TABLE I

DERIVATIVES OF IMINODIACETIC ACID R—N(CH$_2$COOH)$_2$

R	Method	Composition	M. p.,[a] °C.	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
$(CH_3)_2CH$	A	$C_7H_{13}NO_4$	230–231 d.	47.99	47.81	7.48	7.63	7.99	7.87
$(CH_3)_3C$	A	$C_8H_{15}NO_4$	199–200.5 d.	50.78	50.88	7.99	8.09	7.41	7.50
$CH_3(CH_2)_3$	A	$C_8H_{15}NO_4$	184–185.5	50.78	50.93	7.99	8.12	7.41	7.53
$CH_3(CH_2)_4$	A	$C_9H_{17}NO_4$	156–158	53.3	53.33	8.45	8.54	6.92	6.95
$CH_3(CH_2)_5$—	B	$C_{10}H_{19}NO_4$	130–131	55.28	55.44	8.82	8.89	6.44	6.55
$CH_3(CH_2)_6$—	B	$C_{11}H_{21}NO_4$	133–134	57.12	57.06	9.15	9.03	6.05	6.00
$CH_3(CH_2)_7$—	B	$C_{12}H_{23}NO_4$	137–137.5	58.75	58.88	9.45	9.50	5.71	5.64
$CH_3(CH_2)_8$—	B	$C_{13}H_{25}NO_4$	159.5–161.5	60.2	60.17	9.72	9.88	5.40	5.41
$CH_3(CH_2)_9$—	C	$C_{14}H_{27}NO_4$	135–136	61.51	61.62	9.96	10.10	5.12	5.23
$CH_3(CH_2)_{11}$—	C	$C_{16}H_{31}NO_4$	135.5–136.5					4.63	4.69
$CH_3(CH_2)_{15}$—	C	$C_{20}H_{39}NO_4$	128.2–129.3	67.19	67.24	10.92	11.06	3.97	4.03

[a] All melting points uncorrected. [b] Analyses by Dr. Ritter, Basel, Switzerland.

Although formation constants have been reported for isopropyl- and *t*-butyliminodiacetic acids,[2] and the synthesis of the isopropyl and *n*-butyl compounds has been mentioned in the patent literature,[3,4] no characterization of the compounds has been given.

The procedure used to obtain the pure acids varied with the water solubility of the acid. The less soluble acids were precipitated by direct acidification of the reaction mixture of the amine and sodium chloroacetate, and were purified by fractional crystallization from water or aqueous alcohol (procedure B). Those acids which were quite soluble in water were obtained pure by precipitation of the barium salt followed by sulfuric acid decomposition[5] (procedure A). The high molecular weight amines required use of an aqueous alcoholic solvent (procedure C).

Preliminary studies indicate that these compounds behave similarly to imino-[6] and methyliminodiacetic acid[7] as regards reactions with metal ions in solution. Further work is in progress and results will be published at a later date.

Experimental

Isopropyliminodiacetic Acid. Procedure A.—Distilled isopropylamine (7.4 g., 0.125 mole) was added to 24 g. (0.25 mole) of chloroacetic acid neutralized to phenolphthalein with 5 *N* sodium hydroxide in a 250-ml. flask equipped with thermometer, dropping funnel and reflux condenser. The temperature was maintained at 50° for 10 hours, during which time 5 *N* alkali was added so as to keep the solution alkaline to phenolphthalein; the alkali was consumed rapidly initially but more slowly as the reaction progressed.

Addition of 32.0 g. (0.13 mole) of barium chloride dihydrate dissolved in 60 ml. of hot water caused immediate precipitation. The mixture was warmed, with stirring, on a steam-bath for 30 minutes, and the precipitate was collected on a suction filter. The dry barium salt was added to 75 ml. of boiling water, and a stoichiometric amount of 5 *N* sulfuric acid was added slowly (30 minutes) to the well-stirred mixture. The mixture was then suction filtered through a layer of Super-Cel filter aid, and the filtrate evaporated to dryness in vacuum. Alternatively, the mixture was concentrated to a sirup in vacuum and crystallization was induced by addition of absolute methanol and cooling in ice. Recrystallization from a small quantity of hot water gave pure, white, crystalline product.

Procedure B.—Direct acidification of the reaction mixture with concentrated hydrochloric acid rather than precipitation of the barium salt differentiates procedure B from A. Longer reaction times were necessary with the higher molecular weight amines. The precipitated acids were purified by fractional recrystallization from boiling water.

Dodecyliminodiacetic Acid. Procedure C.—A solution of 24 g. (0.25 mole) of chloracetic acid in 100 ml. of alcohol and 10 ml. of water was neutralized to phenolphthalein with 10 *N* sodium hydroxide. Twelve grams (0.065 mole) of dodecylamine was added and the solution was allowed to stand 3 days at room temperature, and finally 5 hours at 80–95°; over this entire period of time there were added 30 ml. of 10 *N* alkali. Acidification of the solution with concentrated hydrochloric acid gave a crude product which was purified by several recrystallizations from 95% alcohol.

The authors wish to thank the Office of Naval Research for the support given this study.

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(2) J. K. Suder and W. C. Fernelius, "Symposium on Chelate Compounds," Polytechnic Institute of Brooklyn, April 26, 1952. We wish to thank Dr. W. C. Fernelius for allowing us precedence in publishing the preparation of these two compounds.

(3) G. O. Curme, H. C. Chitwood and J. W. Clark, U. S. Patent 2,384,816 (1945).

(4) F. C. Bersworth, U. S. Patent 2,407,645 (1946).

(5) G. J. Berchet, *Org. Syntheses*, **18**, 56 (1938).

(6) S. Chaberek, Jr., and A. E. Martell, THIS JOURNAL, **74**, 5052 (1952).

(7) G. Schwarzenbach, E. Kampitsch and R. Steiner, *Helv. Chim. Acta*, **28**, 1133 (1945).

Steroids. LXII.[1] Synthesis of Progesterone 3-Cycloethylene Ketal

BY FRANZ SONDHEIMER, M. VELASCO AND G. ROSENKRANZ

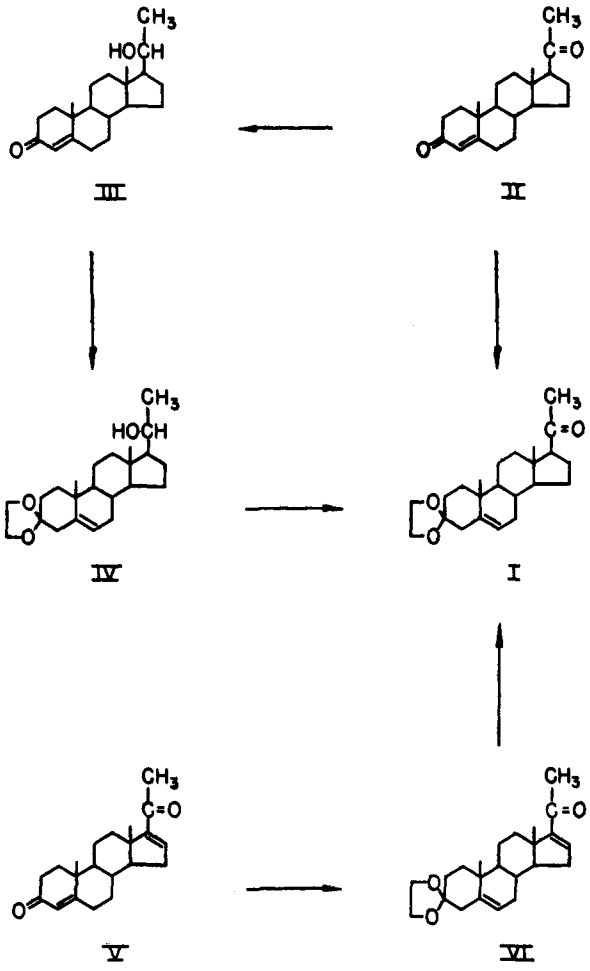
RECEIVED JULY 26, 1954

We have been interested in these Laboratories in carrying out certain transformations involving the side-chain of progesterone. In this connection it was necessary to make available a progesterone derivative appropriately protected at C-3 and progesterone 3-monocycloethylene ketal (I) seemed to be a suitable compound.[2] In the present communication we describe the formation of this substance by three different routes.[3]

(1) Paper LXI, A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **77**, 148 (1955).

(2) *Cf.*, the conversion of the 3-monocycloethylene ketal of 11-ketoprogesterone to 11-dehydrocorticosterone and cortisone [L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *ibid.*, **74**, 4974 (1952); G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, *ibid.*, **76**, 5031 (1954)].

(3) Since this manuscript was prepared, A. Ercoli and P. de Ruglieri [*Gass. chim. ital.*, **84**, 312 (1954)] have described the preparation of the ketal I [m.p. 171–173°, $[\alpha]^{18}D$ +54° (pyridine)] by an independent method as well as its conversion to desoxycorticosterone acetate.



The 11-keto derivative of I, 11-ketoprogesterone 3-monocycloethylene ketal, had previously been prepared directly from 11-ketoprogesterone (together with the 3,20-diketal) by an interchange dioxolanation reaction[4] and also from Δ^4-pregnen-20β-ol-3,11-dione by ketalization at C-3 and subsequent oxidation at C-20 with a chromium trioxide–pyridine complex.[4] Both these methods have now been applied to the 11-desoxo series. The direct reaction of progesterone (II) with boiling 2-methyl-2-ethyl-1,3-dioxolane in the presence of *p*-toluenesulfonic acid[5] was carried out under various conditions, the best yield (25%, after chromatography) of the desired 3-monocycloethylene ketal (I) being obtained by distillation for 10 minutes.[6] The structure of the product followed from the elementary analysis, absence of high-intensity absorption in the ultraviolet and presence of a band at 1700 cm.$^{-1}$ (saturated ketone) in the infrared.

The second method utilized Δ^4-pregnen-20β-ol-3-one (III) as starting material, a compound most readily prepared from progesterone (II) by reduction with lithium aluminum hydride and re-oxidation at C-3 with manganese dioxide.[7] Ketalization of III with ethylene glycol and *p*-toluenesulfonic acid in benzene smoothly furnished the 3-cycloethylene ketal IV (67%), which on oxidation at C-20 with the chromium trioxide–pyridine complex[4,8] produced the same progesterone 3-ketal (I) as had been obtained by the direct method.

Neither of the above two routes to I is particularly satisfactory due to the poor yield given by the first and the rather indirect nature of the second. The poor yield given by the direct dioxolanation of progesterone is probably caused by the fact that the greater reactivity of the C-3 over the C-20 carbonyl group, determined by steric factors, is counterbalanced by the α,β-unsaturated nature of the former. These considerations led us to expect that the preferential C-3 dioxolanation of 16-dehydroprogesterone (V) would proceed considerably more smoothly, for in this compound both carbonyl groups are equally deactivated due to α,β-unsaturation and the steric preference for reaction at C-3 should be the determining factor.[9] In fact, when 16-dehydroprogesterone (V) was distilled with methylethyldioxolane and *p*-toluenesulfonic acid (30 minutes) the 3-monoketal VI could be isolated easily by direct crystallization in 62% yield. The Δ^{16}-double bond of VI was preferentially hydrogenated over a 10% palladium–calcium carbonate catalyst, whereby progesterone 3-cycloethylene ketal (I) was produced in over 90% yield. This constitutes a satisfactory route to the last-named compound, since 16-dehydroprogesterone (V) is readily available from $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (the degradation product of diosgenin) by saponification and Oppenauer oxidation.[10]

Experimental[11]

3-Ethylenedioxy-Δ^5-pregnen-20β-ol (IV).—A stirred mixture of 0.95 g. of Δ^4-pregnen-3-one-20β-ol (III)[7] and 0.05 g. of *p*-toluenesulfonic acid hydrate in 65 cc. of benzene and 2 cc. of ethylene glycol was boiled for 8 hours, a water separator being employed. The cooled mixture was then poured into sodium carbonate solution and the organic layer was washed with water, dried and evaporated. Crystallization from acetone yielded 0.73 g. (67%) of the 3-ketal IV with m.p. 190–192°, no appreciable absorption in the ultraviolet. The analytical sample showed m.p. 194–195°, $[\alpha]^{20}D$ +3° (pyridine), $\nu_{max.}$ free hydroxyl band only.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.96; H, 10.15.

3-Ethylenedioxy-$\Delta^{5,16}$-pregnadien-20-one (VI).—A mixture of 10 g. of $\Delta^{4,16}$-pregnadiene-3,20-dione (16-dehydroprogesterone) (V)[10] and 0.4 g. of *p*-toluenesulfonic acid dihydrate in 160 cc. of 2-methyl-2-ethyl-1,3-dioxolane (previously freed of ethylene glycol by distillation over lithium aluminum hydride) was heated to boiling (580 mm.) and then slowly distilled for 30 minutes, by which time *ca.* 50 cc. of distillate had been collected. The solution was chilled

(4) J. M. Constantin, A. C. Haven and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953).

(5) H. J. Dauben, B. Löken and H. J. Ringold, *ibid.*, **76**, 1359 (1954).

(6) It has been shown (reference 5) that progesterone with these reagents after 5 hours distillation produces the 3,20-diketal in 71% yield.

(7) F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953).

(8) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(9) *Cf.*, the relative reactivity orders in the dioxolanation reaction: saturated 20-ketone > Δ^4-3-ketone > Δ^{16}-20-ketone (reference 5).

(10) R. E. Marker, T. Tsukamoto and D. L. Turner, THIS JOURNAL, **62**, 2525 (1940); A. Butenandt and J. Schmidt-Thomé, *Ber.*, **72**, 182 (1939).

(11) Melting points are uncorrected. Ultraviolet absorption spectra were determined (Beckman D.U. spectrophotometer) in 95% ethanol and infrared spectra (Perkin-Elmer model 12C spectrometer with sodium chloride prism) in chloroform solution, unless otherwise specified. We would like to thank Mrs. P. Lopez and staff for these measurements and Mrs. A. Gonzalez for the microanalyses.

in ice and the precipitated 3-monoketal VI (5.28 g. with m.p. 227–230°) was collected. The filtrate was diluted with benzene and was then washed with sodium bicarbonate solution and water, dried and evaporated. Crystallization of the residue from acetone furnished another 1.81 g. of the monoketal VI with m.p. 230–233° (total yield 7.09 g., 62%). Further crystallization from acetone led to the analytical specimen with m.p. 234–236°, $[\alpha]^{20}D$ +8° (pyridine), $\lambda_{max.}$ 238 mμ (log ε 4.03), $\nu_{max.}$ 1656 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.31; H, 8.69.

3-Ethylenedioxy-Δ⁵-pregnen-20-one (Progesterone 3-Cycloethylene Ketal) (I). (a) From Progesterone (II).—A mixture of 5 g. of progesterone and 0.2 g. of *p*-toluenesulfonic acid dihydrate in 80 cc. of methylethyldioxolane (freshly distilled over lithium aluminum hydride) was heated to boiling (580 mm.) and then distilled for 10 minutes (25 cc. of distillate collected). The solution was diluted with benzene and was then washed with sodium bicarbonate solution and water, dried and evaporated. The oily residue ($\lambda_{max.}$ 240 mμ, log ε 3.96) was chromatographed on 250 g. of neutral alumina. The fractions eluted with hexane and hexane–benzene (9:1) yielded a small amount (*ca.* 50 mg.) of progesterone bis-cycloethyleneketal with m.p. 179–180°, $[\alpha]^{20}D$ −29° (chloroform) [reported[5] m.p. 180–181°, $[\alpha]^{24}D$ −27° (chloroform)]. The fractions eluted with hexane–benzene (6:4 to 4:6) on crystallization from acetone–hexane produced 1.41 g. (25%) of the 3-monoketal I with m.p. 180–181°, $[\alpha]^{20}D$ +28° (chloroform), +53° (pyridine), no high-intensity absorption in the ultraviolet, $\nu_{max.}^{mull}$ 1700 cm.$^{-1}$ A m.p. depression of *ca.* 20° was observed on admixture with the diketal.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.78.

When the distillation time was increased to 30 minutes, the yield of the monoketal I was decreased to 22% and that of the diketal increased to 8%.

(b) From **3-Ethylenedioxy-Δ⁵-pregnen-20β-ol** (IV).—Chromium trioxide (0.3 g.) was added slowly with stirring and cooling to 6 cc. of dry pyridine (temperature kept below 30°). A solution of 0.3 g. of 3-ethylenedioxy-Δ⁵-pregnen-20β-ol (IV) in 6 cc. of pyridine was then added dropwise with continued cooling and the mixture was allowed to stand at room temperature overnight. Water and then equal parts of benzene and ether were added, the mixture was filtered through celite and the organic layer was well washed with water, dried and evaporated. Crystallization from acetone–hexane furnished 0.18 g. of the ketal I with m.p. 173–175°, $[\alpha]^{20}D$ +50° (pyridine). Identity with that prepared by method a was established by mixture m.p. determination and infrared comparison.

(c) From **3-Ethylenedioxy-Δ⁵,¹⁶-pregnadien-20-one (VI).**—A solution of 3 g. of 3-ethylenedioxy-Δ⁵,¹⁶-pregnadien-20-one (VI) in 250 cc. of ethyl acetate was shaken in hydrogen with 0.3 g. of a 10% palladium–calcium carbonate catalyst at 21° and 585 mm. In 5 hours 1.02 moles of gas had been absorbed and uptake had stopped. Removal of catalyst and solvent followed by crystallization of the residue from acetone–hexane produced 2.74 g. (91%) of the ketal I with m.p. 178–180°, $[\alpha]^{20}D$ +52° (pyridine), no high-intensity absorption in the ultraviolet. Identity with samples prepared by methods a and b was confirmed by mixture m.p. and infrared comparison.

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Preparation of Tetraethylene Glycol Dimethacrylate

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RECEIVED JUNE 21, 1954

Various methods are available for the preparation of dimethacrylate esters of glycols.[1] These include reaction of the glycol with methacrylic acid, methacrylyl chloride or methacrylic anhydride or transesterification with methyl methacrylate. Of these, the last reaction is the most attractive from the standpoint of economics and convenience. However, in the preparation of tetraethylene glycol dimethacrylate (TEGMA), it was found that the usual procedures of transesterification were not satisfactory. Only moderate yields of TEGMA were obtained using hydroquinone or *o*-phenylenediamine as inhibitors under acidic or basic conditions, and the reactions were frequently accompanied by polymerization and gelation of the TEGMA.[2] In addition, it was difficult to remove those inhibitors, when they were used in high concentration, from TEGMA, which cannot be purified by distillation (b.p. > 160° at <1 mm.) or crystallization (forms a glass at −65°).

For these reasons, two new procedures were devised for the transesterification reaction. These methods involved the use of inhibitor–catalyst combinations of oxygen–sodium alcoholate or picric acid–sulfuric acid. The former is preferred since it gives somewhat faster rates of reaction and better yields. Both of the inhibitors prevented polymerization effectively and could be conveniently and completely removed to give good yields of satisfactory TEGMA.

Oxygen has been successfully used as an inhibitor of the polymerization of methyl methacrylate and several other monomers.[3] However, it has not been used widely as an inhibitor during the synthesis or chemical reactions of reactive vinyl monomers.[4] Contrariwise, in many such reactions oxygen is rigidly excluded. The present work indicates that the use of oxygen as a transient inhibitor can offer advantages.

The use of oxygen as an inhibitor leads to the formation of peroxidic oxidation products.[3] In our work, peroxides were substantially absent in the products formed under basic conditions. However, when sulfuric acid–air was used as the catalyst–inhibitor system, the TEGMA which was produced contained reactive peroxides (0.3% active oxygen as determined by the acetic acid–potassium iodide method[5]). These active peroxides were capable of inducing the polymerization of TEGMA in the absence of oxygen.

Base-catalyzed Transesterification Using Oxygen as Inhibitor.—Methyl methacrylate (100 g., 1.0 mole, coml.), tetraethylene glycol (59.5 g., 0.30 mole, redistilled), sodium hydride (1.3 g., 0.05 mole) and benzene (100 g., C.P.) were charged into a flask fitted with a fractionating column. Air (0.5 l./min.) was passed into the stirred reaction mixture which was immersed in a heated oil-bath (bath temperature, 95–100°; internal temperature, 81–82°). The take-off temperature of the benzene–methanol azeotrope was maintained at 54° for the first hour and below 70° for two additional hours, at the end of which nearly the theoretical amount of methanol had been collected. More benzene

(1) R. S. Corley, "Esters of Methacrylic Acid Other than Methyl Methacrylate," in E. R. Blout and H. Mark, "Monomers," Interscience Publishers, Inc., New York, N. Y., 1951.

(2) Ethylene glycol dimethacrylate, the parent compound of this series gels at only 2.9% reaction. *Cf.* C. Walling, THIS JOURNAL, **67**, 441 (1945).

(3) F. A. Bovey and I. M. Kolthoff, *Chem. Revs.*, **42**, 502–505 (1948).

(4) There is a report in the patent literature of the use of oxygen as an inhibitor during the preparation of methacrylic acid or methyl methacrylate from acetone cyanhydrin; H. R. Dittmar, U. S. Patent 2,373,464 (1945).

(5) W. E. Cass, THIS JOURNAL, **68**, 1981 (1946).