[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Cortical Steroid Analogs. II. The Synthesis of Open-chain Dihydroxyacetones from 2,3-Butanedione[1]

BY GARDNER W. STACY, RICHARD A. MIKULEC, STEPHEN L. RAZNIAK AND LAURENCE D. STARR[2]

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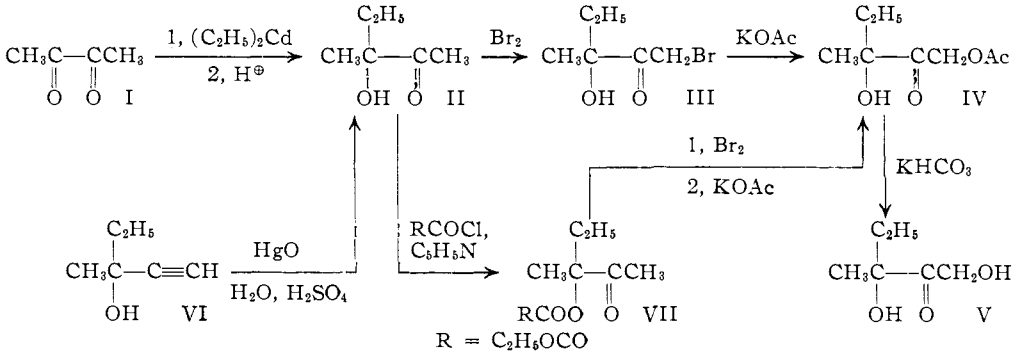
The synthesis of 1,3-dihydroxy-3-methyl-2-pentanone (V), an open-chain or acyclic dihydroxyacetone derivative which had resisted prior attempts at synthesis, has been accomplished. The synthetic scheme employed appears to have rather general potentialities for the preparation of a series of such dihydroxyacetone derivatives with 2,3-butanedione (I) as the starting point. It has been demonstrated that from I it is possible to prepare conveniently by reaction with appropriate organocadmium reagents a number of representative acetylcarbinols similar to II, these latter substances being key compounds in the synthesis of dihydroxyacetones. Biological evaluation of V and its corresponding 1-acetate IV has revealed that neither substance has significant anti-inflammatory or glucocorticoid activity.

Syntheses of alicyclic analogs of cortisone have been reported,[3] and studies in the same direction also have been carried out in this Laboratory.[1,4] It now has been decided to investigate the synthesis and possible biological activity of open-chain (acyclic) analogs because of the number of compounds of lesser structural complexity that might possibly be synthesized. A survey of the literature revealed that apparently no acyclic dihydroxyacetone derivatives with a tertiary hydroxyl group had been prepared previously, although an attempted synthesis of such compounds had been reported by Diels and Johlin.[5]

A synthetic scheme, similar to that attempted by Diels and Johlin[5] and employed more recently with success in respect to steroid[6] and analog syntheses,[3] was undertaken. Accordingly, this resulted in the successful preparation of 1,3-dihydroxy-3-methyl-2-pentanone (V), one of the compounds that Diels and Johlin[5] previously had failed to obtain and a representative example of the type of acyclic analog that may be derived from 2,3-butanedione (I).



Acetylcarbinols such as II are the key intermediates for the synthesis of acyclic analogs (V) in respect to the scheme outlined. A method of readily obtaining a series of such acetylcarbinols, where one alkylcarbinol substituent remained constant as a methyl group, suggested itself. It seemed quite possible to derive such a series from 2,3-butanedione (I) by reaction of this substance with an appropriate organometallic reagent. The use of Grignard reagents appeared to be unsatisfactory, for it had been reported that such a reaction results in bis addition to the very reactive twin carbonyl grouping of I to yield pinacols.[7] Although Lapkin and Golovkova[8] more recently had observed that Grignard reagents involving radicals of large size will react under the proper conditions to give acetylcarbinols, a procedure more general in scope was desired for the present application. Since it had been noted that organocadmium reagents, which are relatively unreactive with isolated carbonyl groups, react readily with the twin carbonyl group of α-keto esters to form α-hydroxy esters,[9] it appeared likely that a similar reaction would occur in the case of organocadmium reagents and 2,3-butanedione. This hope was indeed realized, and a number of acetylcarbinols were prepared in yields of 38–70% (Table I). It was found that a 0.5 equivalent excess of organocadmium reagent in respect to the 2,3-butanedione gave optimum results. For example, when an equivalent amount of diethylcadmium was used in the preparation of II, a 28% yield was obtained; however, when the excess was used the yield was 68%. With one exception, the acetylcarbinols were characterized as semicarbazones (Table II).

(1) Presented in part before the Division of Organic Chemistry at the 128th Meeting of the American Chemical Society, Minneapolis, Minn., Sept. 15, 1955; Paper I, G. W. Stacy and R. A. Mikulec, THIS JOURNAL, **76**, 524 (1954).

(2) In part abstracted from a thesis submitted by Laurence D. Starr in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the State College of Washington, June, 1955.

(3) (a) *Cf.* J. D. Billimoria and N. F. Maclagen, *J. Chem. Soc.*, 3067 (1951); J. D. Billimoria, *ibid.*, 1126 (1955); (b) D. Papa, H. F. Ginsberg and F. J. Villani, THIS JOURNAL, **76**, 4441 (1954); (c) G. I. Poos and L. H. Sarett, *ibid.*, **78**, 4100 (1956).

(4) G. W. Stacy and C. A. Hainley, *ibid.*, **73**, 5911 (1951).

(5) O. Diels and J. M. Johlin, *Ber.*, **44**, 403 (1911).

(6) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

(7) (a) N. Zelinsky, *Ber.*, **35**, 2138 (1902); (b) E. Pace, *Atti accad Lincei*, **8**, 309 (1928); *C. A.*, **23**, 1615 (1929).

(8) I. I. Lapkin and A. I. Golovkova, *J. Gen. Chem. (U.S.S.R.)*, **19**, 701 (1949).

(9) (a) G. W. Stacy and R. M. McCurdy, THIS JOURNAL, **76**, 1914 (1954); (b) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

TABLE I

ACETYLCARBINOLS $CH_3C(R)(OH)CCH_3$ (O)

R	Yield, %	B.p., °C.	Mm.	$n^{25}D$	d^{25}_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-C_6H_{13}[a]	38	102–103	14	1.4333	0.8998	$C_{10}H_{20}O_2$	69.72	69.66	11.70	11.45
n-C_8H_{17}	39	132–133	14	1.4378	.8799	$C_{12}H_{24}O_2$	71.95	72.11	12.07	12.13
n-$C_{10}H_{21}$	43	160–162	15	1.4425	.8902	$C_{14}H_{28}O_2$	73.63	73.80	12.35	12.15
n-$C_{12}H_{25}$	39	141–142	1.5	1.4453	.8799	$C_{16}H_{32}O_2$	74.94	75.20	12.58	12.68
$C_6H_5CH_2CH_2$	41	101–105	1	1.5103	1.0289	$C_{12}H_{16}O_2$	74.96	75.16	8.39	8.30

[a] In addition to the new compounds listed in the table, the following known acetylcarbinols were prepared: R = C_6H_5, 44% yield, b.p. 48–50° (0.1 mm.), $n^{25}D$ 1.5133; J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 101 (1946), reported b.p. 132° (10 mm.). R = 1-$C_{10}H_7$, 34% yield, b.p. 120–135° (0.15–0.25 mm.), $n^{25}D$ 1.6071; Lapkin and Golovkova (ref. 8) reported b.p. 155–156° (3 mm.). R = C_2H_5, 68% yield, b.p. 74–75° (50 mm.), $n^{25}D$ 1.4195; J. Kapron and J. Wiemann, *Bull. soc. chim. France*, [5] **12**, 945 (1945), reported b.p. 52° (17 mm.), $n^{19}D$ 1.4230. R = n-C_4H_9, 70% yield, b.p. 81–84° (20 mm.), $n^{25}D$ 1.4274, d^{25}_4 0.9075; L. Leers, *ibid.*, [4] **39**, 423 (1926), reported b.p. 74° (10 mm.), d^0_4 0.931.

TABLE II

SEMICARBAZONES OF ACETYLCARBINOLS

R	Yield,[a] %	M.p.,[b] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-C_6H_{13}[c]	80	132–133	$C_{11}H_{23}N_3O_2$	57.61	57.54	10.11	9.85	18.32	18.00
n-C_8H_{17}	79	131.5–132.5[d]	$C_{13}H_{27}N_3O_2$	60.66	60.76	10.58	10.74	16.33	16.50
n-$C_{10}H_{21}$	82	123–126	$C_{15}H_{31}N_3O_2$	63.12	62.91	10.95	10.80	14.72	14.75
n-$C_{12}H_{25}$	98	125–128	$C_{17}H_{35}N_3O_2$	65.13	65.15	11.25	11.22	13.41	13.44
n-$C_{16}H_{33}$	91	129–130[e]	$C_{21}H_{43}N_3O_2$	68.24	68.43	11.73	11.97	11.37	11.42
$C_6H_5CH_2CH_2$	94	185–186[f]	$C_{13}H_{19}N_3O_2$	62.63	62.67	7.68	7.95	16.86	16.87

[a] Yields were based on the weight of crude product. [b] M.p. of analytical sample. All samples were recrystallized from aqueous ethanol unless otherwise stated. [c] In addition to the derivatives listed in the table, the following known semicarbazones were prepared for purposes of comparison: R = C_6H_5, 82% yield, m.p. 187°; Wegmann and Dahn (ref. *a*, Table I) reported m.p. 183–184°. R = C_2H_5, 69% yield, m.p. 150.5–151°; Kapron and Wiemann (ref. *a*, Table I) reported m.p. 148.5–149.5°. R = n-C_4H_9, 63% yield, m.p. 152–153°; Leers (ref. *a*, Table I) reported m.p. 152°. [d] Recrystallized from aqueous acetone. [e] Recrystallized from 95% ethanol. [f] In this instance purification was difficult; the crude product, m.p. 93.5–114°, was recrystallized five times, twice from aqueous ethanol and three times from 2-propanol.

The acetylcarbinol derived from 1-naphthylmagnesium bromide was converted to a picrate and to a 2,4-dinitrophenylhydrazone. Extension of the study to R = n-$C_{16}H_{33}$ and R = n-$C_{18}H_{37}$ gave products which could not be purified. In the case of R = n-$C_{16}H_{33}$, however, it was possible to prepare a pure semicarbazone from the crude acetylcarbinol.

In some instances small amounts of hydrocarbons, formed as coupling products from the organocadmium reagents, were observed in the reaction mixture. For example, eicosane and tetracosane were isolated from the reaction mixtures involving the C_{10}- and C_{12}-organocadmium reagents, respectively. To confirm the structure of the acetylcarbinols obtained from I by the method just described, II was prepared by hydration of the ethynylcarbinol (VI). The identity of these compounds prepared by the two different methods was established through comparison of semicarbazones by a mixture melting point determination. As a result of the study of this procedure involving the reaction of organocadmium reagents with 2,3-butanedione, it is to be concluded that it constitutes a useful supplement to the ethynylcarbinol hydration for the preparation of acetylcarbinols, particularly where the prerequisite ethynylcarbinols are not readily available.

In continuation of the description of the synthesis of the dihydroxyacetone derivative V, the intermediate bromo ketone III was obtained in yields of about 60% by addition of bromine to a chloroform solution of the acetylcarbinol II. Although III seemed stable when kept in chloroform solution in the crude state, attempts at distillation under reduced pressure by ordinary procedures led to decomposition. The product always rapidly discolored, the colorless liquid turning brown as it was collected in the receiver. Catch and co-workers[10] had observed that bromoacetone exhibited a similar instability, but by storing this bromo ketone over magnesium oxide, they were able to keep samples indefinitely in a purified state. Application of this principle led to solution of the distillation problem just described, and our bromo ketone was obtained as a colorless liquid when it was distilled from magnesium oxide into a receiver containing magnesium oxide. Although the bromo ketone III failed to yield typical carbonyl derivatives, a solid derivative in the form of a 2-naphthyl ether could be prepared in low yield.

The intermediate acetate IV was formed by a modification of the procedure of Rosenkranz, *et al.*,[11] in yields ranging from 24 to 33%, as based on the acetylcarbinol II (it was unnecessary to isolate and purify the unstable bromo ketone). Finally, the desired dihydroxyacetone derivative V was obtained in yields of 41–43% by the reaction of IV with methanolic potassium bicarbonate. A molecular distillation of this substance gave a colorless product, which reduced both Benedict

(10) J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(11) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin and C. Djerassi, THIS JOURNAL, **72**, 4081 (1950).

solution and Tollens reagent. The infrared absorption spectrum was compatible with a dihydroxy ketone structure. There was no sign of an absorption band corresponding to the carbon–hydrogen stretching frequency that might be related to an aldehyde group. Therefore, an aldose type structure isomeric with V did not seem probable for the product obtained. Attempts to characterize V by solid derivatives were not at first successful. Using standard procedures, we were unable to prepare common carbonyl derivatives (semicarbazone, thiosemicarbazone, phenylhydrazone, osazone, 2,4-dinitrophenylhydrazone, *p*-nitrophenylhydrazone, or oxime). By way of comparison, it was interesting to note that the very similar acetylcarbinol II formed a semicarbazone easily in excellent yield. The timely appearance of an article by Reich and Samuels[12] on the preparation of derivatives of dihydroxyacetone resolved the difficulty. When the procedures of these authors were employed, it was possible to prepare both a 2,4-dinitrophenylhydrazone and a 2,4-dinitrophenylosazone of V, although the yields of pure derivative in each instance were relatively low.

In relation to bromination of acetylcarbinols, one is confronted with difficulties which may detract from the yield of the desired bromo ketone. In addition to the well-known ease of reaction of a tertiary hydroxyl group with hydrobromic acid, tertiary alcohols react with bromine to form dibromides.[13] It was thought that such problems might be advantageously circumvented by proceeding through an intermediate where the tertiary hydroxyl group was protected by conversion to an ester. One type of ester that was of particular interest was an oxalate because of the prospective ease with which this group might be reconverted to the hydroxyl group under mild conditions. Accordingly, the ethoxalyl derivative VII was obtained in a 72% yield by reaction of II with ethoxalyl chloride in the presence of pyridine. A bromination product was obtained in a 62% yield, and it was interesting to note that the bromo ketone obtained showed a much lesser tendency to discolor on standing than III. In the treatment of the bromo ketone with potassium acetate in acetone, not only was the bromo group displaced by an acetate group but also the ethoxalyl group was removed to give the acetate IV in a 31% yield. These experiments demonstrated the ease with which the ethoxalyl group is removed and its possible use in analog synthesis as a protective device for the hydroxyl group. However, the method has not yet proved to be advantageous from the standpoint of over-all yield.

Biological Evaluation.—1,3-Dihydroxy-3-methyl-2-pentanone (V) and the corresponding 1-acetate (IV) were investigated for possible biological activity. These compounds revealed no significant anti-inflammatory activity in the granuloma pouch assay[14] in rats; the compounds were applied locally at a level of 1 mg. In comparison, hydrocortisone is very active at a level of 300 μg., so that the activity, if any, is less than 20% of hydrocortisone.

(12) H. Reich and B. K. Samuels, *J. Org. Chem.*, **21**, 68 (1956).

(13) L. J. Andrews and R. M. Keefer, THIS JOURNAL, **75**, 3557 (1953).

(14) A. Robert and J. E. Nezamis, *Acta Endocrin.*, in press (1957).

In the glycogen deposition assay for glucocorticoid activity,[15] these compounds were inactive at levels of 300 mg./kg. subcutaneously in fasted, adrenalectomized rats, and even at higher dosage levels of 1 g./kg., no increase in the weight of liver glycogen over the controls was to be observed.

Experimental[16]

Preparation of Acetylcarbinols.—The procedure for the preparation of the acetylcarbinol where R = *n*-$C_{12}H_{25}$ will serve to illustrate the general method used in all cases. Di-*n*-dodecylcadmium was obtained by reaction of a Grignard reagent, prepared from 7.30 g. (0.30 gram atom) of magnesium turnings in 200 ml. of absolute ether and 74.8 g. (0.30 mole) of *n*-dodecyl bromide in 50 ml. of absolute ether, with 27.5 g. (0.15 mole) of anhydrous cadmium chloride in 100 ml. of absolute ether.[17] After formation of the organocadmium reagent was shown to be complete by a negative Gilman test, 17.2 g. (0.20 mole) of 2,3-butanedione in 50 ml. of absolute ether was added dropwise.[18] After the addition was complete, the reaction mixture was heated under reflux with vigorous stirring for 11 hr. The complex then was decomposed by the slow addition of cold 1 *N* hydrochloric acid. The water phase was separated and in turn was extracted with four 100-ml. portions of ether. The ether extracts and the original ether phase were combined and washed with a saturated sodium bicarbonate solution and then with a saturated sodium chloride solution. The ether solution was dried over anhydrous sodium sulfate. The ether was removed under reduced pressure, and as the solution cooled during the evaporation of the ether, material, which by melting point appeared to be tetracosane, crystallized from solution. As much of the substance as possible was removed by filtration, the remainder of the ether was removed and the residue was fractionally distilled to yield 20.1 g. (39%) of the acetylcarbinol (Table I). The residue, remaining after the distillation had been completed, crystallized and was combined with the material previously removed by filtration. This was recrystallized from toluene–ethanol to give 4.45 g., m.p. 48–50° (tetracosane is reported[19] to melt at 51°).

Semicarbazones (Table II) were prepared according to standard procedures.[20]

3-Hydroxy-3-(1-naphthyl)-2-butanone 2,4-Dinitrophenylhydrazone.—This derivative was prepared[20] from 500 mg. (2.3 mmoles) of the corresponding acetylcarbinol. Two recrystallizations from an ethanol–water–ethyl acetate mixture gave 430 mg. (47% yield) of orange needles, m.p. 193.5–194.5° (uncor.).

Anal. Calcd. for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 61.14; H, 4.69; N, 14.05.

3-Hydroxy-3-(1-naphthyl)-2-butanone Picrate.—This picrate was prepared from 100 mg. (0.46 mmole) of the acetylcarbinol, dissolved in 1 ml. of ethanol, and 3 ml. of a saturated ethanolic solution of picric acid.[20] The product was recrystallized twice from 95% ethanol and washed with a small amount of anhydrous ether to yield fine yellow needles, m.p. 133–135°.

Anal. Calcd. for $C_{20}H_{17}N_3O_9$: C, 54.18; H, 3.86; N, 9.48. Found: C, 54.20; H, 4.00; N, 9.45.

(15) R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955).

(16) All melting points are corrected unless otherwise stated, and boiling points are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn., and Weiler and Strauss Laboratories, Oxford, England. Infrared absorption spectra were determined on pure liquid samples using a Perkin–Elmer double beam infrared spectrometer, model 21.

(17) For a more detailed procedure for the preparation of organocadmium reagents see ref. 9a.

(18) Since the reaction mixture many times becomes viscous and difficult to stir, it is advisable to use a heavy-duty stirrer and motor for this operation. We used a Hershberg-type stirrer constructed from one-quarter-inch nickel rod and No. 15 chromel wire and a "Power-Stir" motor, manufactured by Eberbach and Son Co., Ann Arbor, Mich.

(19) K. Ziegler, F. Dersch and H. Wollthan, *Ann.*, **511**, 13 (1934).

(20) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 218, 219, 229, 244.

3-Hydroxy-3-methyl-2-pentanone (II) from VI.[21]—To a mixture of 380 ml. of water, 16 ml. of concd. sulfuric acid and 10 g. of red mercuric oxide[21] heated to 60° was added dropwise 78.5 g. (0.80 mole) of 3-hydroxy-3-methyl-1-pentyne[22] over a 1-hr. period. The product was distilled through a 20-cm. column packed with glass helices to give 79.5 g. (86%) of II, b.p. 74–78° (50 mm.), $n^{25}D$ 1.4205 (see footnote, Table I).

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3450 cm.$^{-1}$, s), *t*-OH (1350 cm.$^{-1}$, s; 1170 cm.$^{-1}$, s) and C=O (1705 cm.$^{-1}$, s).

A mixture melting point determination of a semicarbazone prepared from this material and that derived from the organocadmium procedure showed no depression.

1-Bromo-3-hydroxy-3-methyl-2-pentanone (III).—To a solution of 20.0 g. (0.17 mole) of II in 800 ml. of chloroform was added dropwise over a 3.5-hr. period 28.9 g. (0.18 mole) of bromine in 400 ml. of chloroform. The reaction mixture was washed with 190 ml. of ice-cold 5% sodium hydroxide solution and two 100-ml. portions of water. The organic layer was separated and dried over 100 g. of anhydrous sodium sulfate, to which had been added 0.1 g. of magnesium oxide.[10] After the solvent had been removed, the product was fractionally distilled under nitrogen from magnesium oxide using as short a pathway of distillation as possible (fraction cutter directly attached to distilling flask). Seven fractions were collected amounting to 20.4 g. (61%), b.p. 49–56° (0.1–0.15 mm.), $n^{25}D$ 1.4790–1.4847. The first four fractions distilled as a colorless liquid and turned tan to brown as collected. The third fraction was subjected to molecular distillation at 43–45° (oil-bath temperature) (0.005 mm.) from magnesium oxide and collected in a receiver containing magnesium oxide.[23] The sample submitted for analysis ($n^{25}D$ 1.4831) was stored over magnesium oxide.

Anal. Calcd. for $C_6H_{11}BrO_2$: C, 36.94; H, 5.69; Br, 40.97. Found: C, 36.75; H, 5.84; Br, 41.20.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3485 cm.$^{-1}$, s), *t*-OH (1375 cm.$^{-1}$, s; 1175 cm.$^{-1}$, s) and C=O (1720 cm.$^{-1}$, s).

A 2-naphthyl ether[20] was prepared from 2.00 g. (0.01 mole) of III, which had been obtained by a molecular distillation. One recrystallization from petroleum ether (b.p. 90–120°) gave 330 mg. (13%) of fine colorless needles, m.p. 114.5–115°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.27; H, 7.12.

1,3-Dihydroxy-3-methyl-2-pentanone 1-Acetate (IV).—A mixture of 54.3 g. of glacial acetic acid and 86.2 g. of potassium bicarbonate in 516 ml. of acetone was heated under reflux with stirring for 30 minutes.[11] Crude III, obtained from 20.0 g. (0.17 mole) of II, in 70 ml. of acetone was added dropwise with stirring to the acetone–potassium acetate suspension. The resulting mixture was heated under reflux for 12 hr. and then was allowed to stand for 2 days. The reaction mixture was cooled for 1 hr. in an ice-bath to precipitate dissolved potassium acetate, filtered and dried over 50 g. of anhydrous potassium carbonate. After the acetone had been removed, the residue was distilled under nitrogen through a 15-cm. Vigreux column to give four fractions of IV amounting to 10.0 g. (33%), b.p. 75–77° (0.1 mm.), $n^{25}D$ 1.4400–1.4410. A portion of a middle fraction was subjected to molecular distillation[23] at 55–60° (oil-bath temperature) (0.025 mm.) to give a colorless analytical sample, which was stored under nitrogen; $n^{25}D$ 1.4403, d_4^{25} 1.0933.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10; M_D, 42.34. Found: C, 55.32; H, 8.25; M_D, 42.02.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3470 cm.$^{-1}$, s), *t*-OH (1355 cm.$^{-1}$, s; 1165 cm.$^{-1}$, m) and C=O (1725 cm.$^{-1}$, s).

A semicarbazone was prepared from 1.00 g. (5.7 mmoles) of IV. Recrystallization from water afforded 690 mg. (52%) of colorless needles, m.p. 174.5–175.5°.

Anal. Calcd. for $C_9H_{17}N_3O_4$: C, 46.75; H, 7.40; N, 18.17. Found: C, 46.95; H, 7.30; N, 18.24.

1,3-Dihydroxy-3-methyl-2-pentanone (V).—A mixture of 12.6 g. (0.072 mole) of IV and 52.7 g. of potassium bicarbonate in 275 ml. of methanol was stirred under nitrogen for 48 hr. at room temperature.[3b] The mixture was filtered and was concentrated by distilling the solvent under reduced pressure through a 20-cm. Vigreux column. The residual mixture was dissolved in 500 ml. of water, which then was saturated with sodium chloride. The solution was continuously extracted with ether for 2 days. Then the ether phase was separated and dried over 100 g. of anhydrous sodium sulfate. After the ether was removed by distillation, the residue was fractionally distilled through a 15-cm. Vigreux column to give three fractions of product; yield 4.20 g. (44%), b.p. 51–58.5° (0.1–0.25 mm.), $n^{25}D$ 1.4548. Molecular distillation[23] of a small portion of this material at 25° (0.005 mm.) gave a colorless, analytical sample, $n^{25}D$ 1.4537, d^{25}_4 1.0998.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16; M_D, 32.97. Found: C, 54.48; H, 9.19; M_D, 32.52.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3400 cm.$^{-1}$, s), *t*-OH (1350 cm.$^{-1}$, m; 1160 cm.$^{-1}$, s) and C=O (1710 cm.$^{-1}$, s).

A 2,4-dinitrophenylhydrazone was prepared[12] by heating under reflux for 22 hr. a mixture of 132 mg. (1.0 mmole) of V, 200 mg. (1.0 mmole) of 2,4-dinitrophenylhydrazine and 5 ml. of absolute ethanol. The reaction mixture was concentrated to a small volume from which was obtained 42 mg. (13%) of product, m.p. 140.5–144°. Two recrystallizations from aqueous ethanol gave 22 mg. (7%) of yellow needles, m.p. 147.5–148°.

Anal. Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.32; H, 5.02; N, 17.74.

A 2,4-dinitrophenylosazone also was prepared[12] by heating under reflux for 1 hr. a mixture of 132 mg. (1.0 mmole) of V, 790 mg. (4.0 mmoles) of 2,4-dinitrophenylhydrazine and 200 ml. of 2 *N* hydrochloric acid. The reaction mixture was allowed to stand overnight; yield 412 mg. (84%), m.p. 256–258° dec. Six recrystallizations from ethylene chloride gave 168 mg. (34%) of bright-red, microscopic prisms, m.p. 269.5–270° dec.

Anal. Calcd. for $C_{18}H_{18}N_8O_9$: C, 44.08; H, 3.70; N, 22.85. Found: C, 44.18; H, 3.50; N, 22.74.

3-Ethoxaloxy-3-methyl-2-pentanone (VII).—To a mixture of 81.3 g. (0.70 mole) of II and 119.5 g. (0.875 mole) of ethoxalyl chloride[24] in 140 ml. of absolute ether was added 69.2 g. (0.875 mole) of anhydrous pyridine in 140 ml. of absolute ether with stirring at such a rate as to produce moderate reflux (85 minutes). The reaction mixture was stirred for an additional 10 minutes, was allowed to cool and was filtered. The filter cake (pyridine hydrochloride) was washed with three 70-ml. portions of anhydrous ether. The combined ether filtrates were washed with two 50-ml. portions of saturated sodium chloride solution and were dried over sodium sulfate. The ether was removed under reduced pressure through a 15-cm. helices-packed column, and the residue was distilled; yield 108.1 g. (72%), b.p. 102–106° (3 mm.), $n^{25}D$ 1.4342, d^{25}_4 1.0859.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46; M_D, 51.71. Found: C, 55.32; H, 7.35; M_D, 51.88.

1,3-Dihydroxy-3-methyl-2-pentanone 1-Acetate (IV) **from VII.**—A solution of 21.6 g. (0.10 mole) of VII in 320 ml. of chloroform was treated with 0.6 ml. of 30% hydrobromic acid in acetic acid. The mixture was heated to 50° and, with stirring, a solution of 16.8 g. (0.105 mole) of bromine in 120 ml. of chloroform was added dropwise over a period of 2.5 hr. After the solvent was removed under reduced pressure, the residue was distilled through a 15-cm. Vigreux column to give 18.4 g. (62%) of an intermediate bromo ketone, b.p. 94–98° (0.07 mm.), $n^{25}D$ 1.4645–1.4740.

To a solution of 17.9 g. of the crude bromo ketone in 630 ml. of acetone was added 143 mg. of potassium iodide, 40.0 g. of potassium acetate and 6.3 ml. of glacial acetic acid.[25]

(21) This preparation is similar to one previously reported for 1-acetylcyclopentanol (ref. 1). A modification of the original procedure which was employed here to advantage involved sprinkling the mercuric oxide on the surface of the sulfuric acid solution with stirring; this greatly facilitated the dissolving of the material.

(22) Generously furnished by Reilly Tar and Chemical Corporation, Indianapolis, Ind.

(23) A micro distilling apparatus was employed.

(24) P. L. Southwick and L. L. Seivard, THIS JOURNAL, **71**, 2532 (1949).

(25) R. H. Levin, *et al.*, *ibid.*, **76**, 546 (1954).

The mixture was heated under reflux with stirring for 16 hr., filtered and the filter cake washed well with acetone. The acetone was removed by distillation, and the dark-brown residue was distilled through a 15-cm. Vigreux column; yield 5.17 g. (31%), b.p. 79–105° (0.2–0.5 mm.), $n^{25}D$ 1.4422–1.4435.

A sample of semicarbazone of this substance was prepared in a 48% yield, m.p. 174.5–175.5°, and when admixed with a sample of semicarbazone as derived above (III→IV), no depression in melting point was observed.

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PULLMAN, WASHINGTON

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

Preparations of Synthetic Estrogens. VIII.[1a] New Syntheses of 1,1,2-Tri-*p*-anisylethylene and Diethylstilbestrol

BY KEIITI SISIDO, KÔITI OKANO, MINORU SINDÔ AND HITOSI NOZAKI[1b]

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1,1,2-Tri-*p*-anisylethylene (VI) has been obtained by the condensation of α-chloro-*p*-methoxyacetophenone (I) with 2 moles of anisole in the presence of titanium tetrachloride. A similar condensation of α-chloroacetophenone (VII) with 2 moles of anisole gave 1,2-di-*p*-anisyl-1-phenylethylene (VIII). When these condensations were carried out with sulfuric acid or aluminum chloride as a catalyst, 1,1,1,2- and 1,1,2,2-tetra-*p*-anisylethanes as well as 1,1-di-*p*-anisylethylene were obtained instead of triarylethylenes. 2,3-Di-*p*-anisylbutene-2 (X) and diethylstilbestrol dimethyl ether (XII) were prepared by the condensation of 3-chlorobutanone (IX) and 4-chlorohexanone-3 (XI) with 2 moles of anisole in the presence of titanium tetrachloride.

In the previous paper[1a] it was reported that the treatment of *p*-methoxy-α,α-di-*p*-anisylacetophenone with phosphorus pentachloride effected simultaneous chlorination and dehydrochlorination giving 1,1,2-tri-*p*-anisyl-2-chloroethylene. The usual preparation[2] of 1,1,2-tri-*p*-anisyl-2-chloroethylene is the chlorination of tri-*p*-anisylethylene (VI) with chlorine in carbon tetrachloride. Recent studies in this Laboratory have given a new preparation of the key intermediate, tri-*p*-anisylethylene (VI), using a Grignard reaction between α-chloro-*p*-methoxyacetophenone (I) and *p*-anisylmagnesium bromide.[1] It has now been discovered that the condensation of α-chloro-*p*-methoxyacetophenone (I) with 2 moles of anisole in the presence of titanium tetrachloride gives tri-*p*-anisylethylene (VI) in a 53% yield. This method, in which the use of a Grignard reaction is avoided, seems to be suitable for large scale preparation.

The condensation of α-haloketones with phenol in the presence of an acidic catalyst has been studied by Lippmann.[3] Zaheer, *et al.*,[4] have reported recently that the reaction between chloroacetone and phenol or its ether in the presence of sulfuric acid or aluminum chloride as a catalyst gives 4,4′-dihydroxy- or -dialkoxy-α-methylstilbene, respectively. They have reported further that the similar condensation of 4-chlorohexanone-3 (XI) with anisole gives 3,3,4-tri-*p*-anisylhexane in addition to 1,1-di-*p*-anisyl-2-ethylbutene-1, and that phenol reacts with 1,3-dichloroacetone only at its carbonyl group to give 1,3-dichloro-2,2-di-*p*-hydroxyphenylpropane.[5] It was observed in the present experiments, in which sulfuric acid or aluminum chloride was used, that anisole reacted with α-chloro-*p*-methoxyacetophenone (I) to give various condensation products, among which, however, the desired tri-*p*-anisylethylene (VI) could not be found. The treatment of the chloroketone I with 2 moles of anisole in the presence of concentrated sulfuric acid in glacial acetic acid solution resulted in almost quantitative recovery of the starting materials. Essentially the same result was obtained in a reaction without the solvent, but further experiments in which the chloroketone I was dissolved in a large excess of anisole gave 1,1,1,2-tetra-*p*-anisylethane (III) and 1,1,2,2-tetra-*p*-anisylethane (IV).

$$\underset{\text{I}}{ClCH_2COC_6H_4OCH_3\text{-}p} + \underset{\text{II}}{3C_6H_5OCH_3} \xrightarrow{\text{concd. } H_2SO_4} \underset{\text{III}}{p\text{-}CH_3OC_6H_4CH_2C(C_6H_4OCH_3\text{-}p)_3} + \underset{\text{IV}}{(p\text{-}CH_3OC_6H_4)_2CHCH(C_6H_4OCH_3\text{-}p)_2}$$

As to the mechanism of the initial step of the condensation of chloroketone with phenol, Zaheer, *et al.*, postulated either a Friedel–Crafts type removal of the chlorine atom involving combination of phenol at that position,[4a] or an addition of one mole of phenol at the carbonyl group and a subsequent rearrangement involving a dehydrochlorina-

(1) (a) Previous paper: K. Sisido, K. Okano, T. Isida and H. Nozaki, THIS JOURNAL, **77**, 6580 (1955). (b) Department of Chemistry, Cornell University, Ithaca, N. Y.

(2) R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, THIS JOURNAL, **75**, 5491 (1953).

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(5) S. H. Zaheer, B. Singh, B. Bhushan, I. K. Kacker, K. Ramachandran and N. S. Rao, *ibid.*, 1706 (1955).