with an additional 150 cc. of ether. The combined ether solutions were dried with magnesium sulfate. The drying agent and ether were removed, and the residue was distilled from a 50-cc. Claisen flask. The *p*-dimethylaminostyrene boiled at 85–90° (2.5 mm.). If any dehydration occurred on distillation the water was separated, the product redissolved in ether and dried again. Redistillation in a three-plate, helices-packed column gave a boiling point of 90–91° (2.5–3 mm.); $n^{20}D$ 1.6010. The yield was 11 g. or 45% of the theoretical amount. Several experiments produced lower yields with a large amount of polymeric residue. A high-boiling polymeric residue could not be distilled.

Anal.[14] Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.89. Found: C, 81.44; H, 8.91.

A picrate was obtained as a yellow powder from 95% ethanol, m. p. 93–94°.

If the product from the decomposition of the Grignard complex was not distilled, a small yield of white crystals was obtained, which, when recrystallized from petroleum ether, melted at 58.5–59°. Sachs and Sachs[12] report 60° for *p*-N,N-dimethylaminophenylmethylcarbinol.

Anal. Calcd. for $C_{10}H_{15}ON$: N, 8.39. Found: N, 8.37.

Polymerization of *m*-Trifluoromethylstyrene and *m*-Methylstyrene.—In a Pyrex test-tube was placed 1 g. of the monomer. The test-tube was suspended under an ultraviolet lamp and left there until a hard polymer had been formed (twenty-four hours). The polymer was dissolved in 50 cc. of benzene and precipitated by slowly dropping the solution into 300 cc. of methanol with vigorous mechanical stirring. This process was repeated and the powder obtained was dried for one week in a vacuum desiccator.

Polymerization of *p*-N,N-Dimethylaminostyrene. (A) Bulk.—About 1 g. of *p*-N,N-dimethylaminostyrene was heated for twenty-four hours at 120° in a small test-tube. At the end of this period a hard resin, completely soluble in benzene, had formed.

(B) Solution.—In a 25-cc. Erlenmeyer flask was placed 0.8 g. of *p*-N,N-dimethylaminostyrene, a small amount of benzoyl peroxide, and 15 cc. of purified dioxane. This was gently refluxed for twenty-four hours. The cooled solution was slowly dropped into 200 cc. of methyl alcohol with vigorous stirring. No powder or gum precipitated, and the solution was then evaporated to dryness. A heavy gum resulted, completely soluble in benzene. An attempt to precipitate this gum as a powder failed.

The following table summarizes the data on these polymers.

TABLE I

Polymer, -styrene		*m*-Trifluoromethyl	*m*-Methyl-	*p*,N,N-Dimethylamino- bulk
Approx. mol. wt.[a]		7346	33000	1620
Softening point, °C.		130–155	117–122	80–95
Solubility in benzene		+	+	+
Empirical formula		$C_9H_7F_3$	C_9H_{10}	$C_{10}H_{13}N$
Analyses, %	Calcd. C	62.79	91.46	81.58
	Calcd. H	4.10	8.54	8.89
	Calcd. N	...	...	9.51
	Found C	62.73	90.08	80.45
	Found H	4.25	8.26	8.09
	Found N	...	...	8.77

[a] These approximate molecular weights were determined by viscosity measurements with the use of an equation developed by Kemp and Peters for the determination of the molecular weight of polystyrene using the K' value for styrene [Kemp and Peters, *Ind. Eng. Chem.*, **34**, 1097 (1942)].

Summary

1. The preparation of *m*-trifluoromethyl-styrene is described. New procedures for the preparation of *m*-methylstyrene, *m*-nitrostyrene and *p*-N,N-dimethylaminostyrene have been developed.

2. The polymers of these monomers, except *m*-nitrostyrene, have been prepared and characterized.

URBANA, ILLINOIS RECEIVED JANUARY 15, 1946

(14) Microanalyses by Miss Theta Spoor, University of Illinois.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Studies in the Synthesis of the Antirachitic Vitamins. II. Δ^5-Androstenol-3 and its Partial Dehydrogenation with Benzoquinone[1,2]

BY NICHOLAS A. MILAS AND CHARLES R. MILONE[3]

The simplest sterol which would have the same nuclear structure as that found in the antirachitic provitamins is $\Delta^{5,7}$-androstadiene-3-ol. This could be prepared from Δ^5-androstenol-3, either by the method of Windaus, Lettré and Schenck[4] or that of Milas and Heggie.[5] When the latter method was used, a product was obtained which contained 16% of $\Delta^{5,7}$-androstadiene-3-ol. Irradiation of this crude product under standard conditions produced a mixture which was biologically inactive at a level of 4000 U. S. P. XI units of vitamin D per gram.[6] $\Delta^{5,7}$-Androstadiene-3,17-diol,[7] another simple sterol containing the provitamin D nuclear structure, was found to form no antirachitic products upon irradiation.[6,8] Two explanations may be advanced for the failure of these simple substances to form antirachitically active products upon irradiation. Much longer time of irradiation than that used under standard conditions may be

(1) Last paper, Milas and Alderson, Jr., THIS JOURNAL, **61**, 2534 (1939).

(2) The present paper was originally submitted on March 20, 1940.

(3) Abstracted from a portion of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, M. I. T., August, 1939. Present address: Goodyear Rubber Company.

(4) Windaus, Lettré and Schenck, *Ann.*, **520**, 98 (1935).

(5) Milas and Heggie, THIS JOURNAL, **60**, 984 (1938); Sah, *Rec. trav. chim.*, **59**, 454 (1940); *cf.* Criegee, *Ber.*, **69B**, 2758 (1935); Arnold and Collins, THIS JOURNAL, **61**, 1407 (1939).

(6) Reported to the authors by Professor Robert S. Harris.

(7) Butenandt, Hausemann, Dresler and Meinster, *Ber.*, **71B**, 1316 (1938).

(8) Dimroth and Paland, *ibid.*, **72B**, 187 (1939).

necessary to cause the opening of ring B. It may also be possible that the side chain plays a specific biological rôle in imparting antirachitic properties to the rest of the molecule, and even if ring B were opened the substance formed without the side chain may be devoid of antirachitic properties.

Attempts to prepare Δ⁵-androstenol-3 through a sequence of reactions by reducing catalytically dehydroandrosterone acetate, replacing the hydroxyl group on carbon seventeen by bromine and subsequently replacing this by a hydrogen atom were unsuccessful, since we were unable, after several trials, to reduce the keto group by the method of Ruzicka and Wettstein.[9]

This was finally prepared by way of the Wolff–Kishner reduction.[10] While our work was under way, Raoul and Meuniers[11] used the same reduction for the same purpose but the product obtained did not agree in properties with our preparation. Since our work, Heard and McKay[12a] and Butenandt and Suranyi[12b] have made the same product by the same procedure. The physical properties of our product and the acetate derived from it correspond closely to those given by Heard and McKay.

TABLE I

PHYSICAL PROPERTIES OF Δ⁵-ANDROSTENOL-3 AND DERIVATIVES

Investigator	Melting points, °C. Alcohol	Acetate	Benzoate
De Fazzi and Pirrone	202–203[a]	185–186[a]	.....
Raoul and Meunier	104[a]	114	.....
Heard and McKay	137	94	.....
Butenandt and Suranyi	131[a]	91–93[a]	.....
Present authors	136–138[a]	92–94[a]	173–174[a]

[a] Analysis reported.

Experimental

Δ⁵-Androstenol-3 (*cis* 3:10).—The semicarbazone (1.15 g.) of dehydroandrosterone[13] was heated in a sealed tube for seven hours at 180–185° with a solution of 14 cc. of absolute ethanol containing 1 g. of sodium. The mixture was then poured in 90 cc. of water, neutralized with dilute sulfuric acid and extracted with ether. The gummy material obtained from the ether extract, was dissolved in 10 cc. of absolute alcohol and to the solution added 1 g. of Girard reagent P,[14] 1 cc. of glacial acetic acid, and the mixture refluxed for one hour, then poured in 80 cc. of ice water containing an amount of alkali equivalent to 0.9 of the acidity of the solution. The non-ketonic oily precipitate was extracted with ether, the ether removed and the residue distilled at 150° (0.0005 mm.) whereby 150 mg. of a white solid was obtained; m. p. 99–105°. This melting point could not be improved even after several recrystallizations. The difficulty of crystallizing this product was attributed to the presence in the mixture of traces of the epimeric Δ⁵-androstenol-3 (*trans* 3:10).

The desired *cis* isomer was separated from the mixture by means of its insoluble digitonide, the digitonide of the *trans* isomer being much more soluble in ethanol. The digitonide of the *cis* isomer was decomposed with pyridine and the final product recrystallized from ethyl acetate (needles); m. p. 136–138°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.2; H, 11.0. Found: C, 82.0; H, 11.1.

The *cis* isomer was produced in much higher yields when the Wolff–Kishner reduction was carried out at a temperature of 165–170° for a slightly longer period of nine hours. A product was obtained which, without purification via the digitonide, had a m. p. of 130–132° and a mixed m. p. with the purified material of 133–136°.

Δ⁵-Androstenol-3-acetate (*cis* 3:10).—This substance was prepared by refluxing Δ-⁵androstenol-3 (*cis* 3:10) with acetic anhydride. The acetate was recrystallized from methanol; m. p. 92–94°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.1. Found: C, 78.9, 79.3; H, 9.7, 9.9.

Δ⁵-Androstenol-3-benzoate (*cis* 3:10).—This ester was prepared in pyridine from Δ⁵-androstenol-3 (*cis* 3:10) and benzoyl chloride. The crude benzoate was recrystallized from a 50–50 ether–methanol mixture; m. p. 173–174°.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.5; H, 9.0. Found: C, 82.5, 82.4; H, 9.3, 9.3.

Dehydrogenation of Δ⁵-Androstenol-3-benzoate with Benzoquinone.[5]—A mixture of Δ⁵-androstenol-3-benzoate (0.5 g.) and benzoquinone (0.28 g.) was heated in a sealed evacuated tube at 140° for four and one-half hours. The reaction product was then dissolved in ether and the ethereal solution shaken first with a 20% solution of sodium hydrosulfide to reduce any unused quinone to hydroquinone, then extracted with a 10% solution of sodium hydroxide to remove the hydroquinone. The final product exhibited in the ultraviolet a strong bluish fluorescence which is characteristic for the presence of a conjugated system similar to that present in the antirachitic provitamins. The benzoate was then saponified with methyl alcoholic potash and the product obtained purified from methyl alcohol. An ultraviolet absorption spectrum of the final product in absolute ethanol showed the presence of two bands: a prominent band with a maximum at 255 mμ having a molecular extinction coefficient of 1650, and a weaker one at 280–282 mμ. Δ⁵-Androstenol-3 exhibited no selective absorption in this region. A comparison of the coefficient of the prominent band with the analogous band of ergosterol indicated that Δ⁵,⁷-androstadiene-3-ol was present in the mixture to the extent of about 16%. An attempt to purify the dienol by chromatographic absorption was unsuccessful.

Addition of Maleic Anhydride to Δ⁵,⁷-Androstadiene-3-benzoate.—A quantity of 0.37 g. of the crude dehydrogenated Δ⁵-androstenol-3-benzoate in 4 cc. of dry xylene was heated in a sealed evacuated tube for ten hours at 135–140° with 0.1 g. of freshly distilled maleic anhydride. The xylene and excess maleic anhydride were then distilled in vacuum and the residue saponified with methyl alcoholic potash. After acidification and extraction with ether, a solid product was obtained which was freed from benzoic acid by a thorough digestion with boiling petroleum ether. The final maleic acid adduct was further purified by precipitating it from chloroform with petroleum ether; m. p. 185–190° (with decomposition).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.14; H, 8.25. Found: C, 71.7; H, 8.48.

Irradiation of Δ⁵,⁷-Androstadiene-3-ol.—Fifty-five mg. of the crude Δ⁵,⁷-androstadiene-3-ol was dissolved in 190 cc. of anhydrous ether and the solution irradiated for thirty minutes in a quartz flask and in an atmosphere of nitrogen with a quartz-mercury lamp under conditions exactly identical with those used for irradiation of ergosterol. The product was then tested biologically by Professor Robert S. Harris who reported no activity at a level of 4000 U. S. P. XI vitamin D units per gram.

Δ⁵-Androstene-3,17-diacetate.—Δ⁵Androstene-3,17-diol (1.85 g.), prepared from dehydroandrosterone, was acetylated with acetic anhydride. The crude diacetate was recrystallized from methanol, yield 1.7 g.; m. p. 158–159°,

(9) Ruzicka and Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).
(10) Wolff, *Ann.*, **394**, 86 (1912).
(11) Raoul and Meuniers, *Compt. rend.*, **207**, 681 (1938).
(12a) Heard and McKay, *J. Biol. Chem.*, **140**, lvi (1941).
(12b) Butenandt and Suranyi, *Ber.*, **75**, 591 (1942).
(13) Butenandt, *Z. physiol. Chem.*, **237**, 69 (1935).
(14) Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

which agrees with that reported by Ruzicka and Wettstein.[9]

Δ^5-Androstene-3,17-dibenzoate.—The dibenzoate was prepared by heating on the water-bath a mixture of Δ^5-androstene-3,17-diol, benzoyl chloride and pyridine. The crude dibenzoate was recrystallized from methanol; m. p. 203–205°.

Anal. Calcd. for $C_{33}H_{38}O_4$: C, 79.5; H, 7.6. Found: C, 79.3; H, 7.8.

Dehydrogenation of Δ^5-Androstene-3,17-diacetate with Benzoquinone.—A mixture of 0.3 g. of the diacetate and 0.094 g. of benzoquinone was heated in a sealed evacuated tube at 130° for three hours. The product from this reaction was dissolved in ether and the solution thoroughly shaken with a 20% solution of sodium hydrosulfite, then extracted several times with a 10% sodium hydroxide solution, dried, and the ether removed. The slightly discolored residue was purified from methanol and a product was obtained the spectrum of which showed a single band with a maximum at 288 mμ having a molecular extinction coefficient of 1116. Δ^5-Androstene-3,17-diacetate exhibited no selective absorption in this region. A comparison of the extinction coefficient with that of ergosterol (10,600 at 282 mμ) indicated that the material contained the desired dehydrogenated product to the extent of about 10%.

Irradiation of $\Delta^{5,7}$-Androstadiene-3,17-diol.—A sample of the partially dehydrogenated diacetate was hydrolyzed with methyl alcoholic potash and the non-saponifiable diol irradiated in ether for four hours using a quartz-mercury lamp. The product was then assayed biologically by Professor R. S. Harris who reported no activity at a level of 10,500 U. S. P. XI vitamin D units per gram. Almost a year after these experiments were performed, Dimroth and Paland[8] reported similar biological results with this substance made by a different procedure.

The authors wish to express their appreciation for a generous sample of dehydroandrosterone supplied to one of us (N. A. M.) by the Schering Corporation through the courtesy of Dr. Erwin Schwenk.

Summary

1. Δ^5-Androstenol-3(*cis* 3:10) and its acetate and benzoate were prepared in the pure state.

2. The partial dehydrogenation of Δ^5-androstenol-3-benzoate and Δ^5-androstene-3,17-diacetate with benzoquinone has been studied. The irradiated dehydrogenation products were devoid of antirachitic action when tested at levels of 4000 and 10,500 U. S. P. XI vitamin D units per gram, respectively.

CAMBRIDGE, MASSACHUSETTS
RECEIVED NOVEMBER 30, 1945

[CONTRIBUTION FROM THE ARMOUR LABORATORIES]

The Ultraviolet Absorption Spectra of Allyl and Propenyl Substituted Derivatives of Diethylstilbestrol and Hexestrol

BY EMIL KAISER AND VIRGIL L. KOENIG

In a previous communication[1] the preparation of 3,3′-allyl and 3,3′-propenyl diethylstilbestrol and hexestrol are described. The 3,3′-allyl substituted derivatives were rearranged by heating in alkaline solution to compounds which were assumed to be 3,3′-propenyl derivatives in analogy to reactions reported in the literature.[2]

Obviously, the reaction described by Balbiano[3] for the differentiation between allyl and propenyl groups cannot be applied here inasmuch as the large number of double bonds would introduce complications. For this reason it was decided to examine the ultraviolet absorption spectra of these compounds. An important difference in the structure of the 3,3′-allyl and 3,3′-propenyl derivatives under discussion here resides in the position of the double bonds of the side chains. In the propenyl compounds the double bonds are in a conjugated position to the double bonds of the aromatic nuclei; in the allyl derivatives the double bonds are not conjugated. Since the presence of the double bonds is shown by the shape of the ultraviolet absorption curves of organic compounds, it was thought possible to demonstrate the shifting of the double bonds by comparing the absorption spectra of 3,3′-allyl derivatives of diethylstilbestrol and hexestrol with the absorption spectra of 3,3′-propenyl derivatives of diethylstilbestrol and hexestrol.

Acknowledgment.—The authors are indebted to Professor F. C. Koch for his helpful criticism of the manuscript and for his encouragement during the work.

Experimental

The ultraviolet absorption curves of the following compounds were determined: diethylstilbestrol, diallyl ether of diethylstilbestrol, 3,3′-allyl diethylstilbestrol, 3,3′-propenyl diethylstilbestrol and hexestrol, hexestrol diallyl ether, 3,3′-allylhexestrol and 3,3′-propenylhexestrol. The diethylstilbestrol and hexestrol were recrystallized from commercial preparations. The other compounds were prepared according to a previous communication.[1] Acetone-free absolute methanol, distilled from alkali, was used as solvent. The concentration of the solutions was 0.005%.

The measurements were made on a Beckman spectrophotometer using the hydrogen discharge tube as the source of light. Transmittance values were determined at 10 millimicron increments from wave length 220 millimicrons to 400 millimicrons. Extinction values were obtained from the transmission values and, from these, molecular extinctions were calculated and used for plotting the graphs.

Discussion

In Fig. 1 the absorption spectra of diethylstilbestrol, diallyl ether of diethylstilbestrol, 3,3′-

(1) Kaiser and Svarz, THIS JOURNAL, **68**, 636 (1946).

(2) "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 19.

(3) Balbiano, *Ber.*, **48**, 394 (1915).