## Preparation and Properties of 2-(2-Methyl-1-propenyl)-3-isopropyl-1,5-diphenyl-1,5-pentanediol

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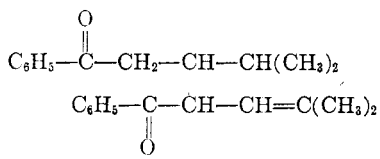
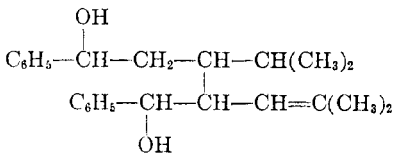
In our note[1] we were primarily concerned with the preparation and properties of 1-phenyl-4-methyl-2-penten-1-one, which we found to be a liquid readily undergoing the usual reactions attributed to a compound of this structure. The solid product, which we derived from this ketone by self-condensation under alkaline conditions, did not exhibit most of the common reactions of an ethylenic linkage; thus we suggested that a dimeric four-membered saturated ring structure was possible.

By studying the NMR spectrum of this compound, Dr. Ragini Anet[2] proposes as its correct structure:



By further investigation, we have found that ozonolysis gives acetone in the predicted yield, which we identified as its 2,4-dinitrophenylhydrazone. This indicates that a terminal isopropylidene group is present. Meanwhile, we have likewise checked the NMR spectrum of this compound and arrived at the same conclusion as Dr. Anet.

It was of interest to prepare the glycol of the above diketone, to which the structure:



can be attributed, and to examine its NMR and infrared spectra.

The resistance of this diketone to catalytic hydrogenation is significant. Neither the double bond, nor the carbonyl groups responded to the attempted catalytic reductions, using various catalysts such as Raney nickel, Adams platinum, and palladium on charcoal at 50 and 100 p.s.i. Thoms and Kahre,[3] who did not obtain the monomer but erroneously assumed the diketone to be the monoketone, were also unsuccessful in their attempts to reduce the compound by catalytic hydrogenation. The unsaturated glycol was eventually obtained by reduction with potassium borohydride. The product is a heavy, transparent liquid, boiling at 204–206° at 1.2 mm. In contrast to the odorless, crystalline diketone, it has a pleasant, faint aromatic odor.

The NMR spectrum of the glycol (as a 10% solution by volume in carbon tetrachloride) was recorded and gives convincing evidence for the assigned structure. A peak at $\tau = 2.93$ shows the presence of the aromatic protons and, as expected, the absence of carbonyl groups *alpha* to the benzene ring. A doublet at $\tau = 4.88$ representing the vinyl hydrogen is clearly visible.

The infrared spectrum of the glycol (as is and also in carbon tetrachloride solution) was recorded. Because of interfering peaks, this spectrum is less suitable for the identification and makes its interpretation more speculative. The olefinic C—H stretch frequencies show up above 3000 cm.$^{-1}$ (3042 medium; 3066 weak). A weak to medium peak at 1670 cm.$^{-1}$ is due to C=C stretching, giving further evidence of the olefinic structure. A medium peak at 840 cm.$^{-1}$ (the undiluted glycol was used) is in the region of the trisubstituted CH out-of-plane branching mode. In addition to the free O—H stretching vibration at 3636 cm.$^{-1}$, a broad band of marked intensity occurs at about 3493 cm.$^{-1}$. It may be attributed to the presence of an internal hydrogen bond between the OH groups, since intermolecular hydrogen bond frequencies occur in the 3360 cm.$^{-1}$ region (confirmed by the presence of an intense band at about 3355 cm.$^{-1}$ in the undiluted glycol). Although there is little evidence for internal hydrogen bonding in the 1,5-pentanediol itself,[4] the presence of large substituted groups may lead to closer position of the OH groups and make this phenomenon possible.

### EXPERIMENTAL

*2-(2-Methyl-1-propenyl)-3-isopropyl-1,5-diphenyl-1,5-pentanediol (crude)* (I). A solution of 54 g. of potassium borohydride, 2 g. of potassium hydroxide (85%) and 250 ml. of water was added to a refluxing, agitated mixture 174 g. of the solid diketone (m.p. 144.5–145°) and 600 ml. of methanol, over a period of 5 hr. The solid diketone, which at the beginning of the reaction was not completely dissolved, went into solution as the reaction progressed. Agitation and reflux were continued for 2.75 hr. The reaction mixture was cooled to 15° and acidified to Congo Red with dilute hydrochloric acid. Hot water (250 ml.) was added to the viscous reaction mixture. The mixture was then extracted with three 150-ml. portions of benzene. The combined organic extracts were washed with 150 ml. of saturated aqueous sodium bicarbonate solution and two 250-ml. portions of water. After removal of the solvent by distillation, a slightly opaque, viscous material remained. Weight: 175 g. (expected: 175 g.). Analysis by acetylation and saponification gave a 90% alcohol content, calculated as the glycol.

(1) K. Kulka, R. J. Eiserle, J. A. Rogers, Jr., and F. W. Richter, *J. Org. Chem.*, **25**, 270 (1960).

(2) Dr. Ragini Anet, University of Ottawa, Ont., Canada, private communication.

(3) H. Thoms and H. Kahre, *Arch. Pharm.*, **263**, 251 (1925).

(4) D. W. Davidson, *Can. J. Chem., in press.*

*Diacetate of* I. One hundred sixteen grams of I was combined with 100 g. of acetic anhydride and 200 ml. of xylene. The acetic acid formed was distilled as an azeotrope with xylene, through a 1.5-ft. Vigreux column. The excess anhydride and xylene were removed by vacuum distillation. The remaining residue amounted to 137.3 g. against 143.5 g. theoretical. It was fractionated without a column: 90% boiled at 186–189° at 0.6 mm. $n_D^{20}$ 1.5230. On saponification it assayed 98.1% as the diacetate of I (II).

*Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.313. Found: C, 76.96; H, 8.203.

*2-(2-Methyl-1-propenyl)-3-isopropyl-1,5-diphenyl-1,5-pentanediol* (purified) (III). Fourty-four grams of II was saponified with a solution of 22.5 g. of potassium hydroxide (85%), 55 ml. of methanol, and 55 ml. of water by refluxing under agitation for 8 hr. The reaction product was cooled, 50 ml. of benzene and 50 ml. of water were added, and the organic layer was separated and washed with successive 50-ml. portions of water neutral to litmus. The solvent was distilled in a vacuum and the remaining residue of 35.5 g. was fractionated without a column. 85% boiled at 204–206° at 1.1 mm. $n_D^{20}$ 1.550 (III). A modified Rast method[1] gave a molecular weight of 348 against 352 theoretical.

*Anal.* Calcd. for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.60; H, 9.20.

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## 16-Hydroxylated Steroids. XVIII.[1] 16-Hydroxylated 19-Norandrogens

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Little information is available on the biological effect of C-16-hydroxylation of androgens in regard to their androgenic and protein anabolic activities.[2] It was decided therefore to prepare the C-16-hydroxylated derivatives of several 19-norandrogens, in particular, the 16α-hydroxy derivatives of 19-nortestosterone and 17α-methyl-19-nortestosterone.

The synthesis of 16α-hydroxy-19-nortestosterone (II) was readily accomplished as follows. Estriol 3-monomethyl ether (I)[3] on Birch reduction according to the procedure of Wilds and Nelson[4] followed by treatment of the intermediate dihydro product with hydrochloric acid in refluxing methanol gave the desired 16α-hydroxy-19-nortestosterone (II).[5]

16α-Hydroxy-17α-methyl-19-nortestosterone (VII) was synthesized in the following manner. 3-Methoxy-1,3,5(10),16-estratetraen-17-ol acetate (III)[6] was treated with perbenzoic acid in benzene followed by a mixture of glacial acetic acid and perchloric acid to give in 45% yield 16α-acetoxy-3-methoxy-1,3,5(10)-estratrien-17-one (IV). Reaction of the latter with methylmagnesium bromide afforded a mixture of diols, 16α,17β-dihydroxy-3-methoxy-17α-methyl-1,3,5(10)-estratriene (V) (38% yield) and 16α,17α-dihydroxy-3-methoxy-17β-methyl-1,3,5(10)-estratriene (VI) (47% yield). While C-17-ketones unsubstituted at C-16 undergo nucleophilic attack with the entering group coming in from the rear or α-face,[7] the formation of V and VI in approximately equal amounts indicates that the orienting effect of the C-13-methyl group is considerably altered by the presence of a 16α-acetoxy group. The stereochemistry of the two diols V and VI is supported by their mode of formation and by the fact that VI forms an acetonide derivative VIII while V under the same conditions is recovered unchanged.

In order to exclude the possibility that the *cis*-diol had not arisen from IV *via* initial attack of the Grignard reagent on the ester carbonyl followed by rearrangement of the intermediate ketol to the more stable[3a] 17β-hydroxy-3-methoxy-1,3,5(10)-estratrien-16-one (X) and subsequent attack at C-16 to give the isomeric diol XI,[8] the latter was prepared for comparison with VI. The base catalyzed rearrangement of IV according to the procedure of Leeds, Fukushima, and Gallagher[3a] afforded X in 45% yield. The latter was treated with methylmagnesium bromide to give 16β,17β-dihydroxy-3-

(1) Paper XVII, S. Bernstein, M. Heller, and S. M. Stolar, *Chem. & Ind. (London)*, 516 (1961).

(2) The preparation of both C-16-epimers of 16-hydroxytestosterone has been described. A Butenandt, J. Schmidt-Thomé, and T. Weiss, *Ber.*, **72B**, 417 (1939), have reported on the synthesis of 16-hydroxytestosterone in nine steps from dehydroisoandrosterone. Although the stereochemistry of the product was not discussed, it was presumably 16β-hydroxytestosterone. This assignment of configuration follows from an analogous set of transformations known to produce the methyl ether of 16-epiestriol in which the C-16, and 17-hydroxyl groups are *cis* to each other and β. In this connection, see M. N. Huffman and H. H. Darby, *J. Am. Chem. Soc.*, **66**, 150 (1944), and M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **69**, 1835 (1947); **75**, 4327 (1953).

The 16α-hydroxy epimer has been prepared by microbiological hydroxylation of testosterone with *Streptomyces roseochromogenus* [J. Fried, D. Perlman, A. F. Langlykke, and E. O. Titus, U. S. Patent **2,855,410** (October 7, 1958)], and by an elaborate synthesis from methyl 3β-hydroxy-16,17-seco-5-androstene-16,17-dioate [W. J. Adams, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 297 (1956)].

(3) (a) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954); (b) A. Butenandt and E. L. Schäffler, *Z. Naturforsch.*, 1, 82 (1946); and (c) S. A. Thayer, L. Levin, and E. A. Doisy, *J. Biol. Chem.*, 91, 655 (1931).

(4) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(5) The preparation of this compound by an identical pathway has been described by O. Schindler, *Helv. Chim. Acta*, **42**, 1955 (1959). Our work was completed prior to this publication.

(6) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2005 (1957).

(7) L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, N. Y., 1959, pp. 467–8.

(8) (a) D. A. Tyner, U. S. Patent **2,949,476** (August 16, 1960); and (b) H. Mori, K. Yasuda, and S. Wada, *J. Pharm. Soc. Japan*, **78**, 813 (1958).