

**6 $\alpha$ -Bromotestosterone Acetate (XIII).**—Bromination of testosterone acetate in carbon tetrachloride solution with a molar equivalent of *N*-bromosuccinimide under strong irradiation with an incandescent bulb gave 6 $\beta$ -bromotestosterone acetate, m.p. 147–148° dec.,  $[\alpha]^{25}_D -13.0^\circ$ ,  $\lambda_{max}$  248 m $\mu$  ( $\epsilon$  13,300). The yield of purified product was 56.8% and the physical properties agreed with those reported<sup>7</sup> for the compound. A portion was then epimerized to the 6 $\alpha$ -bromo (equatorial) epimer by the procedure of Bowers and co-workers.<sup>14</sup>

Dry hydrogen chloride was bubbled through a solution of 1.00 g. (2.44 mmoles) of 6 $\beta$ -bromotestosterone acetate in 100 ml. of glacial acetic acid for 25 min. at room temperature. After standing for 30 min. longer, the solution was diluted with 2 l. of cold water to afford a solid precipitate. The crude product was collected on a filter and washed with water, then air dried. The slightly sticky solid was dissolved in ether and the solution was dried over anhydrous potassium carbonate. After filtration, the ether solution was diluted with *n*-pentane and concentrated by boiling until the product crystallized as plates, m.p. 133–135° dec. One recrystallization from ether–*n*-hexane afforded pure 6 $\alpha$ -bromotestosterone acetate XII, m.p. 147–148° dec.,  $[\alpha]^{25}_D +54.8^\circ$ . Ultraviolet absorption was at  $\lambda_{max}$  237 m $\mu$  ( $\epsilon$  13,600).

*Anal.* Calcd. for C<sub>21</sub>H<sub>29</sub>BrO<sub>3</sub>: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.33; H, 7.18; Br, 19.48.

**Ketalization of Testosterone Acetate with Differing Low Concentrations of Acid Catalyst.**—Testosterone acetate (5.0 g., 15.1 mmoles) was ketalized azeotropically in benzene solution (350 ml.) with 20 ml. of ethylene glycol and 25 mg. of *p*-toluenesulfonic acid. The reaction was carried out by heating at reflux under a water trap for 7 hr. The mixture was then cooled to room temperature and washed with dilute sodium bicarbonate and several times with water. Evaporation of the benzene solution to dryness under reduced pressure gave a solid crystalline residue which was examined for ultraviolet absorption.

The experiment was repeated with 50 mg. of acid catalyst,

then with 75 mg. The three experiments represented catalyst concentrations of 0.00037 *M*, 0.00074 *M*, and 0.00111 *M*, respectively. The crude product of each reaction absorbed at 241 m $\mu$  in the ultraviolet, indicative of unchanged testosterone acetate. Calculations showed the extent of reaction in each case to be (a) 0.00037 *M* catalyst, 49% conversion to ketal; (b) 0.00074 *M* catalyst, 65% conversion to ketal; and (c) 0.00111 *M* catalyst, 75% conversion to ketal.

**Isomerization of Testosterone Acetate  $\Delta^4$ -Ketal II to Its  $\Delta^5$ -Isomer VI.**—A solution of 3,3-ethylenedioxyandrost-4-en-17 $\beta$ -ol acetate (II, 1.00 g., 2.6 mmoles) and 50 mg. (0.26 mmole) of *p*-toluenesulfonic acid monohydrate in 100 ml. of dry benzene was heated under reflux for 3 hr., with the condensate returning through a Dean–Stark water separator. After cooling to room temperature, the solution was washed with dilute sodium bicarbonate, then three times with water. After brief drying over sodium sulfate, the benzene solution was distilled to dryness under reduced pressure to afford a solid residue which was recrystallized from a mixture of acetone and *n*-hexane, 0.45 g., m.p. 180–189° (a 45% yield). No further crystalline material could be obtained from the filtrate. One additional recrystallization from acetone containing a trace of pyridine gave pure 3,3-ethylenedioxyandrost-5-en-17 $\beta$ -ol acetate, m.p. 201–204°,  $[\alpha]^{25}_D -50.9^\circ$ ; lit.<sup>2</sup> m.p. 203–205°,  $[\alpha]^{25}_D -52.1^\circ$ . A mixture melting point with authentic material was undepressed and a comparison of infrared spectra showed no differences.

**Acknowledgment.**—The authors are indebted to Professor H. F. Herbrandson of Rensselaer Polytechnic Institute for many helpful discussions and suggestions, and to Dr. R. O. Clinton of Sterling–Winthrop Research Institute for his interest and encouragement during this work.

## The Base-Catalyzed Self-Condensation of 2-Ethyl-2-hexenal. III. Structure of Isomeric Glycols, C<sub>16</sub>H<sub>30</sub>O<sub>2</sub><sup>1</sup>

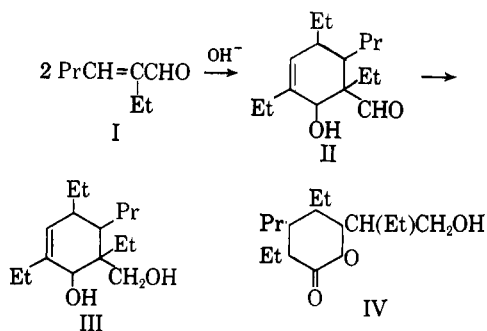
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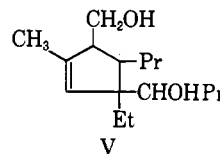
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The self-condensation of 2-ethyl-2-hexenal by heating under reflux with aqueous sodium hydroxide produces four glycol diastereoisomers, C<sub>16</sub>H<sub>30</sub>O<sub>2</sub> (III) (25% total yield), and previously described<sup>4</sup> lactones, C<sub>16</sub>H<sub>30</sub>O<sub>3</sub> (IV) and C<sub>12</sub>H<sub>22</sub>O<sub>2</sub> (XIV). The glycols have all been shown to be 6-hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ols by degradation (two routes) to known 3-propyl-2,4,6-triethylphenol (VIII). They are each produced from the corresponding aldol (II) in a crossed Cannizzaro reaction by oxidation of butanal and 2-ethyl-2-hexenal.

In the previous papers of this series<sup>3,4</sup> the self-condensation of 2-ethyl-1-hexenal (I) was reported to produce three C<sub>16</sub> products: an aldol, C<sub>16</sub>H<sub>28</sub>O<sub>2</sub> (II),



a glycol, C<sub>16</sub>H<sub>30</sub>O<sub>2</sub> (III, 32% yield), and a lactone, C<sub>16</sub>H<sub>30</sub>O<sub>3</sub> (IV) in the presence of aqueous methanolic potassium hydroxide at 25°. Lithium aluminum hydride reduction of II gave III, obtained as a liquid. Publishing simultaneously and independently, Pummerer and Smidt<sup>5</sup> also described the self-condensation of I, employing aqueous sodium hydroxide at reflux temperature (110°). They reported the formation of two diastereoisomeric glycols, C<sub>16</sub>H<sub>30</sub>O<sub>2</sub> (22% total yield), one of m.p. 62° and one a liquid, and to both they assigned a five-membered ring structure (V). Since it seemed unlikely to us that the difference in reaction conditions in the two experiments<sup>4,5</sup> was suf-



(1) Presented at the 135th National American Chemical Society Meeting, Boston, Mass., April, 1959.

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(3) A. T. Nielsen, *J. Am. Chem. Soc.*, **79**, 2518 (1957).

(4) A. T. Nielsen, *ibid.*, **79**, 2524 (1957).

(5) R. Pummerer and J. Smidt, *Ann.*, **610**, 192 (1957).

TABLE I  
 6-METHYLOL-5-PROPYL-2,4,6-TRIETHYL-2-CYCLOHEXEN-1-OL DIASTEREISOMERS (III)

M.p., °C.	Distribution <sup>a</sup> at 110°, % ± ca. 3	—Anal. Found. % <sup>b</sup> —		Bis-3,5-dinitro- benzoate, m.p., °C.	—Anal. Found % <sup>c</sup> —		
		C	H		C	H	N
B.p. 134–135 <sup>d</sup> (0.4 mm.)	55	75.49	12.12	183.5–183.5 <sup>e</sup>	56.65	5.61	8.70
62–62.5 <sup>f</sup>	30	75.46	11.95	159–160 <sup>g</sup>	56.13	5.41	8.67
90–91	10	75.6	11.9	153–154 <sup>g</sup>	56.11	5.33	8.50
112–113	5	75.29	11.93	.. <sup>h</sup>			

<sup>a</sup> Isomer distribution in glycol mixture obtained after 20–96-hr. reflux of 2-ethyl-2-hexenal with aqueous sodium hydroxide. <sup>b</sup> Calcd. for C<sub>16</sub>H<sub>30</sub>O<sub>2</sub>: C, 75.53; H, 11.89. <sup>c</sup> Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>4</sub>O<sub>12</sub>: C, 56.07; H, 5.33; N, 8.72. <sup>d</sup> Bis-*p*-nitrophenylurethan, m.p. 76.5–78.5°. <sup>e</sup> Rectangular prisms; reported m.p. 178° (R. H. Hall and K. H. W. Tuerck, British Patent 608,985 (September 23, 1948); *Chem. Abstr.*, **44**, 4493 (1950)). <sup>f</sup> Bis-*p*-nitrophenylurethan, m.p. 208–210° (prisms from nitromethane). Calcd. for C<sub>30</sub>H<sub>38</sub>N<sub>4</sub>O<sub>8</sub>: C, 61.84; H, 6.57; N, 9.62. Found: C, 61.6; H, 6.73; N, 9.67. Attempts to prepare a crystalline bis-*p*-nitrophenylurethan of the 90° isomer were unsuccessful. <sup>g</sup> Crystals of the 62° glycol bis-3,5-dinitrobenzoate were flat and hexagonal while those of the 90° derivative were rhombic prisms. The melting point of a mixture of these two derivatives was 133–139°. <sup>h</sup> See ref. 6a.

ficient to produce glycols having the same molecular formula, but different structures, the previous experiments were carefully re-examined. In the present paper new evidence is presented affirming 6-hydroxy-methyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol structures (III) for all isomeric glycols, C<sub>16</sub>H<sub>30</sub>O<sub>2</sub>, obtained from I.

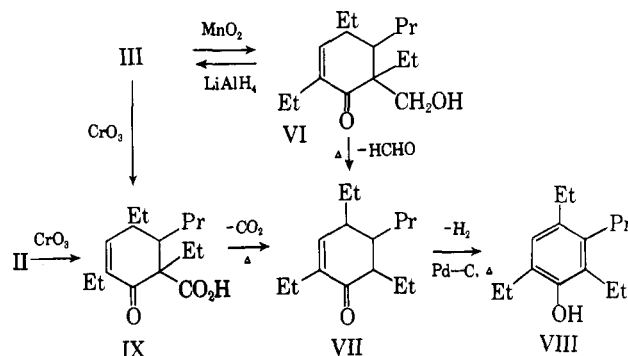
The procedure of Pummerer and Smidt<sup>5</sup> was repeated and found to yield not two, but four isomeric glycols, C<sub>16</sub>H<sub>30</sub>O<sub>2</sub> (25% total yield). Crystallization from petroleum ether was an efficient method of isolating the crystalline glycols and an improved yield (ca. 30% of the total) of the 62° isomer was realized. In addition, smaller amounts of isomers not previously described were obtained, one of m.p. 90–91° (ca. 10% of the total) and one of m.p. 112–113° (ca. 5%). The liquid isomer was the major component of this mixture (ca. 55%). Results are summarized in Table I. Re-examination of liquid glycol samples which we had obtained earlier<sup>4</sup> by condensation of 2-ethyl-2-hexenal at 25° or by lithium aluminum hydride reduction of II revealed 0–6% crystalline isomers. Evidently the isomer distribution depends on reaction conditions; much more of the crystalline isomers are produced by the vigorous conditions of Pummerer and Smidt.

The four glycol samples are diastereoisomers, not polymorphs. They cannot be directly interconverted by physical or chemical means and each forms a distinct bis-3,5-dinitrobenzoate derivative (Table I).<sup>6</sup> Their infrared spectra are similar (strong OH stretching band at 3500 cm.<sup>-1</sup> and a weak C=C stretching band at 1640 cm.<sup>-1</sup>). Small but distinct differences in the spectra are observed in the region 700–1500 cm.<sup>-1</sup>; these affirm, to a rough degree, the isomer distribution determined by crystallization.

Assignment of structure III to the glycol (principally liquid isomer) obtained in our previous work<sup>4</sup> rested on preparation of the same compound from II by lithium aluminum hydride reduction (bis-*p*-nitrophenylurethan derivatives identical). The structure II had been established rigorously by two unrelated degradation schemes.<sup>3</sup>

Each of the four glycols was oxidized with active

manganese dioxide catalyst<sup>7</sup> to a ketol (VI, C<sub>16</sub>H<sub>28</sub>O<sub>2</sub>) having an  $\alpha,\beta$ -unsaturated carbonyl group ( $\epsilon_{\text{max}}^{240\text{m}\mu}$  9000). The ketols (VI) readily lost formaldehyde on heating to form an  $\alpha,\beta$ -unsaturated ketone (VII, C<sub>15</sub>H<sub>26</sub>O;  $\epsilon_{\text{max}}^{241\text{m}\mu}$  7800).



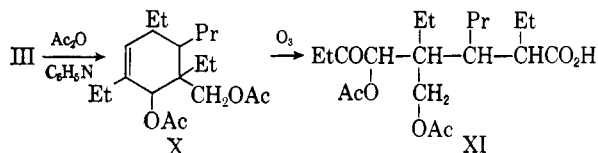
Formation of VI and VII is consistent with an allylic secondary hydroxyl group in III. Lithium aluminum hydride reduction of the ketols (VI) regenerated the glycols (III), thus establishing the position of the double bond (a detailed study of this reaction is in progress).<sup>6b</sup> Dehydrogenation of VII by heating with palladium–charcoal catalyst led to 3-propyl-2,4,6-triethylphenol (VIII), identical with an authentic sample synthesized by an alternate route<sup>3</sup> (phenylurethan derivatives identical). Ketone VII also was prepared from III by chromic acid oxidation (the pure 60° isomer or the mixture of four isomers obtained by the procedure of Pummerer and Smidt<sup>5</sup> gave the same result). The intermediate β-keto acid (IX) was not isolated, but decarboxylated *in situ* to VII, which was then dehydrogenated to VIII (ketol VI also was produced by the chromic acid oxidation since formate is a product). Chromic acid oxidation of aldol II had previously been shown to produce VIII through the following sequence: II → IX → VII → VIII.<sup>3</sup>

Structure V arrived at by Pummerer and Smidt does not agree with our results and it becomes of interest to re-examine their data in terms of structure III. Their experimental findings can easily be reconciled with III except for an apparent discrepancy which rests in assignment of methyl ketone structures to two ketocarboxylic acids obtained by degradation of the glycol diacetate, C<sub>20</sub>H<sub>34</sub>O<sub>4</sub> (X). Cleavage of X with ozone pro-

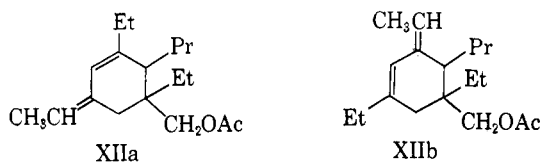
(6)(a) The 112° isomer appeared to be much less reactive than the other isomers and could not be converted into a bis-3,5-dinitrobenzoate derivative. (b) Chemical differences between the isomers have been noted in experiments in progress leading to establishment of stereochemistry; results will appear in a forthcoming publication. The maximum number of isomers possible is believed to be four since stereochemistry at C-4 and C-5 appears to be the same in all.

(7) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

duced a keto acid,  $C_{20}H_{34}O_7$  (XI), which gave a positive iodoform test and was assigned a methyl ketone structure. However, Lieben's iodoform test is not reliable in distinguishing between methyl and ethyl ketones.<sup>8</sup> On the basis of structure III, keto acid XI would be formulated as an ethyl ketone.



The second ketocarboxylic acid giving a positive iodoform test was reported to have formula,  $C_{14}H_{24}O_6$ , and was obtained by ozonolysis of a liquid diene monoacetate, XII ( $\lambda_{max}$  239.5  $m\mu$ ,  $\epsilon_{max}$  17,400; present work) prepared by potassium acid sulfate-catalyzed dehydroacetoxylation of X.<sup>9</sup> The conversion  $X \rightarrow XII$  is subject to rearrangements; if no ring contraction occurs,<sup>10</sup> structures XIIa or XIIb are probable (expected<sup>11</sup>  $\lambda_{max}$  242  $m\mu$ ,  $\epsilon_{max}$  >15,000). A 1,3-cyclohexadiene structure is incompatible with the ultraviolet spectrum (expected<sup>11</sup>  $\lambda_{max}$  263  $m\mu$ ,  $\epsilon_{max}$  <10,000). The observed formation of acetaldehyde on ozonolysis<sup>5</sup> is in agreement with the presence of an ethylidene group. The alcohol (XIII) derived from XII by saponification is primary, loses formaldehyde on prolonged heating, and produces  $\alpha$ -ethyl- $\beta$ -propylsuccinic, propionic, and acetic acids on permanganate oxidation.<sup>5</sup> A keto acid derived



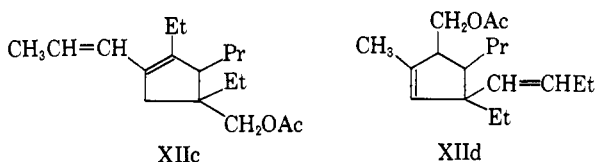
from XIIa, XIIb, or XIIc<sup>10</sup> by ozonolysis would be formulated as an ethyl ketone,  $C_{15}H_{26}O_6$ .<sup>8,9,12</sup>

The identity of the reducing agents in the Cannizzaro reaction leading to III from I now has been clearly established. Aldol isomers (II) are reduced directly to

(8) Several workers have observed that ethyl ketones give a positive iodoform test. The reaction has been studied. (a) A. Fry, I. Ookuni, G. J. Karabatsos, J. D. Graham, and F. Vane, *J. Org. Chem.*, **27**, 1914 (1962); (b) C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.*, 1548 (1957); (c) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **71**, 1496 (1949); cf. other references cited in these papers.

(9) The elemental analysis of the methyl ester of the ketocarboxylic acid obtained by ozonolysis of XII corresponds to a formula  $C_{14}H_{24}O_6$  for the acid; however, the saponification equivalent of the ester is in very close agreement with the keto acid formula,  $C_{15}H_{26}O_6$ .<sup>5</sup>

(10) Contraction to a five-membered ring such as XIIc cannot be ruled out, nor can the formation of mixtures of conjugated dienes. However, the unconjugated structure XIIb, assigned by Pummerer and Smidt,<sup>8</sup> is in disagreement with the observed ultraviolet spectrum.



(11) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Co., New York, N. Y., 1949, pp. 184-198.

(12) Additional data accumulated by Pummerer and Smidt,<sup>8</sup> including degradation of III and XII to various hydrocarbons,  $C_{15}H_{26}$  and  $C_{15}H_{24}$ , appear to be less informative and need not be considered. None of these data would appear to be in disagreement with structure III.

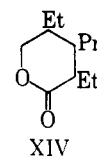
III isomers,<sup>13</sup> but not by II itself (as stated by Pummerer and Smidt<sup>8</sup>) for the following reasons. (1) No III is produced from II alone under conditions whereby I yields III.<sup>4</sup> (2) No  $C_{16}$  carboxylic acid (such as one obtained by oxidizing II) was found to be a significant reaction product. (3) The total mole-equivalents of butyric and 2-ethyl-2-hexenoic acids produced account for 90% of the acid formed in the reaction. The reducing agents in the crossed Cannizzaro reaction, based on the number of equivalents of acid produced are butanol (69% of the total reduction), 2-ethyl-2-hexenal (21.5%), and unknown high molecular weight material (9.5%). [About 10% of the high molecular weight material produced a distillable methyl ester when treated with diazomethane; the amount of  $C_{16}$  acid (if any) is estimated to be less than 2% of the total carboxylic acid produced.] In addition to glycol III other alcohols formed were butanol (0.3% yield) and 2-ethyl-2-hexen-1-ol (1%). Table II summarizes the material balance of alcohol and carboxylic acid products involved in the Cannizzaro reaction (38.5 hr. at 110°).

TABLE II  
YIELDS OF CANNIZZARO PRODUCTS FROM 2-ETHYL-2-HEXENAL (I)

	Yield, %	Mole-equivalents from 10 moles of I
<b>Alcohols<sup>a</sup></b>		
1-Butanol	0.3	0.05
2-Ethyl-2-hexen-1-ol	1.0	0.09
Glycols (III)	25	1.24
		1.38 total
<b>Acids</b>		
Butyric	4.8	0.96
2-Ethyl-2-hexenoic	1.5	0.30
Unidentified <sup>b</sup>	(7.6 <sup>c</sup> )	0.13
		1.39 total

<sup>a</sup> Yield of undistillable neutral residue was 2% by weight. The amount of Cannizzaro derived alcohol in this residue was not determined; it cannot exceed 0.1 mole-equivalent, but is probably much less than this figure. <sup>b</sup> Undistillable acid residue, "neut. equiv.," 730. <sup>c</sup> Weight per cent yield (grams produced from 100 g. of I).

In the present study two lactones (IV and XIV) were obtained from I by the procedure of Pummerer and Smidt in yields of 30% and 9%, respectively.



Evidence establishing these structures has been presented.<sup>8,4,14</sup> The amount of IV produced, relative to XIV, decreases as reaction conditions become more vigorous (higher temperature, higher base concentration). Yields of IV and XIV, respectively, under various conditions are 25°, 16 hr. (56 and 0%); 110°, 38.5 hr. (30 and 9%); 160-200°, 21 hr. (0 and 36%).<sup>14</sup> The values at 25° are with aqueous methanolic potassium hydroxide (0.5 mole-equivalent), the others with

(13) The glycol isomers are believed to form from the corresponding aldol isomers (II), not by base-catalyzed epimerization of III (only possible at C-1). Equilibration of II with its acyclic precursor would lead to a mixture of II diastereoisomers epimeric at C-1 and C-6.

(14) M. Häusermann, *Helv. Chim. Acta*, **34**, 1482 (1951). Other products reported were 1-butanol (8.3%), 2-ethyl-1-hexanol (2.1%), butyric acid (5.1%), 2-ethyl-2-hexenoic acid (2.5%), and a liquid glycol,  $C_{16}H_{30}O_2$  (8.4%).

aqueous sodium hydroxide (0.72 mole-equivalent at 110° and 1.0 mole-equivalent at 160–200°). With more vigorous reaction conditions XIV evidently forms at the expense of IV in agreement with the mechanism<sup>4</sup> of the intramolecular formation of these compounds from their common precursor, II.

### Experimental<sup>15</sup>

**Self-Condensation of 2-Ethyl-2-hexenal (Neutral Products).**—The procedure of Pummerer and Smidt<sup>5</sup> was used with slight modifications. To a solution of 250 g. (6.25 moles) of sodium hydroxide in 750 ml. of water was added 1100 g. (8.7 moles) of purified,<sup>3</sup> freshly distilled 2-ethyl-2-hexenal<sup>16</sup> during 4.5 hr., with vigorous stirring (temperature, 67°). The mixture was then refluxed (110° within the liquid), with stirring, for 38.5 hr. (nitrogen atmosphere). The mixture was separated into neutral and acidic products using the procedure previously described. The isolation of acidic products is described subsequently.

The neutral portion was distilled to yield the following fractions: (1) 8 ml., b.p. 60–90° (29 mm.); (2) 18.2 g., b.p. 90–123° (29 mm.), mainly 2-ethyl-2-hexen-1-ol; (3) 44 ml., b.p. 86–142° (1.8 mm.); (4) 296 g., b.p. 145–151° (1.5 mm.), crude glycol mixture; and (5) 22.5 g. of residue. Redistillation of fraction 1 at 740 mm. gave 3 g. of 1-butanol, b.p. 118–120°, and 2.4 g. of 3-heptanone, b.p. 146–151° ( $n_D^{20}$  1.4115; 2,4-dinitrophenylhydrazine, m.p. 82–83°, alone, and when mixed with an authentic sample). The possibility that the 3-heptanone was an impurity in the 2-ethyl-2-hexenal employed cannot be discounted.

**2-Ethyl-2-hexen-1-ol.**—Redistillation of fraction 2 (above) gave 11.6 g., b.p. 95–97° (27 mm.),  $n_D^{20}$  1.4490, of 2-ethyl-2-hexen-1-ol (1% yield). (Found: C, 74.36; H, 12.74.) Quantitative bromination by direct titration with bromine in acetic acid indicated 1.03 double bonds (assuming mol. wt., 128.2). The  $\alpha$ -naphthylurethan derivative melted at 80–80.5°, alone, and when mixed with an authentic sample (see following). The infrared spectrum was identical with the authentic sample.

An authentic sample of 2-ethyl-2-hexen-1-ol was prepared as follows. To a solution of 10 g. (0.264 mole) of lithium aluminum hydride in 400 ml. of dry ether was added 70.0 g. (0.555 mole) of purified 2-ethyl-2-hexenal during 4 hr., with refluxing and stirring continued for 1 hr. after addition of the aldehyde was complete. After standing at room temperature for 12 hr. and decomposing the reaction mixture with dilute hydrochloric acid in the usual manner, the product was separated by extraction with ether and the extracts dried with magnesium sulfate. Distillation gave 61.5 g. (87%) of the alcohol, b.p. 94–96° (26 mm.),  $n_D^{20}$  1.4488. A redistilled, analytical sample had b.p. 93–93.5° (24 mm.),  $n_D^{20}$  1.4489; infrared bands at (cm.<sup>-1</sup>) 3400 (OH) and 1670 (C=C).

*Anal.* Calcd. for C<sub>8</sub>H<sub>16</sub>O: C, 74.94; H, 12.58. Found: C, 75.04; H, 12.67.

The  $\alpha$ -naphthylurethan derivative was obtained as needles from petroleum ether (b.p. 60–70°), m.p. 80–80.5° (79% yield).

*Anal.* Calcd. for C<sub>15</sub>H<sub>23</sub>NO<sub>2</sub>: C, 76.73; H, 7.80; N, 4.71. Found: C, 77.05; H, 7.86; N, 4.83.

**6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol Isomers (III).**—Fraction 4, from the condensation described before, was redistilled<sup>17</sup> to yield 275 g. (25% yield) of viscous glycol mixture, b.p. 146–150° (1.5 mm.),  $n_D^{20}$  1.4960. Fractional crystallization from 350 ml. of petroleum ether (b.p. 60–70°) at –15° gave 52.3 g., m.p. 55–60°, and 18.5 g., m.p. 47–55°, after one week. Recrystallization from the same solvent gave feathery needles, m.p. 62–62.5° (42 g.). Samples of glycol obtained by self-condensation of 2-ethyl-2-hexenal for 19 hr. (24% yield) and 96 hr. (25% yield), under the same conditions, gave essentially the same amount of each isomer.

From the sample of mixed glycols (250 g., b.p. 137–142°, 0.5 mm., 25.2% yield) obtained in a 96-hr. run there was isolated by crystallization from 600 ml. of petroleum ether (–15°, 1 week) 69 g., m.p. 45–60°. The filtrate was concentrated to ca. one-half its volume and chilled again to –15° to yield, by fractional crystallization, 23.8 g., m.p. 85–90°, and 7.5 g., m.p. 100–105°, after 12 days. Recrystallization of these latter fractions from hexane gave pure samples of glycols, m.p. 90–91° and 112–113°, respectively (*cf.* Table I). The mother liquors were diluted with ether, washed several times with *N* sodium hydroxide solution and water,<sup>17</sup> dried with magnesium sulfate, and distilled to yield 130.5 g., b.p. 155–160° (3 mm.), of glycol from which an additional 8.1 g. of crystals, m.p. 45–59°, was obtained by crystallization from cold hexane (20 days, –15°). A sample of liquid glycol, from which no additional crystals could be obtained, had b.p. 134–135° (0.4 mm.),  $n_D^{20}$  1.4960. Analytical data for the four isomers are given in Table I. The isomers could not be interconverted by heating with acid or basic catalysts under a variety of conditions.

A sample of C<sub>16</sub> glycol (21.1 g.) obtained in 74% yield by lithium aluminum hydride reduction of 2-hydroxy-6-propyl-1,3,5-triethyl-3-cyclohexene-1-carboxaldehyde (II)<sup>8</sup> was crystallized from hexane at –15° to yield 1.6 g. (5.7% yield from II), m.p. 90–111°; no 60° isomer was obtained. Recrystallization gave 1.12 g., m.p. 110–112°. The remaining liquid glycol,  $n_D^{20}$  1.4957, from which no additional crystals could be obtained had the same infrared spectrum as the previous liquid glycol from the condensation and formed the same bis-*p*-nitrophenylurethan and bis-3,5-dinitrobenzoate derivatives (Table I).

A sample of C<sub>16</sub> glycol obtained by self-condensation of 2-ethyl-2-hexenal at 25° (4-hr. reaction time) was dissolved in petroleum ether and stored at –15° for 11 months; seeding with crystalline isomers produced no crystals during this time. Similarly, a sample (3 g.) obtained by a 7-hr. reaction time at 25° produced 0.04 g. (1.3%), m.p. 87–91°, as the only crystalline product.

The infrared spectra of the solid glycol isomers were determined in potassium bromide; that of the liquid, neat. All showed strong OH stretching absorption at 3500 cm.<sup>-1</sup> and weak, broad C=C absorption at 1640 cm.<sup>-1</sup>. No carbonyl absorption was present. Small, but significant differences in the spectra of the four isomers were evident in the region 700–1500 cm.<sup>-1</sup>. A band of medium intensity which appears at 1080–1090 cm.<sup>-1</sup> in each of the crystalline isomers is absent in the liquid isomer. A synthetic mixture of isomers prepared to agree closely in composition with the amounts isolated in a particular run (55% liquid, 30% 62°, 10% 90°, and 5% 112°) had the same infrared spectrum as the distilled uncrystallized mixture obtained from the condensation.

The bis-3,5-dinitrobenzoate derivatives listed in Table I were prepared by heating one mole-equivalent of glycol with two mole-equivalents of 3,5-dinitrobenzoyl chloride in dry pyridine solution under reflux for 20–40 hr. The derivatives were isolated by pouring the reaction mixture into ice-cold *N* hydrochloric acid and recrystallizing the precipitated product from ethanol. Several attempts to prepare a crystalline bis-3,5-dinitrobenzoate derivative of the 112° isomer by a variety of procedures were unsuccessful.

**Self-Condensation of 2-Ethyl-2-hexenal (Acidic Products).**—Distillation of the acidic portion of the reaction mixture (from 1100 g. of 2-ethyl-2-hexenal—condensation described earlier) gave the following principal fractions: (1) 48.3 g., b.p. 72–89° (28 mm.) mainly butyric acid; (2) 132 g., b.p. 95–114° (0.5–1.9 mm.), mainly a mixture of 2-ethyl-2-hexenoic acid and XIV; (3) 352 g., b.p. 171–178° (1.5–2.0 mm.), of crude 3-propyl-2,4,6-triethyl-5-hydroxy-1,7-heptanedioic acid 1,5-lactone (IV) (30% yield); and (4) 84 g. of brown, semisolid, undistillable residue.

**Butyric Acid.**—In addition to the butyric acid obtained in fraction 1, preceding, some also was isolated from the aqueous portion of the reaction mixture. (Previously,<sup>4</sup> the aqueous part had not been investigated for acidic material. In this run about 24% of the total free acid was found in the water.) The combined aqueous solution from the previous condensation reaction was acidified with sulfuric acid and steam-distilled until essentially no more acid was found in the distillate (total volume, 61 l.; total of 0.288 gram-equivalent of acid present by direct titration). The distillate was made slightly alkaline with sodium hydroxide and concentrated to a volume of 200 ml. Acidification of this concentrate with sulfuric acid followed by continuous extraction with ether for 31 hr. led to the isolation of 18.9 g. (0.213 mole) of butyric acid, b.p. 77–79° (26 mm.). The total butyric acid

(15) Melting points were determined on a Kofler hot stage and are uncorrected. Ultraviolet spectra were measured in 95% ethanol; infrared spectra of liquids were determined neat.

(16) A generous supply of 2-ethyl-2-hexenal was supplied by the Carbide and Carbon Chemicals Corp., South Charleston, W. Va.

(17) Acidic and/or peroxide impurities often accumulate in samples of the glycols stored in the presence of air and cause decomposition (primarily dehydration) on subsequent distillation. These impurities may be removed by several washings of an ether solution of the sample with *N* sodium hydroxide solution.

yield from 8.7 moles of I is 0.83 mole, including both previously distilled samples (67.2 g., combined, 0.765 mole, neut. equiv., 88.4, corrected for traces of neutral impurity) and 6.1 g. of miscellaneous foreruns and residues (*cf.* Table II).

**2-Ethyl-2-hexenoic Acid.**—Fraction 2 was extracted with saturated sodium bicarbonate solution to remove 2-ethyl-2-hexenoic acid. Distillation gave, as one fraction, 22.6 g. (0.16 mole), b.p. 95–99° (1 mm.),  $n_D^{25}$  1.445, of 2-ethyl-2-hexenoic acid; neut. equiv., 143.8 (calculated for  $C_8H_{14}O_2$ , 142.2); infrared spectrum identical with authentic sample. The total yield of 2-ethyl-2-hexenoic acid from 8.7 moles of I is 0.26 mole including the previous purified sample and 14 g. (0.1 mole) of miscellaneous foreruns and residues (*cf.* Table II).

**2,4-Diethyl-3-propyl-1,5-pentanone (XIV).**—The material not removed by the sodium bicarbonate extraction of fraction 2 was isolated and distilled, yielding 79 g. (9%), b.p. 111–117° (1.9 mm.),  $n_D^{25}$  1.466, of lactone XIV as the main product. The infrared spectrum was identical with that of an authentic sample, previously obtained.<sup>3</sup>

*Anal.* Calcd. for  $C_{12}H_{22}O_2$ : C, 72.68; H, 11.18; mol. wt., 198.3. Found: C, 72.91; H, 10.74; sapon. equiv., 204.

**Acid Residue.**—The 84 g. of viscous acid residue was found to contain a total of 0.115 gram-equivalent of acidic material (neut. equiv., 730). Separation of this sample into neutral and carboxylic acid fractions by extraction with sodium bicarbonate solution gave 53 g. of viscous acid mixture (neut. equiv., 470) and 27 g. of neutral residue. Treatment of 39.6 g. of the acidic material, dissolved in ether, with excess diazomethane gave 5.3 g., b.p. 124–127° (1 mm.), 4.0 g., b.p. 135–172° (0.7 mm.), and 30.4 g. of undistillable residue. None of the previous substances was investigated further. The distilled material (9.3 g.) would represent *ca.* 0.03 mole, assuming mol. wt., 282.

**6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-one (VI).**—Glycol III, isomer, m.p. 88–90° (5.0 g.), manganese dioxide catalyst<sup>7</sup> (30 g.), and 60 ml. of cyclohexane were mixed and the mixture shaken continuously at room temperature for 89 hr. The mixture was filtered and washed with cyclohexane to yield 4.86 g. of colorless oil after removal of solvent. Distillation gave 4.0 g. (80%) of ketol VI, b.p. 117–118° (0.5 mm.),  $n_D^{25}$  1.491; infrared bands at 3500 and 1650  $cm^{-1}$  (C=O, conjugated) in chloroform solvent; ultraviolet spectrum,  $\lambda_{max}$  240  $\mu$  ( $\epsilon_{max}$  9000). Oxidation of the other three glycol isomers also gave ketols,  $C_{16}H_{28}O_2$ , having similar properties.<sup>6b</sup>

*Anal.* Calcd. for  $C_{16}H_{28}O_2$ : C, 76.14; H, 11.18. Found: C, 76.12; H, 11.4.

The ketol derived from the 90° glycol isomer was dissolved in ether (10 ml.) and added to a solution of 1.0 g. of lithium aluminum hydride in 50 ml. of ether and the mixture was refluxed for 22 hr. Decomposition in the usual manner with dilute hydrochloric acid led ultimately to 0.71 g. of glycol, m.p. 88–89°, after crystallization from hexane. Reduction in a similar manner of ketols derived from the other glycol isomers also led to regenerated glycols.<sup>6b</sup>

**5-Propyl-2,4,6-triethyl-2-cyclohexen-1-one (VII).** **A. By Demethylation of VI.**—A 1.05-g. sample of ketol VI (derived from liquid glycol isomer) was heated for 15 min. with a flame in a stream of nitrogen. The exit gases were passed through Johnson's reagent to produce formaldehyde 2,4-dinitrophenylhydrazine (0.09 g.), m.p. 160–165°. During the heating, gas evolution was noted and the loss in weight was 0.13 g. (calculated loss of weight due to formaldehyde evolution, 0.123 g.). The residue (0.90 g.) was distilled to yield 0.6 g. of ketone VII, b.p. 85–90°

(0.25 mm.),  $n_D^{25}$  1.4770, and 0.3 g. of residue; infrared band (chloroform) at 1660  $cm^{-1}$  (conjugated C=O); ultraviolet,  $\lambda_{max}$  241  $\mu$ ,  $\epsilon_{max}$  7630 (lit.<sup>3</sup>  $\lambda_{max}$  242  $\mu$ ,  $\epsilon_{max}$  5600). This procedure yields the purest sample of VII.

*Anal.* Calcd. for  $C_{16}H_{28}O$ : C, 81.02; H, 11.79. Found: C, 81.28; H, 12.13.

**B. By Oxidation of III.**—A 12.7-g. (0.05 mole) sample of glycol III (isomer, m.p. 61–62°) was oxidized with chromic oxide in aqueous acetic acid using a slight modification of the procedure developed earlier<sup>3</sup> for oxidation of aldol II. The decarboxylation at 70° gave a 20% yield of carbon dioxide; the liquid glycol mixture gave the same result. Addition of mercuric oxide and additional heating did not increase the yield of carbon dioxide.

The reaction mixture was made alkaline with sodium hydroxide and steam-distilled to yield 4.6 g. (41%) of ketone VII, b.p. 96–105° (0.8 mm.); redistillation gave 3.3 g., b.p. 90–92° (0.7 mm.),  $n_D^{25}$  1.4790. A similar oxidation of the liquid glycol mixture gave a 43% yield of VII, b.p. 87–88° (0.5 mm.),  $n_D^{25}$  1.4770 (Found: C, 80.20; H, 11.82); infrared bands at 1670 (C=O) and 1625 (C=C)  $cm^{-1}$ ; ultraviolet,  $\lambda_{max}$  241  $\mu$ ,  $\epsilon_{max}$  7800.

The aqueous alkaline residue was acidified with sulfuric acid and heated with mercuric oxide and the liberated carbon dioxide collected as previously<sup>3</sup> to assay formic acid; yields were 21% and 24% from the 62° and liquid glycol mixture, respectively. The combined yields of carbon dioxide and formic acid (41–44%) correspond closely to the yield of VI (41–43%).

**2,4,6-Triethyl-3-propylphenol (VIII)** was prepared from ketone VII (obtained by chromic acid oxidation of III, m.p. 62°) by dehydrogenation with palladium-charcoal catalyst as previously described.<sup>3</sup> From 6.0 g. of ketone was isolated 2.0 g., b.p. 90–91° (0.45 mm.),  $n_D^{25}$  1.4975, and 1.2 g., b.p. 91–93° (0.45 mm.),  $n_D^{25}$  1.5070;  $\lambda_{max}$  283.5,  $\epsilon_{max}$  1780; reported<sup>3</sup> for authentic sample, b.p. 96–98° (0.4 mm.),  $n_D^{25}$  1.519,  $\lambda_{max}$  282  $\mu$ ,  $\epsilon_{max}$  2040; infrared spectrum identical with the authentic sample except for some slight carbonyl absorption at 1678  $cm^{-1}$ . The phenylurethan derivative melted at 123–124° (lit.<sup>3</sup> m.p. 122–122.5°) and when mixed with an authentic sample the melting point was not depressed.

**6-Hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ol Diacetate (X).**—The procedure of Pummerer and Smidt<sup>5</sup> was followed to yield the diacetate X from the liquid glycol isomer, 78–79% yield, b.p. 136–138° (0.95 mm.),  $n_D^{25}$  1.4733 (lit.<sup>5</sup>  $n_D^{25}$  1.4745); strong acetate band at 1750  $cm^{-1}$  (C=O).

*Anal.* Calcd. for  $C_{26}H_{44}O_4$ : C, 70.97; H, 10.13. Found: C, 71.04; H, 10.13.

**Dehydroacetoxylation of diacetate X** to the diene monoacetate (XII) was accomplished by the procedure of Pummerer and Smidt.<sup>5</sup> A 39.0-g. sample of X was mixed with 55.6 g. of freshly melted and powdered potassium acid sulfate and heated in an oil bath maintained at 86–96° for 3 hr. The mixture was distilled under reduced pressure to remove the acetic acid (2-hr. heating at bath temperature of 92°). There was obtained 6.4 g. (0.925 mole-equivalent) of acetic acid distillate (neut. equiv., 61). The residue was diluted with water, extracted with ether, and the combined extracts washed several times with water and dried; removal of the ether gave 28.7 g. of orange oil. Distillation under nitrogen gave 22.4 g. (70% yield) of dienemonoacetate, b.p. 100–106° (0.4 mm.),  $n_D^{25}$  1.489; infrared bands, 1740 (C=O, ester) and 1640 (C=C)  $cm^{-1}$ ; ultraviolet,  $\lambda_{max}$  239.5  $\mu$ ,  $\epsilon_{max}$  17,400.