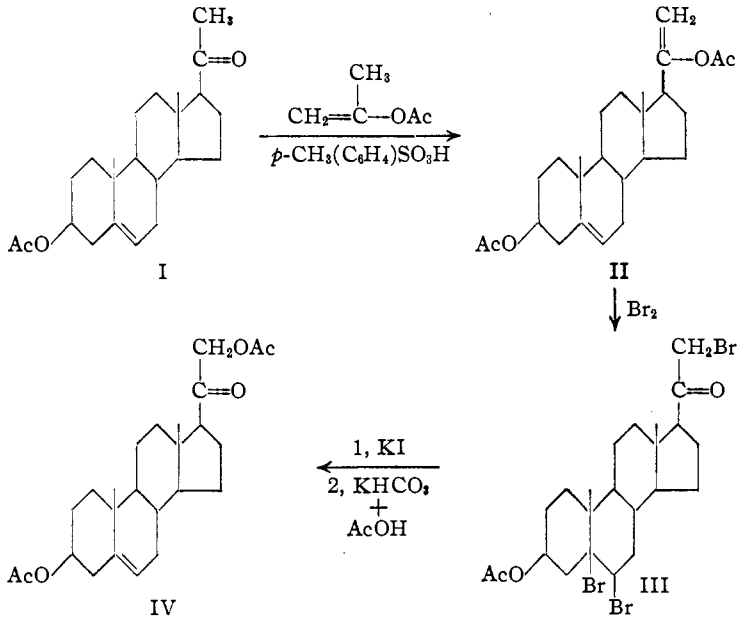
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

$\Delta^{20(21)}$-Steroid Enol Acetates[1]

BY ROBERT BRUCE MOFFETT AND D. I. WEISBLAT

Isopropenyl acetate with an acidic catalyst has been found to convert many steroid ketones to enol acetates. The enol acetates formed by this method from 20-keto steroids have the double bond between the 20- and 21-carbon atoms.

Enol acetates have been prepared from various steroid carbonyl compounds by a variety of reagents. For example cholestenone, progesterone, testosterone and androsten-3,17-dione have been converted to the corresponding 3-acetoxy-$\Delta^{3,5}$-dienes by the use of acetic anhydride with acetyl chloride,[2,3] or with sodium or potassium acetate.[4] Similarly, the latter reagent has been used to prepare enol acetates of steroid aldehydes.[5,6]



The use of acetic anhydride and *p*-toluenesulfonic acid to prepare $\Delta^{17(20)}$ enol acetates from 20-keto-steroids[7] is the basis for the excellent method of Gallagher[8] for introducing the 17α-hydroxyl group.

When the action of isopropenyl acetate with an acidic catalyst was tried on 5-pregnen-3β-ol-20-one acetate (I) we were surprised to obtain a good yield of an enol acetate different from either the the α- or β-forms prepared by Fieser and Huang-Minlon.[9] This was unequivocally found to be 3β,20-diacetoxy-5,20-pregnadiene (II) by bromination to 3β-acetoxy-5,6,21-tribromo-pregnan-20-one (III) followed by conversion to 3,21-diacetoxy-5-pregnen-20-one (IV). The bromination of an enol acetate to the corresponding α-bromoketone was employed by Fieser and Huang-Minlon[9] to prove the structure of their $\Delta^{17(20)}$ enol acetates.

A series of other 20-ketosteroids was subjected to the same treatment with isopropenyl acetate and *p*-toluenesulfonic acid. In all cases where reaction occurred the $\Delta^{20(21)}$ enol acetates (Table I) were obtained.[10] One of these, the dimethyl ester of the maleic anhydride adduct of 3β,20-diacetoxy-$\Delta^{5,7,9(11),20}$-pregnatetraene (VI) was treated with one molar equivalent of ozone and the corresponding etio acid (VII) was obtained in excellent yield.

All of the enol acetates (Table I) obtained from 20-ketosteroids with isopropenyl acetate show a characteristic band in their infrared absorption spectra[11] at about 1670 cm.$^{-1}$ produced by the terminal 20–21 carbon–carbon double bond. This band is not present in the spectra of the $\Delta^{17(20)}$-enol acetates prepared by the method of Gallagher[7] or Fieser.[9]

The action of isopropenyl acetate on 3- and 17-ketosteroids[12] and on a 22-aldehyde results in the formation of the same type of enol acetates that have been reported for other reagents.[1-4] For example, progesterone gives 3,20-diacetoxy-$\Delta^{3,5,20}$-pregnatriene whose ultraviolet absorption spectrum,[13] given in Fig. 1, is consistent with the $\Delta^{3,5}$-diene structure.[14]

The presence of a double bond in the 16–17-position did not interfere with the formation of $\Delta^{20(21)}$-enol acetates, as is shown by two examples whose ultraviolet[13] absorption spectra (Fig. 1) show conjugated diene systems, and whose infrared[11] absorption spectra include the bands at about 1670 cm.$^{-1}$ indicative of terminal carbon–carbon double bonds.

A number of steroid ketones failed to give enol

(1) This material was originally submitted in the form of a Communication to the Editor on October 23, 1951.

(2) H. H. Inhoffen, *Ber.*, **69**, 2141 (1936).

(3) U. Westphal, *ibid.*, **70**, 2128 (1937).

(4) L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, **19**, 806, 1371 (1936); U. S. Patent 2,248,438 (1941).

(5) F. W. Heyl and M. E. Herr, THIS JOURNAL, **72**, 2617 (1950).

(6) W. Bergmann and P. G. Stevens, *J. Org. Chem.*, **13**, 10 (1948).

(7) C. W. Marshall, T. H. Kritchevsky, S. Lieberman and T. F. Gallagher, THIS JOURNAL, **70**, 1837 (1948).

(8) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(9) L. F. Fieser and Huang-Minlon, THIS JOURNAL, **71**, 1840 (1949).

(10) Since the completion of this work C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951), have reported that *in benzene solution* isopropenyl acetate and *p*-toluenesulfonic acid do not react with 20-ketosteroids.

(11) The infrared absorption spectra of these enol acetates were obtained by Dr. James L. Johnson and associates in our Physics Department and will be published separately.

(12) W. G. Dauben, J. F. Eastham and R. A. Micheli have recently reported the use of isopropenyl acetate with an acid catalyst to prepare enol acetates from 3-keto sterols: THIS JOURNAL, **73**, 3260, 4496 (1951).

(13) The ultraviolet absorption spectra were obtained by Dr. James L. Johnson and Mr. Lambertus Scholten in our Physics Department.

(14) Louis and Mary Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 188.

TABLE I

ENOL ACETATES

Name	Yield,[a] %	M.p., °C.	Crystallizing solvent	$[\alpha]^{25}D$[15][b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found[15]	Hydrogen Calcd.	Hydrogen Found[15]	Acetyl Calcd.	Acetyl Found[15]
3β,20-Diacetoxy-5,20-pregnadiene	67	122.5–123.5	MeOH	−45.8	$C_{25}H_{36}O_4$	74.95	74.98	9.06	8.76	21.49	21.98
3β,20-Diacetoxy-5,7,9(11),20-pregnatetraene	31	163–166	CH_2Cl_2 + MeOH	+262.3	$C_{25}H_{32}O_4$	75.76	75.86	8.14	8.06	21.71	22.43
3,20-Diacetoxy-3,5,20-pregnatriene	62.5	83–87	MeOH	−119	$C_{25}H_{34}O_4$	75.36	75.44	8.60	8.53	21.61	22.88
3β,20-Diacetoxy-5,16,20-pregnatriene	58	144–146	MeOH	−57.7	$C_{25}H_{34}O_4$	75.36	75.36	8.60	8.50	21.61	21.13
3β,20-Diacetoxy-16,20-allopregnadiene	65	152.5–154	Me_2CO	+10	$C_{25}H_{36}O_4$	74.95	75.04	9.06	8.90	21.49	21.63
Maleic anhydride adduct of 3β,20-diacetoxy-5,7,9(11),20-pregnatetraene[c]	48	219–220.5	Me_2CO + i-Pr_2O	+79	$C_{29}H_{34}O_7$	70.42	70.40	6.93	6.82	17.41	17.82
Dimethyl ester of the maleic anhydride adduct of 3β,20-diacetoxy-5,7,9(11),20-pregnatetraene[c]	63	196.5–198	Me_2CO	+86.3	$C_{31}H_{40}O_8$	68.86	68.73	7.46	7.42	15.92	15.93
Maleic anhydride adduct of 3β,20-diacetoxy-9,11-oxido-5,7,20-pregnatriene[c]	76	245–249	Me_2CO	+14.2	$C_{29}H_{34}O_8$	68.22	68.43	6.71	6.83	16.86	17.48
Dimethyl ester of the maleic anhydride adduct of 3β,20-diacetoxy-9,11-oxido-5,7,20-pregnatriene[c]	40	215–217	CH_2Cl_2 + MeOH	−3.8	$C_{31}H_{40}O_9$	66.89	67.07	7.24	7.20	15.46	15.51
3β,17-Diacetoxy-5,16-androstandiene	56	146–147	MeOH	−47.7	$C_{23}H_{32}O_4$	74.16	74.28	8.66	8.62	23.11	22.70
3β,22-Diacetoxy-5,20(22)-bisnor-cholediene[d]	35	153.5–157	Me_2CO + H_2O	.....	$C_{26}H_{38}O_4$	...	...	..	..	...	...

[a] The yields are reported for the first crop of crystalline material melting not lower than 10° below the purest sample obtained. Further yields could be obtained from the filtrates. [b] Rotations were taken in chloroform in concentrations of approximately 1 g./100 ml. [c] The steroid ketones containing the maleic anhydride or dimethyl maleate groupings were prepared in these laboratories by Robert H. Levin and co-workers and reported before the Division of Organic Chemistry of the American Chemical Society at its 120th Meeting at New York City, Sept. 3–7, 1951. Abstract p. 6L. [d] This compound was identical with that prepared by Heyl and Herr,[5] and gave no mixed melting point depression with it.

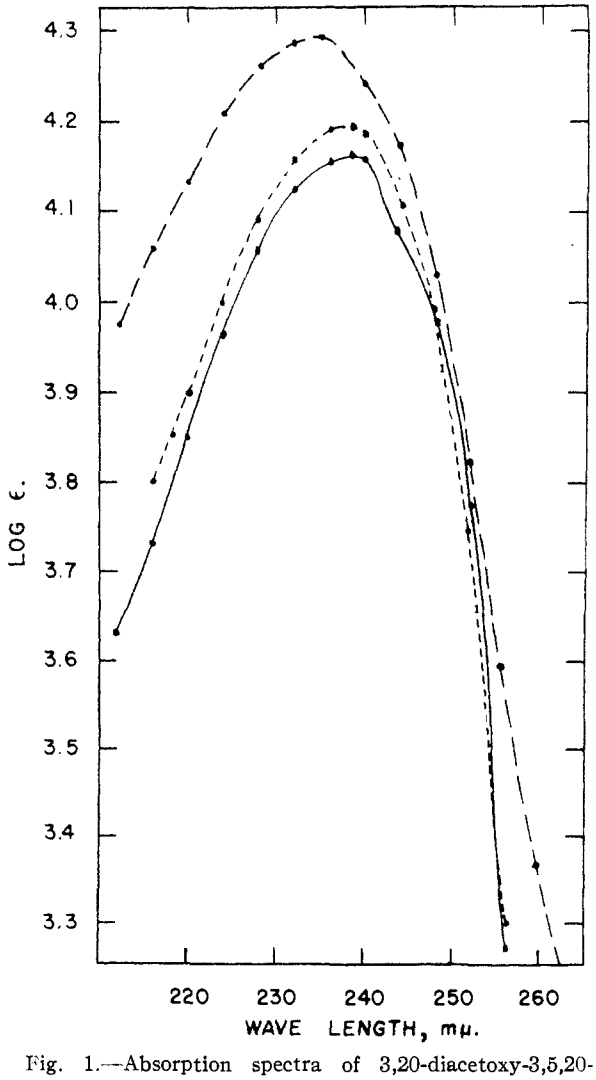
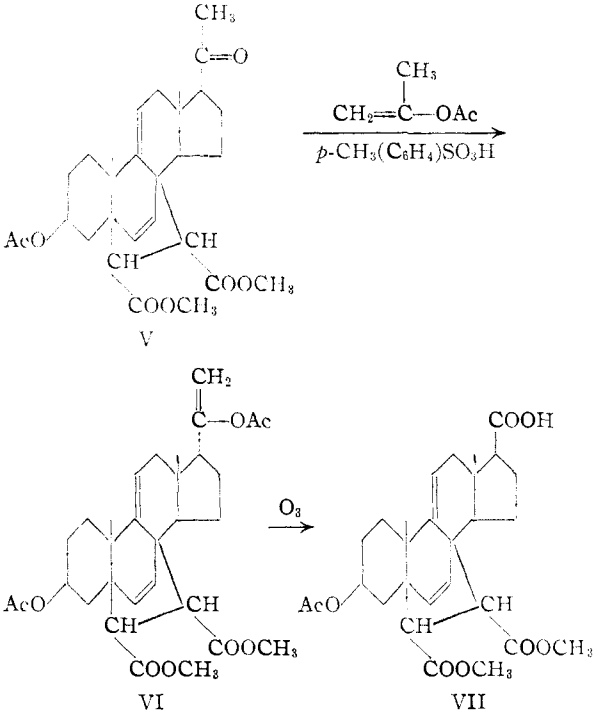


Fig. 1.—Absorption spectra of 3,20-diacetoxy-3,5,20-pregnatriene, (— — —); 3β,20-diacetoxy-16,20-allopregnadiene, (——); 3β,20-diacetoxy-5,16,20-pregnatriene, (------).



acetates with isopropenyl acetate under the conditions of our experiments. Thus 3α-acetoxy-11-keto-24,24-diphenyl-Δ^{23}-cholene, and methyl 3α-acetoxy-12-ketocholanate were recovered unchanged in good yields. Substituents in either the 17 or 21 positions of 20-keto steroids interfered with the formation of enol acetates. Thus 21-acetoxy-5-pregnen-3β-ol-20-one gave only the 3-acetylated derivative and 3β-acetoxy-16,17-oxido-5-pregnen-20-one, the dimethyl ester of the maleic anhydride adduct of 3β-acetoxy-17-bromo-5,7,-9(11)-pregnatrien-20-one, and the dimethyl ester of the maleic anhydride adduct of 3β,21-diacetoxy-5,7,9(11)-pregnatrien-20-one, were recovered unchanged.

Experimental[15]

General Procedure for Preparation of the Enol Acetates.—A solution of 1 g. of the appropriate keto (or aldehydo) steroid and 0.15 g. of *p*-toluenesulfonic acid monohydrate in about 20 ml. of isopropenyl acetate[16] was placed in a 50-ml. flask fitted with a six-inch fractionating column. This solution was slowly distilled for about 10 hours. More isopropenyl acetate was added from time to time to keep the volume above 10 ml. After cooling the solution remaining in the flask, about 1 g. of solid sodium bicarbonate was added and the remaining isopropenyl acetate was removed by distillation under reduced pressure at less than 30°. The residue was shaken with ether[17] and ice-water and the aqueous layer was extracted with more ether. The combined ether solution was washed with water, then with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure at less than 30° and the residue crystallized from the solvent indicated in Table I.

3β,21-Diacetoxy-5-pregnen-20-one (IV).—A solution of 1 g. (0.0025 mole) of 3β,20-diacetoxy-5,20-pregnadiene (II) in 25 ml. of methylene chloride was cooled to below −10° in an ice–salt-bath. To this was added dropwise during 25 minutes with stirring 16.6 ml. (0.005 mole) of a 0.602 normal bromine solution in methylene chloride. The resulting colorless solution was distilled to dryness under reduced pressure at a temperature below 20°. The residue of crude bromo compound (III) was dissolved in 25 ml. of benzene and a solution of 5 g. of sodium iodide in 25 ml. of absolute ethanol was added.[18] After standing at room temperature for 26 hours the mixture was diluted with water and extracted twice with ether. The ether solution was washed twice with cold 1% sodium hydroxide solution, then well with water and dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure at a temperature below 30° gave crude crystalline 3β-acetoxy-21-iodo-5-pregnen-20-one. This was dissolved in 35 ml. of acetone and 5 g. of potassium bicarbonate and 3 ml. of glacial acetic acid were added.[19] The mixture was refluxed with stirring for 12 hours and then diluted with ice-water and extracted twice with ether. The ether solution was washed with water, then with cold dilute sodium thiosulfate, then twice with water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure at a temperature below 30° and the residue was reacetylated with 5 ml. of pyridine and 3 ml. of acetic anhydride at room temperature for one hour. Ice-water was added and the mixture was extracted twice with ether. The ether solution was washed with cold dilute hydrochloric acid, water, cold dilute sodium bicarbonate solution, twice with water, and dried over anhydrous sodium sulfate. The ether solution was distilled at atmospheric pressure. When the volume of the solution was about 10 ml. crystallization started. After cooling the crystals were collected, washed with ether and dried giving 0.44 g. of white crystals, m.p. 159–162°. A mixed melting point with an authentic sample of 3β,21-diacetoxy-5-pregnen-20-one gave no depression. An additional yield of 0.07 g. was obtained from the filtrate.

Dimethyl Ester of the Maleic Anhydride Adduct of 3β-Acetoxy-5,7,9(11)-etiocholatrienic Acid (VII).—A solution of 0.69 g. (1.27 millimoles) of the dimethyl ester of the maleic anhydride adduct of 3β,20-diacetoxy-5,7,9(11),20-pregnatetraene (VI) in 35 ml. of methylene chloride was cooled by a Dry Ice–acetone mixture and ozonized oxygen was passed in until 61 mg. (17% excess) of ozone was absorbed. The reaction mixture was diluted with 20 ml. of acetic acid and concentrated under reduced pressure below 40° to a volume of about 10 ml. This was diluted with 25 ml. more acetic acid and 5 g. of zinc dust was added in several portions. After filtering, the solution was poured into about 20 ml. of water. The white precipitate which formed was collected and dried, weight 0.55 g., m.p. 231–248°.[20]

This was recrystallized first from acetone and then from methanol giving white crystals m.p. 255–259° (dec.), $[\alpha]^{25}D$ +80.6° (0.57% in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{36}O_8$: C, 67.17; H, 7.25; neut. equiv., 501. Found: C, 67.16; H, 7.13; neut. equiv., 520.

The filtrates were worked up for neutral product but only a small amount of unchanged enol acetate was obtained.

(15) All melting points were taken on a Fisher–Johns melting point block. Elementary analyses and rotations are by Mr. Wm. A. Struck and associates of our Microchemical Laboratory.

(16) In some cases the ketosteroids were not soluble in isopropenyl acetate but they dissolved as the reaction proceeded.

(17) In a few cases the enol acetates were not soluble in ether and methylene chloride was used for the extraction.

(18) This conversion of the tribromide to 3β-acetoxy-21-iodo-5-pregnen-20-one is essentially the method described by P. L. Julian and W. J. Karpel [THIS JOURNAL, **72**, 362 (1950)] for an analogous conversion.

(19) This method for converting a 21-iodo compound to a 21-acetoxy compound is essentially that of G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4081 (1950).

(20) The above part of this experiment was carried out by Dr. A. Vern McIntosh, Jr., in these laboratories.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON]

Reactions of 3-Thianaphthenylmethylmagnesium Chloride

BY RUSSELL GAERTNER

Mixtures of the products formed by both the normal and abnormal reactions were obtained when this Grignard reagent was treated with carbon dioxide, formaldehyde and ethylene oxide. Benzoyldurene and benzophenone reacted normally. Exclusively abnormal reaction occurred with ethyl chlorocarbonate. The implications concerning the aromaticity of thianaphthene are considered.

If, as suggested in preceding reports,[1,2] the extent of abnormal reaction of an heteroarylmethyl Grignard reagent is a criterion of the aromatic character of the nucleus, or more accurately a measure of the interaction of the neighboring unsaturation with the remainder of the nucleus, the position of the halomethyl group in an unsymmetrical nucleus should not affect the ratio of the two types of product. Since 2-thianaphthenylmethylmagnesium chloride reacted exclusively with rearrangement,[2] a comparison with the properties of the 3-isomer afforded a test of the hypothesis.

3 - (Chloromethyl) - thianaphthene (I) was smoothly converted to the Grignard reagent (II) in the cyclic reactor; in some runs a small amount of a coupling product, probably 1,2-bis-(3-thianaphthenyl)-ethane, was isolated. The reagent was treated with carbon dioxide, ethyl chlorocarbonate, ethylene oxide, formaldehyde, benzoyldurene and benzophenone. Only ethyl chlorocarbonate gave exclusively the abnormal product, 3-methyl-2-thianaphthoic acid (III), also prepared

(1) R. Gaertner, THIS JOURNAL, **73**, 3934 (1951). This paper contained a summary of previous work in the field.

(2) R. Gaertner, *ibid.*, **74**, 766 (1952). Benzoyldurene was an exception in that it reacted normally; the carbinol was isolated and dehydrated.