydroxide. The rate of addition was controlled so as to maintain a reaction temperature of  $18-21^{\circ}$ . The mixture was then stirred 4 hr. longer, at a reaction temperature of  $20-23^{\circ}$ , after which 1.57 g. of tartaric acid and a few drops of alcoholic phenolphthalein were added. The pink color of the indicator was discharged after a few minutes of stirring. Anhydrous sodium sulfate was added, and the mixture was stirred for 0.5 hr. After separating the drying agent by filtration and washing it with ether, the combined filtrates were distilled *in vacuo*. A fraction was collected at  $79-83^{\circ}$  (0.06 mm.),  $n_D^{25} 1.4720-1.4723$ , and weighed 49.4 g. (56%). A sample, redistilled for analysis, had b.p.  $61.0-61.5^{\circ}$  (0.03 mm.) and  $n_D^{25} 1.4703$ . The infrared spectrum of the neat liquid showed absorption bands at 2.86 (m, broad, OH st.), 5.87 (s, H-bonded C=O st.), and  $7.62 \mu$  (m, C=O).

*Anal.* Calcd. for  $C_{10}H_{18}O_2$ : C, 70.54; H, 10.66. Found: C, 70.37; H, 10.42.

A solution of the ketol in 95% ethanol containing a trace of concentrated hydrochloric acid absorbed at  $245 \mu$  ( $\epsilon$  3800) (calculated<sup>22</sup> for 2-butylidene-cyclohexanone: 242  $\mu$ ).

**2,6-Bis(1-hydroxy-*n*-butyl)cyclohexanone.**—In preparations of 2-(1-hydroxy-*n*-butyl)cyclohexanone (11a) which were distilled very slowly *in vacuo* the amount of high-boiling residue increased considerably at the expense of ketol.<sup>21</sup> Since the distillation was performed in the presence of excess tartaric acid, it is presumed that a retroaldol condensation occurred and was followed by an aldol condensation of the product 11a with the liberated *n*-butyraldehyde.<sup>21</sup>

In one run there was isolated a viscous oil, b.p.  $126-130^{\circ}$  (0.03 mm.),  $n_D^{26} 1.4918$ , which crystallized on long standing. After two recrystallizations from hexane, the melting point of the white crystals remained constant at  $100.5-101.5^{\circ}$ . In the infrared spectrum of a Nujol mull, strong peaks were observed at  $3.00$  (broad, OH) and  $5.87 \mu$  (C=O).

*Anal.* Calcd. for  $C_{14}H_{26}O_3$ : C, 69.38; H, 10.81; O, 19.81. Found: C, 69.55; H, 10.57; O, 20.07.

A solution of the ketodiol in 95% ethanol containing a trace of concentrated hydrochloric acid absorbed at  $254 \mu$  ( $\epsilon$  3850).<sup>22</sup>

**2-(1-Hydroxy-*n*-butyl)cyclohexanone Acetate (11b).**—The product from the reaction of 17.0 g. (0.10 mole) of 2-(1-hydroxy-*n*-butyl)cyclohexanone (11a) and 35 ml. of acetic anhydride in 50 ml. of pyridine distilled at  $77-79^{\circ}$  (0.02 mm.),  $n_D^{27} 1.4645-1.4655$ , and weighed 16.1 g. (76%). The analytical fraction was collected at  $77.5-78^{\circ}$  (0.02 mm.),  $n_D^{27} 1.4648$ ;  $\lambda_{max}^{acet} 5.76$  (s),  $5.84$  (s), and  $8.11 \mu$  (s).

*Anal.* Calcd. for  $C_{12}H_{20}O_3$ : C, 67.89; H, 9.50. Found: C, 68.06; H, 9.42.

**2-(1-Hydroxy-*n*-butyl)cyclohexanone 3,5-Dinitrobenzoate (11c).**—Since 1,3-ketols undergo elimination readily, a modification of the procedure of Brewster and Ciotti,<sup>30</sup> for the esterification of similarly sensitive alcohols, was employed. The crude product 11c, from 1.70 g. (0.01 mole) of the ketol 11a, after

filtration and washing with cold water followed by isopropyl ether, was a white powder which weighed 1.91 g. (52%), m.p.  $93-105^{\circ}$ . Recrystallized twice from isopropyl ether, the ester showed a constant melting point at  $104.5-106^{\circ}$ ;  $\lambda_{max}^{Nujol} 5.75$  (s),  $5.80$  (s),  $5.85$  (s),  $6.13$  (m),  $6.44$  (s), and  $7.82 \mu$  (s).

*Anal.* Calcd. for  $C_{17}H_{20}N_2O_7$ : C, 56.04; H, 5.53; N, 7.69. Found: C, 56.03; H, 5.75; N, 7.94.

**2-(1-Hydroxy-*n*-butyl)cyclohexanol (13).**—A mixture of 51.1 g. (0.30 mole) of 2-(1-hydroxy-*n*-butyl)cyclohexanone (11a), 75 ml. of ethyl acetate, and 80 ml. of a settled Raney nickel suspension in ethyl acetate was hydrogenated at room temperature, under an initial pressure of 55 p.s.i., for 22 hr. After removing the catalyst and the solvent, the residual oil was distilled *in vacuo*. The product, b.p.  $96-99^{\circ}$  (0.1 mm.),  $n_D^{25} 1.4778-1.4781$ , weighed 36.7 g. (80%). The analytical sample had b.p.  $97.2-98.2^{\circ}$ ,  $n_D^{25} 1.4780$ ;  $\lambda_{max}^{acet} 3.00$  (s, broad),  $9.51$  (s), and  $9.75 \mu$  (s).

*Anal.* Calcd. for  $C_{10}H_{20}O_2$ : C, 69.72; H, 11.70. Found: C, 69.65; H, 11.78.

**2-Ethyl-1,3-hexanediol *m*-Nitrobenzylidene Acetal.**—A mixture of 14.6 g. (0.10 mole) of 2-ethyl-1,3-hexanediol, 15.1 g. of *m*-nitrobenzaldehyde, 50 mg. of *p*-toluenesulfonic acid monohydrate, and 160 ml. of dry benzene was heated under reflux, using a Dean-Stark water trap, for 2 hr. When the mixture had cooled, it was washed once with saturated aqueous sodium bicarbonate, dried over anhydrous potassium carbonate, and stripped of solvent *in vacuo*. The product, collected at  $138.5^{\circ}$  (0.02 mm.),  $n_D^{25} 1.5257-1.5259$ , weighed 17.6 g. (63%). A middle fraction,  $n_D^{25} 1.5257$ , was submitted for analysis.

*Anal.* Calcd. for  $C_{15}H_{21}NO_4$ : C, 64.49; H, 7.58; N, 5.01. Found: C, 64.30; H, 7.69; N, 5.05.

**Small-Scale Preparation of Benzylidene Acetals of 1,3-Glycols.**—A mixture of 1.0 to 10.0 mmoles of the 1,3-diol with an equivalent amount of benzaldehyde or its *m*- or *p*-nitro derivative was heated for 4-8 hr. in 75 ml. of benzene in the presence of 15 mg. of *p*-toluenesulfonic acid monohydrate.<sup>31</sup> The volume was slowly reduced to 20-30 ml. during this heating period. The cooled solution was washed in succession with 25-ml. portions of saturated aqueous sodium bisulfite, water, and saturated aqueous sodium bicarbonate (three times), dried over anhydrous sodium sulfate, and stripped of solvent *in vacuo*. The crude acetals, obtained in this fashion in almost quantitative yield, showed, in the infrared, no carbonyl or hydroxyl bands. The following absorption peaks were found in the spectra of the benzylidene and *m*- and *p*-nitrobenzylidene 1,3-glycol acetals<sup>32</sup> studied in this and a related investigation<sup>2</sup>: 6.15-6.17 (w, *m*-NO<sub>2</sub>), 6.19-6.23 (m, *p*-NO<sub>2</sub>), 6.24-6.25 (w, broad, C<sub>6</sub>H<sub>5</sub>), 6.28-6.30 (w, *m*-NO<sub>2</sub>), 6.66-6.75 (w-m), 6.79-6.90 (m), 7.99-8.06 (w-m), 8.19-8.29 (w-m), 8.52-8.65 (m), 8.73-8.96 (s), 9.01-9.10 (s), 9.14-9.21 (s, absent in *m*-NO<sub>2</sub>), 9.53-9.75 (m-s, usually broad, 2 bands were occasionally found in this region), 14.19-14.25 (s, *m*- and *p*-NO<sub>2</sub>), and 14.34-14.36  $\mu$  (m-s, C<sub>6</sub>H<sub>5</sub>). In addition, the nitrobenzylidene derivatives absorbed strongly at 6.51-6.58 (asym. NO<sub>2</sub> st.) and 7.41-7.44  $\mu$  (sym. NO<sub>2</sub> st.); the *p*-nitrobenzylidene acetals showed an additional strong peak at 9.81-9.86  $\mu$ .

**2-Ethyl-1,3-hexanediol *p*-nitrobenzylidene acetal** was obtained in crystalline form from a hexane solution of the crude product, obtained in the above manner. On recrystallization from hexane, an acetal melting at  $64-65.5^{\circ}$  was obtained.

*Anal.* Calcd. for  $C_{15}H_{21}NO_4$ : C, 64.49; H, 7.58. Found: C, 64.72; H, 7.40.

On chromatographing a petroleum ether (b.p.  $30-60^{\circ}$ ) solution of the crude product, obtained by this method from 2-(1-hydroxy-*n*-butyl)cyclohexanol (13) and *p*-nitrobenzaldehyde on alumina, three products were obtained. The first was eluted with 1:19 benzene-petroleum ether, the second with 1:9 and 1:4 benzene-petroleum ether, and the third with 1:1 benzene-petroleum ether and pure benzene. The infrared spectra of all three were similar, differing somewhat in the fingerprint regions of their spectra.

(31) The amount of *p*-toluenesulfonic acid used in this preparation was rather critical; in smaller preparations where less than this amount was employed, no reaction occurred.

(32) L. J. Bellamy ("The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 116) states that four bands in the 8.33-10.00- $\mu$  region have been regarded as specific for the C-O-C-OC grouping. Y. Klibansky and D. Ginsburg [*J. Chem. Soc.*, 1293 (1957)] found ethylenedioxy ketal bands at 8.45, 8.64, and 9.12-9.23  $\mu$ . C. W. Shoppee, R. E. Lack, and A. V. Robertson, [*ibid.*, 3610 (1962)] associated peaks at 9.18, 9.35, and 9.73  $\mu$  with the C-O-C bond. H. R. Warner and W. E. M. Lands [*J. Am. Chem. Soc.*, **85**, 60 (1963)] found that their aliphatic ethers showed strong absorption near 9.10  $\mu$  and weaker absorption at 8.54, 8.70, and 8.89  $\mu$ .

(30) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

All three showed absorption characteristic of *p*-nitrobenzylidene acetals. The third fraction crystallized on standing and was recrystallized twice from hexane. The large yellow crystals of 2-(1-hydroxy-*n*-butyl)cyclohexanol *p*-nitrobenzylidene acetal melted at 62–63°.

Anal. Calcd. for C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub>: C, 66.86; H, 7.59. Found: C, 67.03; H, 7.57.

The crude benzylidene acetals derived from 2-(1-hydroxy-*n*-butyl)cyclohexanol (13) and perhydro(4 $\alpha$ , $\beta$ ,8 $\alpha$ , $\beta$ )naphthalene-1 $\beta$ ,8 $\alpha$ -diol (9), as well as the *p*-nitrobenzylidene acetal of the latter, obtained by this general procedure, showed infrared absorption characteristic of these acetals but could not be obtained crystalline, even after chromatographic fractionation on alumina.

2-(*n*-Butyryl)cyclohexanone (14a).—The copper salt of the diketone was prepared in 55% yield, m.p. 135–140°, by the Jones oxidation<sup>2</sup> of 2-(1-hydroxy-*n*-butyl)cyclohexanone. This was recrystallized once from hexane, m.p. 151–152°,<sup>33</sup> and then decomposed by stirring for several hours with a mixture of methylene chloride and 4 *N* sulfuric acid. The product 14a, collected at 131–132° (20 mm.), *n*<sup>20</sup><sub>D</sub> 1.4928–1.4932, was obtained in 79% yield (from recrystallized copper salt). In the infrared spectrum of the neat liquid, absorption peaks were evident at 3.20 (w, shoulder), 3.79 (w), 5.82 (m, shoulder), 5.86 (m), 6.25 (s, broad),

(33) This compound has previously been prepared by the condensation of a butyric ester or anhydride with cyclohexanone. J. T. Adams and C. R. Hauser [*J. Am. Chem. Soc.*, **67**, 284 (1945)] reported b.p. 133–134° (20 mm.) for the diketone and m.p. 156–157° for its gray copper salt.

7.06 (m), and 9.38  $\mu$  (m). The n.m.r. spectrum exhibited a singlet at 16.28 p.p.m. (OH), a multiplet centered at 2.38 p.p.m. (allylic protons and hydrogens on the carbons adjacent to the carbonyls), a triplet centered at 0.98 p.p.m. (CH<sub>3</sub>, *J* = 7 c.p.s.), and a broad signal centered at 1.72 p.p.m. (remaining cyclic and acyclic protons).

The copper salt was also obtained, in 53% yield, by oxidation<sup>2</sup> of the diol 13. Recrystallized to constant melting point from hexane, the compound was obtained as gray-green plates possessing a silvery luster, m.p. 153–154.5°,<sup>33</sup>  $\lambda$ <sup>Nujol</sup><sub>max</sub> 6.35  $\mu$  (s, C=O st.).

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## Steroids. CCLI. Lead Tetraacetate Oxidation of 17 $\beta$ -Hydroxy-5 $\alpha$ -androst-1-en-3-one Acetate<sup>1</sup>

STEPHEN KAUFMANN

*The Research Laboratories of Syntex, S. A., Apartado 2679, Mexico, D. F., Mexico*

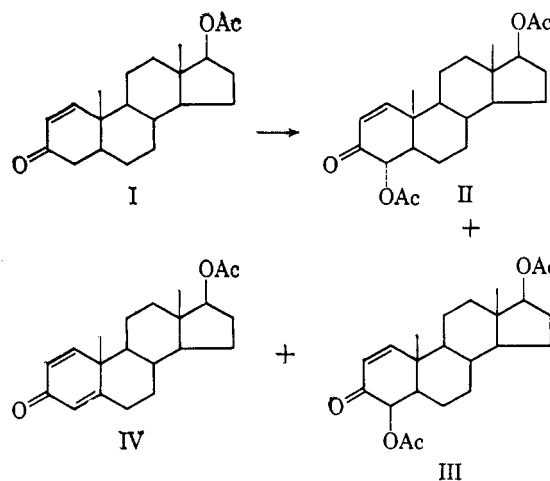
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Oxidation of 17 $\beta$ -hydroxy-5 $\alpha$ -androst-1-en-3-one acetate (I) with lead tetraacetate gave a mixture of 4 $\alpha$ ,17 $\beta$ -dihydroxy-5 $\alpha$ -androst-1-en-3-one diacetate (II), 4 $\beta$ ,17 $\beta$ -dihydroxy-5 $\alpha$ -androst-1-en-3-one diacetate (III), and 17 $\beta$ -hydroxyandrost-1,4-dien-3-one acetate (IV). Alkaline hydrolysis of II and III resulted in the formation of 4-hydroxytestosterone. Proof for the assignment of the steric configuration of the epimeric 4-acetoxy groups in II and III has been presented.

The reaction of ring A  $\alpha,\beta$ -unsaturated keto steroids with lead tetraacetate has been studied in the past. The most important representatives of this group, the  $\Delta^4$ -3-keto steroids have been subjected to the oxidation with this reagent by several investigators.<sup>2,3</sup> It has been established that oxidation results mainly in the introduction of an acetoxy group into the 2 $\alpha$ - and 2 $\beta$ -positions and the formation of the corresponding  $\Delta^1$ -4-3-ketone to a lesser degree. More recently,<sup>4</sup> the lead tetraacetate oxidation of 17 $\beta$ -acetoxy-5 $\alpha$ -estr-1(10)-en-2-one has been described, which yields a mixture of epimeric 3-acetoxy compounds.

In analogy, we have investigated the behavior of a  $\Delta^1$ -3-keto steroid with lead tetraacetate, whereby attack on C-4 could be expected. As a suitable compound, we selected the acetate of 17 $\beta$ -hydroxy-5 $\alpha$ -androst-1-en-3-one (I), the  $\Delta^1$  isomer of testosterone acetate. In accordance with expectations, the 4 $\alpha$ -, 17 $\beta$ -dihydroxy-5 $\alpha$ -androst-1-en-3-one diacetate (II) and 4 $\beta$ ,17 $\beta$ -dihydroxy-5 $\alpha$ -androst-1-en-3-one diacetate (III)

could be isolated from the reaction mixture together with the  $\Delta^1$ -4-3-ketone (IV). The less soluble  $\beta$  isomer (III) was separated by direct crystallization, whereas the  $\alpha$  isomer (II) and the doubly unsaturated ketone (IV) could be obtained only by chromatography of the mother liquors. It is significant that the yield of IV is considerably higher (about 20%) than that obtained by lead tetraacetate oxidation of testosterone acetate,<sup>3</sup> probably because of the easier removal of the



(1) Steroids CCL: J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, in press.

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