Cortical Steroid Analogs. IV. *gem*-Dialkylacetylcarbinols, Hydroxy Enol Ethers, and Hydroxy Ketals from the Reaction of Grignard Reagents and Ethyl Pyruvate Ketal[1a]

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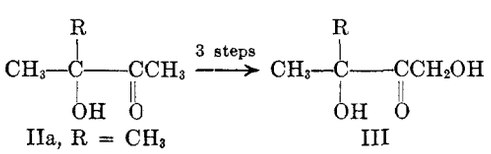
A facile method of synthesizing *gem*-dialkylacetylcarbinols (I), hydroxy ketone intermediates valuable in the synthesis of acyclic cortical hormone analogs, is described. The procedure involves the reaction of Grignard reagents with ethyl pyruvate diethyl ketal (IV). Ten such acetylcarbinols have been synthesized by this method in yields of 45–82%. If the intermediate Grignard complex is acidified with ammonium chloride solution rather than dilute mineral acid, hydroxy enol ethers (VI) are isolated, instead of acetylcarbinols I. Hydroxy ketals similar to V complex are isolated only when the bulkiness of the alkyl group becomes a factor, *e.g.*, *sec*-butyl, but then only a *single* R group is introduced at the site of the ester carbonyl, the process being accompanied by reduction to a secondary hydroxyl function to yield hydroxy ketals of the type X.

As has been discussed in earlier work, acetylcarbinols such as II have shown themselves to be strategic intermediates in the synthesis of dihydroxyacetones III, as acyclic analogs of the antiinflammatory steroids.[2] An additional acyclic dihydroxyacetone, IIIa, was then reported wherein the alkyl substituents attached to the



IIa, R = CH_3 III

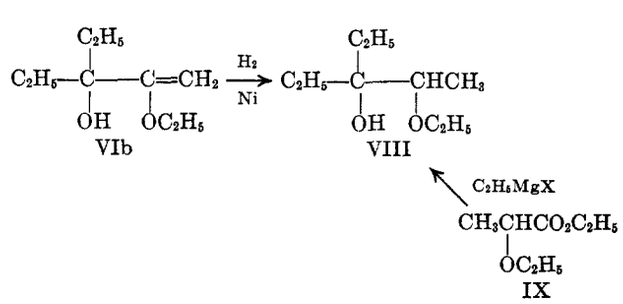
tertiary carbon were methyl groups.[3] The antecedent of IIIa is acetyldimethylcarbinol (IIa = Ia, R = CH_3), the parent member of the *gem*-dialkylacetylcarbinol series (I).

We now describe a convenient method of preparing such *gem*-dialkylacetylcarbinols (I) and subsequently *gem*-dialkyldihydroxyacetone derivatives,[4] wherein the *gem*-dialkyl groups may vary widely in chain length and complexity. The method involves a reaction of Grignard reagents with ethyl pyruvate diethyl ketal (IV) (Scheme I), which results in the introduction of two alkyl groups at the site of the ester carbonyl function. One might suspect that the hydroxy ketal corresponding to V would be initially isolated from a Grignard reaction with the ester function of IV. Although such a product was indeed observed by Stevens and Scherr[5] in their investigation of the original example of this reaction employing phenylmagnesium bromide, we found that it was not the usual case; instead, hydroxy enol ethers (VI) were isolated if the reaction mixture was acidified with ammonium chloride solution. Of course, for preparative purposes, it was unnecessary to isolate the enol ether intermediate VI. In this instance, the *gem*-dialkylacetylcarbinols (I) were obtained directly by acidification with dilute mineral acid rather than with ammonium chloride solution.

Evidence for the hydroxy enol ether structure of VI was conclusive. The infrared absorption spectra of enol ethers have been previously studied.[6] Thus, the data for the hydroxy enol ether VId (R = *n*-C_4H_9, Table I) compared well with those previously observed for 2-ethoxy-1-hexene:[6] an olefinic carbon–hydrogen stretching mode 3125 (w) cm^{-1} compared with 3150 (w) found by Meakins;[6] olefinic carbon–carbon stretching modes 1647 cm^{-1} (s) and 1608 (m) compared with 1655 (s) and 1592 (m), respectively; and olefinic hydrogen out-of-plane bending 970 cm^{-1} (m) and 808 (m) *vs.* 958 (m) and 793 (m). The intensity of the band at 970 cm^{-1} was less than that at 808, which was also consistent with previous findings.[6] In addition, a hydroxyl band of moderate intensity was present at 3472 cm^{-1}.

Further cogent support for the structure VId (R = *n*-C_4H_9) developed from nmr evidence:[7] δ 0.88–2.69 (22 cm) (legend under Experimental Section), 3.68 (q, 2), 3.87 (d, 1), and 4.13 (d, 1). The doublets were assignable to the vinyl protons and the quartet to the methylene group attached to the oxygen in the ethoxy function. Lone-pair conjugation of the oxygen with the unsaturated system with its resulting flow of charge into the β position is the suggested explanation for the extremely high-field positions of the β-vinyl protons.[7]

The hydroxy enol ether VIb (R = C_2H_5) was readily hydrogenated to form the hydroxy ether VIII, which was alternately prepared from ethyl α-ethoxypropionate (IX). Also, VIb was smoothly hydrolyzed to the



VIb VIII IX

(1) (a) Presented in part before the Division of Organic Chemistry at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 1958, and at the 135th Meeting, Boston, Mass., April 1959; (b) B.S. in Chemistry, Washington State University, 1958; (c) in part from the M.S. Thesis of G. T. Davis, Washington State University, June 1957; National Science Foundation Predoctoral Fellow; (d) B.S. in Chemistry, 1961; (e) in part from the Ph.D. Thesis of S. L. Razniak, Washington State University, June 1960.

(2) (a) G. W. Stacy, R. A. Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, **79**, 3587 (1957); (b) G. W. Stacy, R. A. Mikulec, C. R. Bresson, and L. D. Starr, *J. Org. Chem.*, **24**, 1099 (1959).

(3) I. N. Nazarov, M. S. Burmistrova, and A. A. Akhrem., *Zh. Obshch. Khim.*, **29**, 735 (1959); *Chem. Abstr.*, **54**, 1354 (1960).

(4) G. W. Stacy, M. S. Khan, H. Moe, C. R. Bresson, and S. L. Razniak, *J. Org. Chem.*, **31**, 1757 (1966).

(5) C. L. Stevens and A. E. Scherr, *ibid.*, **17**, 1223 (1952).

(6) G. D. Meakins, *J. Chem. Soc.*, 4170 (1953).

(7) R. T. Hobgood, Jr., G. S. Reddy, and J. H. Goldstein, *J. Phys. Chem.*, **67**, 110 (1963).

SCHEME I

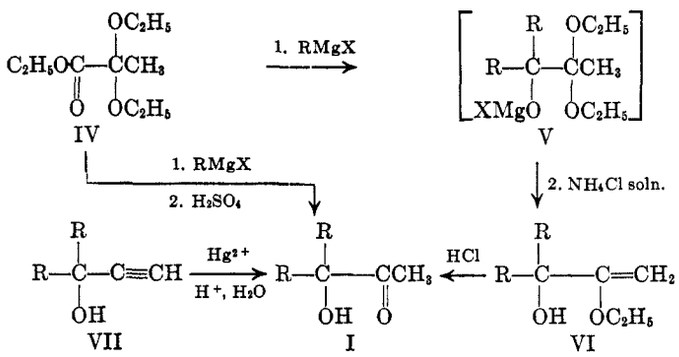
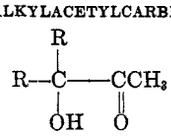


TABLE I

gem-DIALKYLACETYLCARBINOLS (I)



I,	R	Yield, %	Bp, °C	Mm	$n^{25}D$	d^{25}_4	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
d	n-C_4H_9[a]	81	66	4	1.4362	0.9020	$C_{11}H_{22}O_2$	70.91	71.04	11.91	11.91
e	i-C_4H_9	45	57–58	0.6	1.4335	...	$C_{11}H_{22}O_2$	70.91	70.89	11.91	11.98
f	n-C_5H_{11}	70	141–142	14	1.4392	0.8897	$C_{13}H_{26}O_2$	72.84	73.04	12.23	12.34
g	i-C_5H_{11}	68	67	0.2	1.4335	0.8830	$C_{13}H_{26}O_2$	72.84	72.84	12.23	11.96
h	n-C_6H_{13}	82	169–171	14	1.4428	0.8807	$C_{15}H_{30}O_2$	74.32	74.46	12.48	12.36
i	n-C_7H_{15}	65	141	1.1	1.4466	0.8767	$C_{17}H_{34}O_2$	75.50	75.30	12.67	12.57
j	n-C_8H_{17}	60	154–155	0.6	1.4480	0.8736	$C_{19}H_{38}O_2$	76.46	76.61	12.83	12.85
k	C_9H_{19}[b]	72	123–125	0.1	1.4490	0.8716	$C_{21}H_{42}O_2$	77.24	77.25	12.97	12.79

[a] In addition to the new *gem*-dialkylacetylcarbinols (I), two known representatives were also synthesized. These were Ib (R = C_2H_5) and Ic (R = C_3H_7). Ib was obtained in 53% yield: bp 59–61° (14 mm), lit.[8a] bp 56–57° (13 mm); $n^{25}D$ 1.4244, R. Heilmann and R. Glénat reported [*Compt. Rend.*, **240**, 2317 (1955)] $n^{20}D$ 1.4271. Ic: 59% yield; bp 84–85° (13 mm), lit.[8a] bp 86–88° (14 mm); $n^{25}D$ 1.4278, Heilmann and Glénat reported $n^{20}D$ 1.4332; d^{25}_4 0.9020, lit.[7a] d^{25}_4 0.9124. [b] 3,5,5-Trimethylhexyl.

TABLE II

SEMICARBAZONES OF *gem*-DIALKYLACETYLCARBINOLS (I)

R	Yield,[a] %	Mp,[b] °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
n-C_4H_9[c]	..	147–148.5	$C_{12}H_{25}N_3O_2$	59.25	59.00	10.35	10.42	17.27	17.20
i-C_4H_9	80	151–152	$C_{12}H_{25}N_3O_2$	59.25	59.39	10.35	10.49	17.27	17.44
n-C_5H_{11}	82	134	$C_{14}H_{29}N_3O_2$	61.96	61.71	10.77	10.99	15.48	15.52
i-C_5H_{11}	88	142–143[d]	$C_{14}H_{29}N_3O_2$	61.96	62.18	10.77	10.91	15.48	15.85
n-C_6H_{13}	57	114	$C_{16}H_{33}N_3O_2$	64.17	64.02	11.11	11.33	14.03	14.11
n-C_7H_{15}	98	104–104.5	$C_{18}H_{37}N_3O_2$	66.01	66.23	11.40	11.20	12.83	12.59
n-C_8H_{17}	92	103–104	$C_{20}H_{41}N_3O_2$	67.56	67.54	11.62	11.52	11.82	12.05
C_9H_{19}[e]	..	122–123	$C_{22}H_{45}N_3O_2$	68.87	68.55	11.83	11.63	10.96	10.75

[a] Yields are based on the weight of crude product. [b] Melting point of analytical sample; all samples were crystallized from aqueous ethanol. [c] The semicarbazone of known Ic was also prepared in 84% yield: mp 164–165°, lit.[8a] mp 163°. [d] Uncorrected. [e] 3,5,5-Trimethylhexyl.

gem-dialkylacetylcarbinol Ib (R = C_2H_5). As already suggested, in preparative practice the conversion was carried out in a single operation from IV (Scheme I). The procedure proved to be a general and most convenient method for preparing *gem*-dialkylacetylcarbinols (I) with yields ranging from 45–82% (Table I); these products, I, readily formed semicarbazones (Table II). The structure of the acetylcarbinols Ib and d (R = C_2H_5, n-C_4H_9) was confirmed by alternate formation from the ethynylcarbinols VIIb and d.[8] The parallel preparation of *gem*-dialkylacetylcarbinols (I) from the thioketal of ethyl pyruvate was also considered as a possibly competitive method but, since initial experiments were unproductive, this approach was abandoned in favor of that already described.

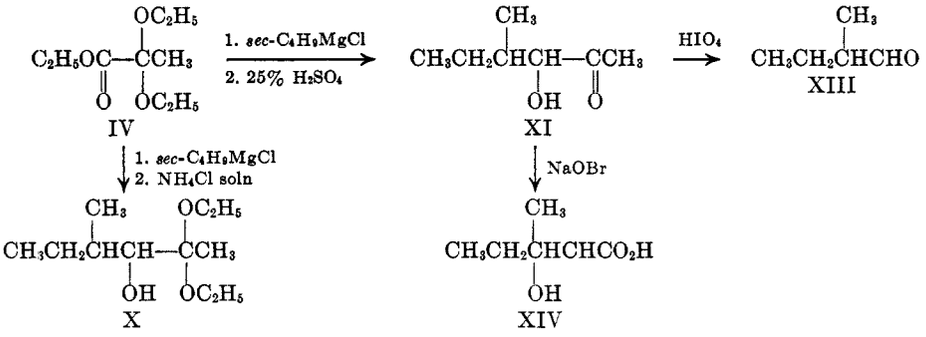
Although the postulated hydroxy ketal of V, as previously noted, was not found in these reaction mixtures, we observed that a hydroxy ketal was indeed obtained if a Grignard reagent with a bulky group was employed. When this occurred, however, only one substituent was introduced with simultaneous reduction,[9] resulting in the formation of a *secondary* hydroxyl group (Scheme II). Hence, it was apparent that steric environment determined whether a hydroxy ketal X or a hydroxy enol ether VI was formed.[9] The hydroxy ketal X had an infrared spectrum consistent with this structural assignment.

If the intermediate complex were treated with 25% sulfuric acid rather than ammonium chloride solution, the acetylcarbinol XI was obtained. In contrast, but

(8) (a) R. Locquin and S. Wouseng, *Compt. Rend.*, **176**, 516 (1923); (b) G. W. Stacy and R. A. Mikulec, *J. Am. Chem. Soc.*, **76**, 524 (1954).

(9) C. R. Noller, W. E. Grebe, and L. H. Knox, *ibid.*, **54**, 4690 (1932).

SCHEME II



as expected for primary alkyl Grignard reagents, the comparative reaction of IV with isobutylmagnesium bromide resulted in the usual dual introduction of alkyl groups to yield a *gem*-dialkylacetylcarbinol (Ie, R = *i*-C_4H_9). On the other hand, *t*-butylmagnesium chloride like *sec*-butyl reacted with IV to give, after sulfuric acid decomposition of the intermediate, 3-hydroxy-4,4-dimethyl-2-pentanone (XII), containing a single *t*-butyl group and isomeric with XI.

The structural assignment for XI was firmly supported by virtue of the fact that it can be oxidized by periodic acid or by sodium hypobromite to yield in each instance the anticipated products (XIII or XIV, respectively).

Experimental Section

All melting points are corrected unless otherwise stated. Boiling points at reduced pressures are uncorrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tenn., and Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratories, England. The infrared spectra were determined on Beckman IR-5 and IR-8 spectrophotometers with sodium chloride optics; the spectra of liquids were run as neat films. The nmr spectra were determined with a Varian A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal reference. The chemical shift in parts per million is followed in parenthesis by the splitting pattern with the symbols: cm, complex multiplet; q, quartet; and d, doublet; and then the number of protons found by integration.

Enol Ethers (VI). 2-Ethoxy-3-ethyl-1-penten-3-ol (VIb).—The following procedure illustrates the general method. To ethylmagnesium bromide, prepared under nitrogen in the usual manner from 65.4 g (0.60 mole) of ethyl bromide and 14.6 g (0.60 g-atom) of magnesium turnings, was added 30.2 g (0.16 mole) of IV[5,10] over a period of 0.5 hr. The mixture then was stirred at room temperature for 2 hr and heated under reflux for an additional 0.5 hr. After the mixture had been cooled in an ice bath, 200 ml of a saturated ammonium chloride solution was added slowly. During this process, the mixture frequently became very viscous, almost stopping the stirrer, but subsequently stirring again proceeded readily. When the addition had been completed, the mixture was stirred for 2 hr. The aqueous phase was separated and extracted with ether, and the combined extracts were dried over anhydrous sodium sulfate. After the solvent had been removed *in vacuo*, the residue was fractionally distilled to give 19.6 g (62%) of product: bp 79–83° (20–22 mm), $n^{25}D$ 1.4342.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.32; H, 11.46. Found: C, 68.50; H, 11.36.

3-Butyl-2-ethoxy-1-hepten-3-ol (VId).—To butylmagnesium bromide [43.5 g (0.32 mole) of butyl bromide and 7.66 g (0.32 g-atom) of magnesium turnings] was added 20.0 g (0.105 mole) of IV in 100 ml of anhydrous ether over a 1-hr period. The reaction mixture was treated in the same way as in the above general procedure to give 15.5 g (68%) of VId: bp 58–68° (0.05–0.1 mm), $n^{25}D$ 1.4420–1.4422.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.27. Found: C, 73.01; H, 12.21.

2-Ethoxy-3-hexyl-1-nonen-3-ol (VIh).—To hexylmagnesium bromide from 81.6 g (0.50 mole) of hexyl bromide and 8.11 g (0.35 g-atom) of magnesium was added 20.0 g (0.105 mole) of IV to yield after the usual work-up 18.6 g (69%) of VIh: bp 106–110° (0.2 mm), $n^{23}D$ 1.4490, d^{23}_4 0.8716.

Anal. Calcd for $C_{17}H_{34}O$: C, 75.57; H, 12.58. Found: C, 75.71; H, 12.56.

2-Ethoxy-3-octyl-1-undecen-3-ol (VIj).—Reaction of octylmagnesium bromide (0.30 mole) with IV (0.105 mole) gave 35.8 g (55%) of a colorless liquid (VIj): bp 133–136° (0.18–0.25 mm), $n^{25}D$ 1.4553, d^{25}_4 0.8742.

Anal. Calcd for $C_{21}H_{42}O_2$: C, 77.23; H, 12.97. Found: C, 77.63; H, 12.92.

2-Ethoxy-3-hexadecyl-1-nonadecen-3-ol (R = $C_{16}H_{33}$).—Reaction of hexadecylmagnesium bromide (0.30 mole) with 20.0 g of IV (0.105 mole) formed 27.0 g (50%) of a white waxy solid. Since purification of this material by recrystallization proved difficult, an analytical sample (mp 51–54°) was obtained by chromatography of the crude material on an alumina column (2.2 × 73 cm).

Anal. Calcd. for $C_{37}H_{74}O_2$: C, 83.07; H, 13.94. Found: C, 83.27; H, 14.10.

2-Ethoxy-3-ethyl-3-pentanol (VIII).—The hydroxy enol ether VIb (3.16 g, 0.02 mole) in 100 ml of absolute ethanol was hydrogenated (6 hr) at 45 psig using W-2 Raney nickel.[11] After work-up, distillation of the residue gave 1.41 g (44%) of a colorless liquid: bp 71–73° (15 mm), $n^{25}D$ 1.4246.

Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.52; H, 12.45.

Ethyl α-Ethoxypropionate (IX).—A procedure reported for the preparation[12] of IX was attempted, but proved to be unsatisfactory in our hands; therefore, the following modification was developed. To a solution of 0.24 mole of sodium ethoxide in 200 ml of absolute ethanol was added dropwise 36.2 g (0.20 mole) of ethyl α-bromopropionate (1 hr). The mixture was then heated under reflux for 1 hr, after which it was allowed to stand at room temperature (6 hr). The precipitated sodium bromide was removed by filtration, and the solution was concentrated to half of its original volume. After 400 ml of water had been added, the mixture was extracted with ether. The residue from the ether solution was distilled to give 10.0 g (35%) of product: bp 57° (17–18 mm), $n^{25}D$ 1.4013; lit.[12] bp 155°.

2-Ethoxy-3-ethyl-3-pentanol (VIII) from Ethyl α-Ethoxypropionate (IX).—To 0.24 mole of ethylmagnesium bromide was added 14.6 g (0.10 mole) of IX in 100 ml of ether over a period of 1.5 hr. When the addition had been completed, the reaction mixture was stirred 10 hr, and then the intermediate complex was decomposed by adding 10% sulfuric acid. After the aqueous phase had been separated and extracted with ether, the combined ether extracts and original ether phase were dried over anhydrous sodium sulfate. The ether was removed by distillation, and the residue was fractionally distilled to give 11.3 g (71%) of VIII: bp 71–72° (14 mm), $n^{25}D$ 1.4248. The infrared spectrum of this substance was identical with that of VIII as formed by hydrogenation of VIb described above.

3-Butyl-3-hydroxy-2-heptanone (Id) from 2-Ethoxy-3-butyl-1-hepten-3-ol (VId).—The enol ether VId (18.0 g, 0.084 mole) was

(10) Ethyl pyruvate diethyl ketal (IV) deteriorates on standing at room temperature; therefore, it should be stored in a freezer.

(11) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 176.

(12) L. Schreiner, *Ann.*, **197**, 1, 13 (1879).

heated under reflux for 0.5 hr in 250 ml of 1% hydrochloric acid with intermittent shaking. After it had been neutralized with solid sodium bicarbonate, the mixture was extracted with ether, and the combined ether extracts were dried over anhydrous sodium sulfate. After ether removal, the residue was fractionally distilled through a 25-cm Vigreux column to yield 12.5 g (80%) of Id: bp 66° (4 mm), $n^{25}D$ 1.4362, d^{25}_4 0.9020. The infrared absorption spectrum of this material was identical with that of a sample prepared by hydration of VIId.

Preparation of *gem*-Dialkylacetylcarbinols (I).—As a general procedure, *ca.* 0.32 mole of the appropriate Grignard reagent was prepared in the usual manner and to this was added dropwise 0.10 mole of IV in 100 ml of absolute ether. Each drop of the ketal solution produced a white vapor as it came in contact with the Grignard solution. The mixture was stirred for an additional 12 hr at room temperature after the addition was complete, and then 340 ml of 10% sulfuric acid was added slowly with cooling.

After the separation of the ether phase and ether extraction, the extracts were dried over anhydrous sodium sulfate. Subsequent to ether removal, the residue was fractionally distilled under reduced pressure through a 15-cm column packed with glass helices. The various *gem*-dialkylacetylcarbinols (I) are described in Table I.

Semicarbazones (Table II) of I were prepared in the usual way.[13]

Ethyl Pyruvate Diethyl Thioketal.—Anhydrous hydrogen chloride was bubbled for 2 hr through a mixture of 11.6 g (0.10 mole) of ethyl pyruvate and 15.3 g (0.25 mole) of ethanethiol. Two phases formed and were separated, and the upper organic phase was extracted with 50 ml of 5% sodium hydroxide solution and was dissolved in ether. The ether solution was dried over anhydrous sodium sulfate, the ether was removed *in vacuo*, and the residue was distilled: yield 12.8 g (58%), bp 124–126° (10 mm), $n^{20}D$ 1.4948, d^{25}_4 1.0629.

Anal. Calcd for $C_9H_{18}O_2S_2$: C, 48.61; H, 8.16; S, 28.84. Found: C, 48.76; H, 8.29; S, 28.65.[14]

3-Butyl-1-heptyn-3-ol (VIId).[15]—While cooled in an ice–salt bath, 22.0 g of potassium hydroxide in 200 ml of anhydrous ether was stirred at high speed[16] for 15 min. To the fine suspension, stirred at intermediate speed, was added dropwise 20.0 g (0.14 mole) of 5-nonanone in 200 ml of anhydrous ether over a period of 7 hr while acetylene (purified by passing through concentrated sulfuric acid and then over anhydrous calcium chloride) was introduced at a moderate rate. At intervals of 0.5 hr, the stirring speed was increased for 1 min to clean the sides of the flask. Upon completion of the addition of 5-nonanone, 250 ml of anhydrous ether was added, and acetylene addition was continued for 2 hr. (Care must be taken that the volume of ether in the reaction flask does not become less than 100 ml) Under these conditions a bis addition product results (see 5,8-dibutyl-6-dodecyne-5,8-diol below). The mixture was extracted with water, the aqueous extracts were then extracted with ether, and the ether extracts were dried over anhydrous sodium sulfate.

After solvent removal, a small amount of the bis addition product was separated by filtration, and the filtrate was fractionally distilled under reduced pressure through a 120-cm Podbielniak column. A forerun of 6.11 g (starting material)[17] and 11.0 g (46% yield; 67% ultimate yield) of VIId, bp 98–101° (15 mm), $n^{25}D$ 1.4440, d^{25}_4 0.8548, was obtained, lit.[18] bp 200–205°, $n^{20}D$ 1.4458, d^{20}_4 0.8552.

5,8-Dibutyl-6-dodecyne-5,8-diol.—In runs where the volume of ether was reduced to below 100 ml., an acetylenic diol[19] was formed in 10% yield, mp 129–130.5° from dioxane, as thin, colorless plates.

Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33. Found: C, 77.20; H, 12.18.

A **2,4-dinitrobenzenesulfenyl chloride adduct of VIId** was obtained by the procedure of Kharasch and Assony.[20] From the reaction of 500 mg (2.98 mmoles) of VIId in 20 ml of dry ethylene chloride and 700 mg (2.99 mmoles) of 2,4-dinitrobenzenesulfenyl chloride was obtained 310 mg (25% yield) of a yellow product, mp 69–73°. Recrystallization from 4:1 petroleum ether (bp 30–75°)–carbon tetrachloride gave yellow prisms, mp 77–78.5°.

Anal. Calcd for $C_{17}H_{23}ClN_2O_5S$: C, 50.69; H, 5.75; S, 7.96. Found: C, 50.26; H, 5.53; S, 7.71.

3-Butyl-3-hydroxy-2-heptanone (Id) by Hydration of 3-Butyl-1-heptyn-3-ol (VIId).—To a mixture of 2.78 g of mercuric oxide, 2.9 ml of concentrated sulfuric acid, and 104 ml of water was added dropwise with stirring 24.6 g (0.15 mole) of VIId over a period of 1 hr, during which time the reaction mixture was maintained at 60°.[8] When the mixture had cooled, the organic phase was taken up in ether, and the aqueous phase was extracted. The combined ether extracts were washed with 35 ml of saturated sodium chloride solution and dried over anhydrous sodium sulfate. A clean silver coin was placed in the flask during the drying operation to amalgamate the free mercury present in suspension in the solution. After ether removal, the residue was fractionally distilled through a 15-cm Vigreux column. Following a forerun of 5.46 g of impure product, 18.8 g (69%) of Id was obtained: bp 119–125° (17 mm), $n^{25}D$ 1.4360, d^{25}_4 0.905. The infrared spectrum was identical with that of the product reported in Table I: ν_{max} (cm^{-1}), 3500(s) (O–H), 1360(s), 1160(s) (*t*-OH), 1705(s) (C=O).

Similarly, diethylethynylcarbinol (VIIb) was converted to Ib in 62% yield.

3-Hydroxy-4-methyl-2-hexanone (XI).—To *sec*-butylmagnesium chloride [8.03 g (0.33 g-atom)] of magnesium and 27.8 g (0.32 mole) of *sec*-butyl chloride] in 100 ml of anhydrous ether was added over a 1-hr period, 19.0 g (0.10 mole) of IV in 200 ml of ether. The mixture was stirred for 2 hr, and then 250 ml of 25% sulfuric acid was added over 1 hr while the temperature was kept below 5°. After work-up, the residue from the ether extracts was fractionally distilled through a 15-cm helice-packed column to give fractions having constant boiling points and refractive indices and amounting to 9.01 g (69%): bp 38–40° (0.70 mm), $n^{25}D$ 1.4280, d^{25}_4 0.9359.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84; MD, 36.07. Found: C, 64.34; H, 10.72; MD, 35.79.

A **semicarbazone** was prepared from 0.93 g (7.1 mmoles) of XI to give 0.90 g (67%), mp 178–180°; recrystallization from 95% ethanol gave mp 180–181° (uncorrected).

Anal. Calcd for $C_8H_{17}N_3O_2$: C, 51.31; H, 9.15; N, 22.45. Found: C, 51.09; H, 9.02; N, 22.55.

3-Hydroxy-4-methyl-2-hexanone Diethyl Ketal (X).—When *sec*-butylmagnesium bromide (0.30 mole) was allowed to react with 0.105 mole of IV, using the experimental procedure which produced enol ethers (acidification with saturated ammonium chloride solution) from primary Grignard reagents, 12.23 g (60%) of the ketal X was obtained: bp 45–47° (0.3–0.5 mm), $n^{25}D$ 1.4114, d^{25}_4 0.8888.

Anal. Calcd for $C_{11}H_{24}O_3$: C, 64.67; H, 11.84. Found: C, 64.89; H, 11.52.

3-Hydroxy-4,4-dimethyl-2-pentanone (XII).—To *t*-butylmagnesium chloride, prepared from 37.0 g (0.40 mole) of *t*-butyl chloride and 9.73 g (0.40 g-atom) of *powdered magnesium*, was added 19.0 g (0.10 mole) of IV. After the reaction mixture had been worked up similarly to XI, 9.66 g (74%) of XII was obtained: bp 26° (0.35 mm), $n^{25}D$ 1.4262, d^{25}_4 0.9162.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.62; H, 10.94.

A **semicarbazone** was prepared from 0.93 g (7.1 mmoles) of XII to yield 1.10 g (90%), mp 187–189°; a sample was recrystallized from aqueous ethanol, mp 192–193°.

Anal. Calcd for $C_8H_{17}N_3O_2$: C, 51.31; H, 9.15; N, 22.45. Found: C, 51.34; H, 9.32; N, 22.00.

Oxidation of 3-Hydroxy-4-methyl-2-hexanone (XI) with Periodic Acid to 2-Methylbutanal (XIII).—A procedure previously reported[8b] was employed. To 130 mg (1.0 mmole) of XI in 8 ml of methanol was added 5 ml of 0.54 *N* periodic acid.[8b] After a 1-hr reaction period, the mixture was neutralized with saturated barium hydroxide solution. After filtration and a methanol

(13) 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, p 218.

(14) The procedure for the preparation of this substance has been reported by T. Posner [*Ber.*, **32**, 2804 (1899)], but no physical properties were included.

(15) Preparation of VIId was developed by Dr. C. R. Bresson.

(16) G. W. Stacy and R. M. McCurdy, *J. Am. Chem. Soc.*, **76**, 1914 (1954).

(17) This material had a bp 78–98° (15 mm), $n^{25}D$ 1.4190–1.4309; it was accumulated from several runs and employed in lieu of pure 5-nonanone to give comparable yields of pure product upon ethynylation.

(18) Y. W. S. Zolkind and K. A. Doliashvili, *Soobshch. Akad. Nauk Gruz.*, **15**, 227 (1954); *Chem. Abstr.*, **50**, 3206 (1956).

(19) E. D. Bergmann, M. Sulzbacher, and D. F. Herman, *J. Appl. Chem.* (London), **3**, 39 (1953); *Chem. Abstr.*, **48**, 4426 (1954).

(20) N. Kharasch and S. J. Assony, *J. Am. Chem. Soc.*, **75**, 1081 (1953).

wash, the combined filtrates were added to 50 ml of 2 *N* hydrochloric acid, saturated with 2,4-dinitrophenylhydrazine. The work-up gave 240 mg (90%) of 2-methylbutanal 2,4-dinitrophenylhydrazone, mp 112–115° (uncorrected), lit.[21] mp 132.5–133°.

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.05. Found: C, 49.60; H, 5.53; N, 20.95.

Cleavage of XI with Sodium Hypobromite to 2-Hydroxy-3-methylpentanoic Acid (XIV).—To a sodium hypobromite solution [8.40 g (0.21 mole) of sodium hydroxide (70 ml of water) and 12.0 g (0.075 mole) of bromine] was added slowly 2.60 g (0.02 mole) of XI, the mixture was stirred in an ice bath for 45 min and then at room temperature for 3 hr. Bromoform was separated, and the aqueous phase was carefully acidified with 10 ml of concentrated sulfuric acid. After ether extraction, the ether solution in turn was extracted with several portions of saturated sodium bisulfite and dried over anhydrous magnesium sulfate. Work-up resulted in 1.60 g of a gummy mass of colorless crystals, but recrystallization from toluene–petroleum ether gave 0.72 g (47% yield) of product, mp 45–48°; sublimation of this material resulted in a pure substance melting sharply at 48°.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.67; H, 9.16.

(21) E. J. Badin and E. Pacsu, *J. Am. Chem. Soc.*, **67**, 1352 (1945). The difference in melting points may be due to *syn-anti* isomerism or crystalline modification of the same isomer.

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Cortical Steroid Analogs. V. Synthesis of *gem*-Dialkyldihydroxyacetones and 3-Butyl-3,6-dihydroxy-1-aroyloxy-2-heptanone[1a]

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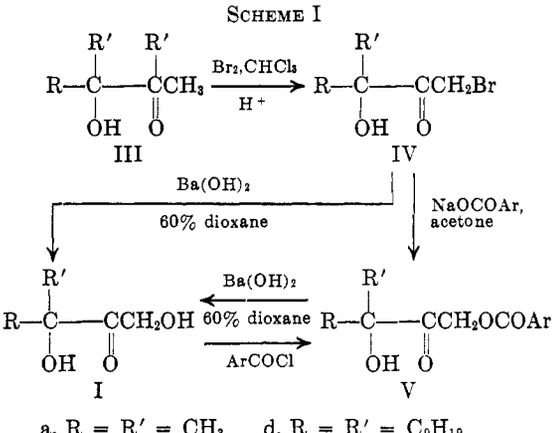
By utilization of the now available *gem*-dialkylacetylcarbinols (III), synthesis of three *gem*-dialkyldihydroxyacetones (I) has been accomplished. One of these (Id) possesses the corticosteroid carbon content of 21 carbon atoms. Thus, the general ease with which this synthetic scheme may be applied is established. In a different but related phase of research, a partial structure, simulating the C and D steroid rings and possessing a hydroxyl group corresponding to that of position 11 in cortisol, is reported. As the free dihydroxyacetone IIa itself resisted isolation, it was obtained as the aromatic ester derivative, *i.e.*, 3-butyl-3,6-dihydroxy-1-aroyloxy-2-heptanone (IIb and c). The over-all synthesis proceeds from ethyl 3-oxoenanthate (VI) through five steps to 3-butyl-3,6-dihydroxy-2-heptanone (XI). This key intermediate then intersects the previously employed scheme for conversion of acetylcarbinols III to dihydroxyacetones I, and its application finally gives IIb and c. None of these analogs showed significant corticoid activity.

Several excellent procedures have been developed for the elaboration of the dihydroxyacetone group common to the antiinflammatory corticosteroids.[2] In the preparation of *open-chain* analogs, there is a greater flexibility of approach in handling this synthetic problem, however, as we have previously demonstrated.[3,4] Contemporarily, the synthesis of the related *gem*-dimethyldihydroxyacetone (Ia) was recorded by a Russian group.[5] Now that a convenient method for the preparation of *gem*-dialkylacetylcarbinols (III) (Scheme I) is at hand, as described in the foregoing companion paper,[6] the synthesis of a series of *gem*-dialkyldihydroxyacetones corresponding to the parent Ia has become feasible. The strategic advantage of this approach is that *gem*-dialkyldihydroxyacetones (I) of high carbon content may be constructed by selection of an appropriate Grignard reagent of less than half as many carbon atoms.[6] Accordingly, we have conveniently synthesized the 21-carbon analog (Id), which has a carbon content identical with that of the corticosteroids.

SCHEME I



a, R = R′ = CH_3 d, R = R′ = C_9H_{19}
b, R = R′ = C_2H_5 e, R = CH_3; R′ = C_6H_5
c, R = R′ = C_4H_9

For purposes of comparison and development of synthetic procedures, the *gem*-diethyl analog Ib and the *gem*-dibutyl analog Ic were prepared in addition to Id. As in earlier work,[3,4] it was found that α-bromo-α′-hydroxy ketones (IV) frequently undergo decomposition on attempted distillation. It was, therefore, ordinarily expedient to employ the freshly prepared crude intermediate for the subsequent step. The crude α-bromo-α′-hydroxy ketone also was on occasion characterized as a crystalline salt resulting from reaction with 3-methylisoquinoline.[7] When the α-bromo-α′-hydroxy ketone was a solid, as in the case of the C-21 analog IVd, it was possible to obtain a pure inter-

(1) (a) Presented in part before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958. (b) In part from the Ph.D. Thesis of S. L. Razniak, Washington State University, June 1960.

(2) *Cf.* G. Rosenkranz and F. Sondheimer, "Progress in the Chemistry of Organic Natural Products," Vol. X, L. L. Zechmeister, Ed., Springer Verlag, Vienna, 1953, p 274.

(3) G. W. Stacy, R. A. Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, **79**, 3587 (1957).

(4) G. W. Stacy, R. A. Mikulec, C. R. Bresson, and L. D. Starr, *J. Org. Chem.*, **24**, 1099 (1959).

(5) I. N. Nazarov, M. S. Burmistrova, and A. A. Akhrem, *Zh. Obshch. Khim.*, **29**, 735 (1959); *Chem. Abstr.*, **54**, 1354 (1960).

(6) G. W. Stacy, I. L. Klundt, G. T. Davis, N. A. Nielsen, M. S. Power, D. L. Rector, and S. L. Razniak, *J. Org. Chem.*, **31**, 1753 (1966).

(7) R. S. Shelton, *J. Am. Chem. Soc.*, **68**, 753 (1946).