

2,2,4,4-Tetramethyl-3-oxetanone

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Recently, two reports on the preparation of 3-oxetanones have appeared.² We wish to report another synthetic approach to this interesting class of compounds. 2,2,4,4-Tetramethyl-3-hydroxyoxetanone-3-carboxylic acid (I) has been prepared from 2,5-dimethyl-3-hexyne-2,5-diol.³ We have prepared tetramethyloxetanone II by the lead tetraacetate oxidation of I. The structure of II is established by: (a) its infrared spectrogram; it shows a strong absorption at 5.5μ , almost identical with the carbonyl absorption of tetraphenyloxetanone^{2b} and β -propiolactone⁴; (b) its characteristic carbonyl behavior in forming an oxime and a 2,4-dinitrophenylhydrazone; (c) its reaction with zinc and acetic anhydride to form two products, IV, presumably α -acetoxydiisopropyl ketone⁵ and V, α, α' -diacetoxydiisopropyl ketone.⁶

Experimental⁷

Preparation of 2,2,5,5-Tetramethyltetrahydro-3-furanone and 4,4-Dibromo-2,2,5,5-tetramethyltetrahydro-3-furanone.—The procedure described by Richet was followed. The yields were above 90% in each step.

Preparation of 2,2,5,5-Tetramethyltetrahydro-3,4-furandione.—Fifty grams of 4,4-dibromo-2,2,5,5-tetramethyltetrahydro-3-furanone, 500 ml. of water and 35 g. of sodium bicarbonate were placed in a 1 liter, 2-neck flask with condenser and stirrer. The mixture was heated at reflux with vigorous stirring until no oily layer was visible. The solution was cooled and continuously extracted with ether for 24 hours. The ether solution was removed at the pump and the diketone dihydrate which precipitated was recrystallized from an ether-petroleum ether mixture, m.p. 79–80°, yield 19.5 g., 68%. Richet³ used potassium hydroxide for this step. We found that the prolonged heating necessary to convert the insoluble dibromide into the soluble diketone gave unpredictable results with potassium hydroxide. We were able to control the reaction much more easily using the weaker base sodium bicarbonate.

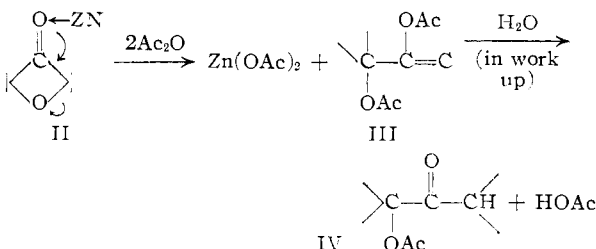
(1) To whom inquiries should be directed.

(2) (a) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952); (b) G. B. Hoey, D. O. Dean and C. T. Lester, *THIS JOURNAL*, **77**, 391 (1955).

(3) (a) H. Richet, R. Dulon and G. Dupont, *Bull. soc. chim. France*, 693 (1947); (b) H. Richet, *Ann. chim.*, [12] **3**, 317 (1948).

(4) We are indebted to Dr. T. L. Gresham of the B. F. Goodrich Co. for a complete spectrogram of β -propiolactone.

(5) The reaction of II with zinc and acetic anhydride was inspired by the reaction of an α -ketol acetate with the same reagents, R. B. Woodward, *et al.*, *THIS JOURNAL*, **74**, 4225 (1952). We presume the reaction proceeded



This reaction was suggested to us by Dr. K. C. Brannock.

(6) The diacetoxy compound V presumably comes from the zinc acetate catalyzed cleavage of the ether linkage of II. V has been reported previously by A. Favorski and A. Umnova, *J. prakt. Chem.*, **88**, 683 (1912).

(7) All b.p.'s and m.p.'s reported are uncorrected. Microanalyses were done by Drs. G. Weiler and F. B. Strauss, Oxford, England.

The Benzoic Acid Type Rearrangement of 2,2,5,5-Tetramethyltetrahydro-3,4-furandione.—Two procedures were used at this stage. In one procedure the pure diketone dihydrate, 12 g., was dissolved in 54 ml. of water, 13.3 g. of C.P. potassium hydroxide added and the mixture refluxed for 45 min. The solution was cooled, acidified to congo red paper, and continuously extracted with ether. The ether was removed at the water-pump and the product crystallized from boiling chloroform, yielding 9.6 g., 79%, of 2,2,4,4-tetramethyl-3-hydroxyoxetanone-3-carboxylic acid (I), m.p. 112°. This product is sufficiently pure for further synthetic procedures. Several recrystallizations will result in a pure compound, m.p. 118°. In the alternate procedure the diketone was not isolated. Fifty grams of dibromoketone, 500 ml. of water and 35 g. of sodium bicarbonate were heated at reflux with stirring for seven hours. The solution was cooled and 100 g. of C.P. potassium hydroxide pellets was added. This solution was heated at reflux for 30 min., cooled, acidified to congo red and continuously extracted with ether. After removal of the ether at the water-pump the acid was recrystallized from chloroform, yielding 26 g., 89%.

The Preparation of II.—Numerous procedures for converting I into II were tried. Among those which were unsuccessful are: (1) pyrolysis,⁸ (2) oxidation with dilute potassium permanganate,⁹ (3) oxidation with N-bromosuccinimide.¹⁰ The following procedure was found satisfactory: 40 g. of the hydroxyoxetanecarboxylic acid was dissolved in 100 ml. of dry chloroform. The solution was heated to gentle reflux with stirring and 102 g. of lead tetraacetate¹¹ in 250 ml. of chloroform was added dropwise with stirring. When addition was complete the mixture was cooled and filtered. The chloroform solution then was washed successively with 2% aqueous hydrochloric acid, water, 5% aqueous sodium bicarbonate and water. The solution was dried over anhydrous calcium sulfate and the chloroform removed by distilling through a Todd column. When the pot temperature reached 120°, the pot was removed and the residue distilled from a simple distilling flask. The portion boiling 116–120° was collected. It immediately crystallized and after two sublimations the product had a m.p. of 48°, yield 16 g., 57%. *Anal.* Calcd. for $\text{C}_7\text{H}_{12}\text{O}_2$: C, 65.62; H, 9.38. Found: C, 65.27; H, 9.39. The oxime of II was prepared in usual manner, m.p. 186–187°. *Anal.* Calcd. for $\text{C}_7\text{H}_{13}\text{O}_2\text{N}$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.89; H, 9.35; N, 9.96. 2,4-Dinitrophenylhydrazone of II, prepared in usual manner, m.p. 128°, mixture m.p. with acetone-2,4-dinitrophenylhydrazone 92–115°. *Anal.* Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_5$: C, 50.64; H, 5.23; N, 18.17. Found: C, 51.03; H, 5.29; N, 17.60.

Reaction of II with Zinc and Acetic Anhydride.—A solution of 15 g. of II in 200 ml. of acetic anhydride was heated with stirring to 120°. Fifty grams of zinc dust was added. After the vigorous reaction subsided, the mixture was stirred for 15 min., cooled and filtered. The filtrate was poured onto 1000 g. of ice and stirred until the acetic anhydride was hydrolyzed. The mixture was extracted with ether and the resulting ether solution washed with water, dilute sodium bicarbonate solution, and water successively. After drying, the ether was removed on a water-bath and the residue steam distilled. In this way two products were separated easily. One lighter than water had a saponification equivalent of 168; calcd. for α -acetoxydiisopropyl ketone, sapon. equiv. 172. The other compound, α, α' -diacetoxydiisopropyl ketone was heavier than water and crystallized on standing, m.p. 53–54°, reported m.p. 51–52°. *Anal.* Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_5$: C, 57.38; H, 7.88; sapon. equiv., 115. Found: C, 57.70; H, 7.81; sapon. equiv., 111. An infrared spectrogram showed a very strong absorption at 8.0 (acetate) and 5.8 μ (ketone). There was no indication of any carbon-to-carbon double bond in the spectrogram.

Acknowledgment.—We wish to express our appreciation to Air Reduction Chemical Co., 60 East

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42nd St., New York 17, N. Y., for generously supplying us with the dimethylhexynediol used as starting material in the synthesis of the oxetanone.

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Steroid α -Naphthylurethans

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The ease of preparation of several steroid α -naphthylurethans in good yields prompted a brief investigation of the stability of this type of derivative in order to determine its possible usefulness in steroid isolation work. Cholesterol α -naphthylurethan was chosen as a model compound in these studies. It was stable at room temperature in concentrated ammonium hydroxide and in ethanol satu-

carbonyl carbon of the urethan with the elimination of the *o*-steroid anion. The data characterizing the derivatives are presented in Tables I and II

Examination of the infrared data in Table II discloses that the N-H band appears to be sensitive to the position of substitution of the α -naphthyl group, while the urethan C=O band remains essentially unaffected, appearing in a range slightly higher than that characteristic of the steroid C=O band.¹ In the urethan of desoxycorticosterone the bands ascribed to the C=O at carbon 3 and carbon 20 are both displaced from 1660 and 1718 cm.⁻¹ in the free steroid to 1653 and 1718 cm.⁻¹ in the urethan.

The C-O stretching mode cannot be assigned unambiguously. It may be identified with the strong bands appearing near 1200 and (or) 1250 cm.⁻¹ in all seven urethans. The frequencies associated with the α -naphthyl group represent merely some characteristic rather than all the bands ascribed to the aromatic group.²

TABLE I

R	M.P., °C. ^a	Yield, %	Recrystallization solvent	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
1 Dehydroepiandrosterone	234-235	97	Benzene-ethyl alc.	C ₃₀ H ₃₅ O ₃ N	78.74	78.44	7.71	7.92
2 Etiocholane-17- β -ol-3-one ^b	229-231	91	Benzene-ethyl alc.	C ₃₀ H ₃₇ O ₃ N	78.39	78.00	8.12	8.22
3 Δ^6 -Pregnenolone	222-223	95	Acetone	C ₃₂ H ₃₉ O ₃ N	79.14	79.17	8.09	8.21
4 Desoxycorticosterone	215-218	84	Acetone	C ₃₂ H ₃₇ O ₄ N	76.95	76.94	7.47	7.55
5 Testosterone	258-259	100	Toluene-ethyl alc.	C ₃₀ H ₃₅ O ₂ N	78.74	78.55	7.71	7.95
6 β -Cholestanol	156-157	75	Ligroin	C ₃₈ H ₅₅ O ₂ N	81.81	81.57	9.94	9.86
7 Cholesterol	169 ^c	100	Ligroin					

^a A Fisher-Johns apparatus was used for the determinations of the melting points, which are uncorrected. ^b We are grateful to F. Sondheimer, Syntex Corp., for a gift of this steroid. ^c V. T. Bickel and H. E. French, THIS JOURNAL, **48**, 747 (1926), report 160°.

TABLE II

CHARACTERISTIC ABSORPTION BANDS (CM.⁻¹) AND EXTINCTION COEFFICIENTS OF STEROID α -NAPHTHYLURETHANS

1 ^a	Molar extinction coefficient $\lambda_{\max}^{\text{EtOH}}$ 290 μ	N-H Stretching	C=O Stretching	Naphthyl group								
				775vs	764vs	770vs	789vs	789s	808s	1493vs	1533vs	1597w
2	7200	3432w ^b	1740vs	775vs	764vs	770vs	789vs	789s	808s	1493vs <td>1533vs <td>1597w</td> </td>	1533vs <td>1597w</td>	1597w
3	7100	3275s	1733vs	764vs	770vs	770vs	789vs	789s	808s	1501vs <td>1532vs <td>1597w</td> </td>	1532vs <td>1597w</td>	1597w
4	7100	3407s	1730vs	770vs	770vs	770vs	789vs	789s	808s	1505vs <td>1553vs <td>1584m</td> </td>	1553vs <td>1584m</td>	1584m
5	6250	3306s	1740vs	789s	789s	789s	808s	808s	808s	1504vs <td>1523vs <td>1602w</td> </td>	1523vs <td>1602w</td>	1602w
6	6100	3290s	1727vs	768vs	768vs	768vs	794vs	794vs	794vs	1502s <td>1534vs <td>1612m</td> </td>	1534vs <td>1612m</td>	1612m
7	6600	3456m	1739vs	772vs	772vs	772vs	793vs	793vs	793vs	1493vs <td>1532vs <td>1562m</td> </td>	1532vs <td>1562m</td>	1562m
7	8600	3487m	1738vs	768s	768s	768s	1491s	1491s	1491s	1525s <td>1525s <td>1603m</td> </td>	1525s <td>1603m</td>	1603m

^a Numbers refer to compounds listed in Table I. ^b Estimated intensities are indicated by w = weak, m = medium, s = strong, vs = very strong.

rated with dry hydrogen chloride gas. The urethan also was stable in refluxing glacial acetic acid and could be recovered unchanged after heating in ethanolamine at 100°. In refluxing ethanolamine the urethan was decomposed to cholesterol. All the steroid α -naphthylurethans which were prepared could be cleaved by refluxing with sodium methoxide in methanol. Cholesterol, β -cholestanol, Δ^5 -pregnenolone and dehydroepiandrosterone were obtained in yields of 66, 69, 57 and 38% from their respective urethans. In addition to the free steroid, the α -naphthylurethan of methyl alcohol was isolated as a product of the cleavage. The dissociation of the steroid urethans apparently proceeded via a nucleophilic attack of the methoxide ion on the

Experimental

Preparation of α -Naphthylurethans (1-5).—One-half ml. of dry benzene containing 200 mg. of the steroid, a slight molar excess of α -naphthyl isocyanate and 10 μ l. of anhydrous pyridine was refluxed for one hour in a centrifuge tube. The steroid α -naphthylurethan was precipitated and washed with a total of 8 ml. of ligroin. It then was crystallized from the appropriate solvents. In the preparation of the steroid α -naphthylurethans 6 and 7, one ml. of dry ligroin was used instead of one-half ml. of benzene. The urethans were washed with a total of 4 ml. of ligroin.

Cleavage of Steroid α -Naphthylurethans.—Thirty mg. of the urethan was refluxed (78°) with 2.5 ml. of 3.5 *N* sodium

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