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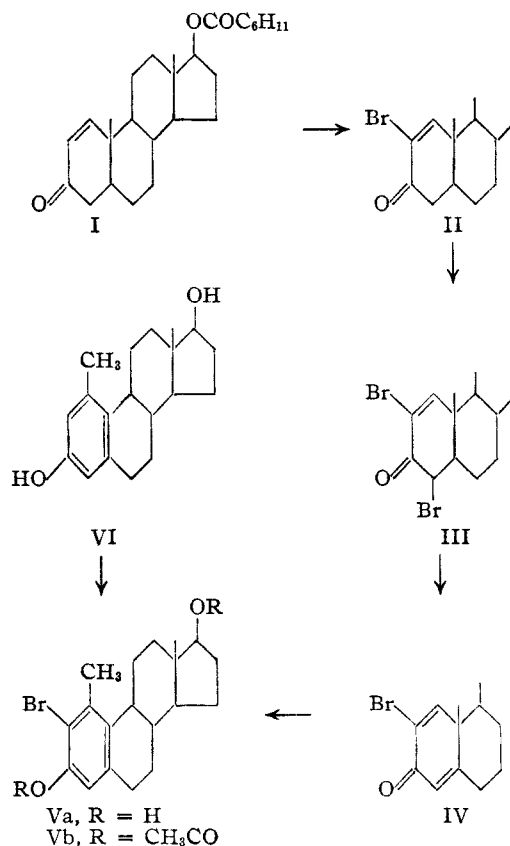
The Preparation and Dienone-Phenol Rearrangement of 2-Bromo-1,4-androstadien-17-ol-3-one 17-Hexahydrobenzoate

BY CARL DJERASSI AND CAESAR R. SCHOLZ

In 1944, Huang-Minlon and co-workers¹ described the dienone-phenol rearrangement of bromosantonin to bromodesmotroposantonin. In connection with our work on such rearrangements in the steroid series,^{2,3} we have studied the preparation and rearrangement of a brominated dienone, 2-bromo-1,4-androstadien-17-ol-3-one-17-hexahydrobenzoate (IV).⁴ A recent report of such a rearrangement in the dihydronaphthalene series⁵ prompts us to record our results at this time.

The Δ^1 -2-bromo derivative II, required as starting material, has been prepared previously by dehydrobromination of the corresponding 2,2-dibromo-3-ketosteroid.^{2,3,6} For comparison purposes, and also as an alternate synthesis for compounds of type II, we have studied the bromination of Δ^1 -testosterone hexahydrobenzoate (I). With either bromine or pyridine hydrobromide perbromide⁷ in glacial acetic acid, the ketone I took up one mole of bromine with the simultaneous evolution of hydrogen bromide. Since the reaction product was the Δ^1 -2-bromo ketone II, it is evident that the primary phase was addition of bromine to the double bond, followed by spontaneous loss of hydrogen bromide. By comparison, the bromination of the Δ^1 -2-bromo-3-ketone II proceeded at a very much slower rate and resulted in the stable substitution product III. The structure of the Δ^1 -2,4-dibromo ketone III was proven by dehydrobromination with collidine, which led in 80% yield to the desired 2-bromo-1,4-androstadien-17-ol-3-one 17-hexahydrobenzoate (IV).⁸ In the bromination of II leading to III, the net result is one of substitution rather than addition, but the reaction may also have occurred through primary addition to the double bond to form a 1,2,2-tribromo-3-ketone which rearranged to the unstable 1,2,4-tribromo isomer, followed by spontaneous loss of hydrogen bromide to yield ultimately III.

The dienone-phenol rearrangement of the brominated dienone IV occurred readily in acetic anhydride-sulfuric acid solution with the formation of 1-methyl-2-bromoestradiol (V),⁹ which was purified in the form of its diacetate (Vb). 1-Methylestradiol (VI),² on monobromination should lead either to Va or the isomeric 1-methyl-4-bromoestradiol. Bromination of VI with pyridine hydrobromide perbromide⁷ was found to proceed rapidly, resulting in a good yield of a monobromo-phenol, which was found to be identical with Va¹⁰ prepared from IV by the dienone-phenol rear-



(1) Huang-Minlon, Lo and Chu, *THIS JOURNAL*, **66**, 1954 (1944).

(2) Wilds and Djerassi, *ibid.*, **68**, 1712, 1715, 2125 (1946).

(3) Djerassi and Scholz, *ibid.*, **69**, 2404 (1947).

(4) We are refraining at this time from assigning a configuration to the 17-hydroxyl group of the compounds described in this paper, which are all derived from dihydrotestosterone. In our earlier papers (ref. 2 and 3), the (α) configuration was employed, but recent work summarized by Miescher ("Recent Progress in Hormone Research," Vol. III, in press) seems to indicate that the 17-hydroxyl group possesses the (β) configuration (*cis* to the C-13 methyl group).

(5) Arnold, Buckley and Richter, *THIS JOURNAL*, **69**, 2322 (1947).

(6) Inhoffen and Zuehlendorf, *Ber.*, **76**, 233 (1943).

(7) Djerassi and Scholz, *THIS JOURNAL*, **70**, 417 (1948).

(8) An examination of the ultraviolet absorption spectra of the three unsaturated ketones II, III and IV (Fig. 1) shows that introduction of a bromine atom in II shifts the maximum from 255 to 261 $m\mu$ (III), but that this bathochromic shift is nullified in converting III to the dienone IV, which again shows a maximum around 255 $m\mu$.

(9) On the basis of the reaction conditions and considering the reaction mechanism (ref. 5), it is unlikely that rearrangement of the 2-bromo substituent to the 4-position should have occurred during the migration of the angular methyl group. Our rearrangement product, therefore, very probably has the assigned structure V. It should be noted, however, that in the two examples of the rearrangement of an α -bromo dienone recorded in the literature (refs. 1 and 5), the alternate position corresponding to C-4 in IV was blocked.

(10) The ultraviolet absorption spectra (Fig. 2) of Va and Vb showed the characteristic differences established previously (see ref. 3) for phenols and their acetates, but the presence of the bromine atom resulted in a bathochromic shift of 5 $m\mu$ for the acetate and 7 $m\mu$ for the phenol. For comparison the spectra of 1-methylestradiol (VI) and its diacetate are also reproduced.

rangement, thus establishing a connecting link between the two series.

Experimental¹¹

Bromination of Δ^1 -Androsten-17-ol-3-one 17-Hexahydrobenzoate (I) (Δ^1 -Testosterone Hexahydrobenzoate).—A solution of 100 mg. of the ketone I^{3,6} in 2 cc. of C. P. glacial acetic acid was treated with 80 mg. of pyridine hydrobromide perbromide and the reaction mixture was warmed slightly until all the reagent dissolved. Decolorization was almost instantaneous and was accompanied by evolution of hydrogen bromide. After standing at room temperature overnight, the crude product was precipitated with water. Although it showed a single maximum at 254.5 m μ , characteristic for the Δ^1 -2-bromo ketone II, the compound was seemingly contaminated by some dibromo derivative (Found: Br, 21.30). The crude product was purified readily by chromatographing over alumina, yielding 50 mg. (42%) of Δ^1 -2-bromoandrosten-17-ol-3-one 17-hexahydrobenzoate (II), which was shown to be identical with authentic material^{3,6} by comparison of the melting points, rotations, absorption spectra and analysis (Calcd.: Br, 16.76, Found: Br, 16.37).

Δ^1 -2,4-Dibromoandrosten-17-ol-3-one 17-Hexahydrobenzoate (III).—To a solution of 1.2 g. of the Δ^1 -2-bromo ketone II^{3,6} in 50 cc. of pure, fractionated glacial acetic acid (containing 13 mg. of water/10 cc. of acid; see ref. 3) was added 3 drops of 4 N hydrogen bromide in acetic acid followed by 6.25 cc. of a standard solution of bromine in acetic acid (1.6 g. of bromine in 25 cc. of pure acetic acid) and the reaction mixture was allowed to stand overnight. Decolorization was nearly complete after six hours. The solution was poured into cold water, the crude product was collected, washed well with water, dried and recrystallized from ethanol to yield 1.08 g. (77%) of Δ^1 -2,4-dibromo ketone III of m. p. 143.5–146°, $[\alpha]_D^{25} + 16.5^\circ$. The analytical sample crystallized from ethanol as colorless, prismatic needles with m. p. 147–148°, $[\alpha]_D^{25} + 11.3^\circ$, maximum at 261 m μ , log $E = 3.81$, minimum at 230.5 m μ , log $E = 3.27$ (Fig. 1).

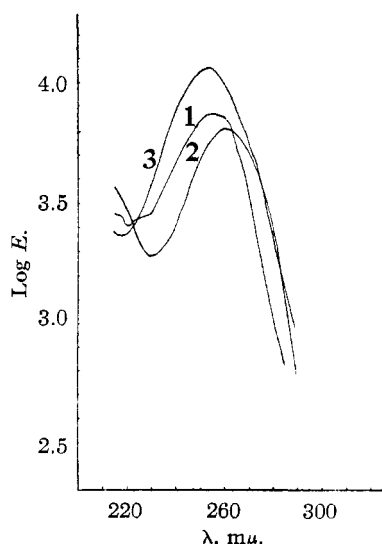


Fig. 1.—Ultraviolet absorption spectra (in 95% ethanol): curve 1, compound II; curve 2, compound III; curve 3, compound IV.

(11) All melting points are corrected. The optical rotations were determined on 5–10 mg. of sample in 1.2 cc. of chloroform using a 1-dm. tube of 1-cc. capacity. The ultraviolet absorption spectra measurements were carried out in 95% ethanol solution using a Beckman Quartz Photoelectric Spectrophotometer; $E = 1/c \log I_0/I$ for a 1 cm. cell, where c is the concentration in moles per liter.

*Anal.*¹² Calcd. for $C_{28}H_{38}O_3Br_2$: C, 56.12; H, 6.52; Br, 28.73. Found: C, 56.14; H, 6.69; Br, 29.24.

Pyridine hydrobromide perbromide⁷ could be substituted for bromine to effect bromination in the 4-position.

2-Bromo-1,4-androstadien-17-ol-3-one 17-Hexahydrobenzoate (IV).—Dehydrobromination of the dibromo ketone III was effected by refluxing 0.5 g. of the ketone with 2.5 cc. of collidine¹³ for one-half hour. The amount of collidine hydrobromide (0.17 g.), isolated by dilution with ether, filtering and washing with the same solvent, corresponded to 93% of the calculated quantity. The ether solution was washed several times with 5% hydrochloric acid solution, water, 5% sodium hydroxide solution, and again water, dried over sodium sulfate and the solvent was removed in a current of air. Trituration of the residue with hexane gave 0.35 g. (82%) of nearly colorless dienone of m. p. ranging from 132–137° to 139–142° which was satisfactory for the next step (Found: Br, 16.76). The compound crystallized from hexane as rosettes of colorless, prismatic needles which retained solvent very tenaciously. When dried at 55° and 30 mm., the material melted at ca. 105–111° (turbid), resolidified and melted at 142–144°. The solvent was removed completely on drying at 130° and 0.1 mm. for five hours (m. p. 144°). The rotations of three different, dry samples were: $[\alpha]_D^{25} + 7.4^\circ$, 8.1° , 12.9° . The absorption spectrum is shown in Fig. 1, and exhibited a maximum at 254.5 m μ , log $E = 4.06$, and a minimum at 218 m μ , log $E = 3.36$.

Anal. Calcd. for $C_{28}H_{38}O_3Br$: C, 65.68; H, 7.42; Br, 16.81. Found: C, 65.76, 65.85; H, 7.73, 7.60; Br, 16.49.

1-Methyl-2-bromoestradiol-3,17-diacetate (Vb). (a) By Dienone-Phenol Rearrangement of 2-Bromo-1,4-androstadien-17-ol-3-one 17-Hexahydrobenzoate (IV).—The

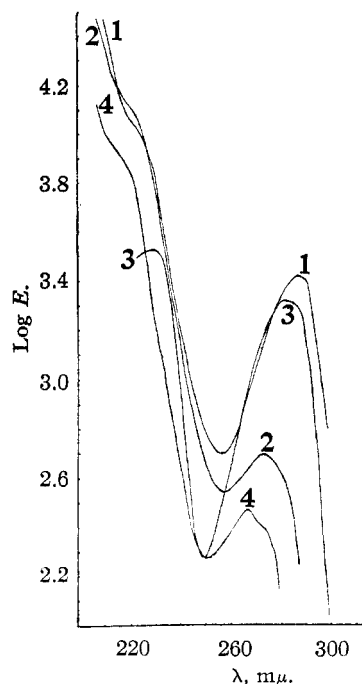


Fig. 2.—Ultraviolet absorption spectra (in 95% ethanol): curve 1, 1-methyl-2-bromoestradiol (Va); curve 2, 1-methyl-2-bromoestradiol diacetate (Vb); curve 3, 1-methylestradiol (VI); curve 4, 1-methylestradiol diacetate.

(12) All microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J., and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh.

(13) The γ -collidine used for the dehydrobromination was Eastman Kodak Co. white label product, which was fractionated before use.

dienone-phenol rearrangement was carried out by treating 0.26 g. of the 2-bromodienone IV in 5 cc. of acetic anhydride with 0.09 g. of concentrated sulfuric acid and allowing the solution to stand at room temperature for five hours. The mixture was poured into water, swirled to hydrolyze most of the acetic anhydride and the product was extracted with ether. After saponification by refluxing with 5% methanolic potassium hydroxide for seventy-five minutes, the crude 1-methyl-2-bromoestradiol was acetylated by means of acetic anhydride and pyridine, and the diacetate was precipitated by dilution with 5% hydrochloric acid. After recrystallization from ethanol, the colorless crystals (0.13 g., 53%) melted at 185–191°, $[\alpha]^{25}_D + 126^\circ$. The analytical sample crystallized as colorless rosetts of shiny needles and had the following constants: m. p. 192.5–194°, $[\alpha]^{25}_D + 128^\circ$, maximum at 273 m μ , log $E = 2.67$, minimum at 256.5 m μ , log $E = 2.44$ (Fig. 2).

Anal. Calcd. for $C_{23}H_{30}O_4Br$: C, 61.47; H, 6.51; Br, 17.78. Found: C, 61.66; H, 6.58; Br, 18.10.

(b) By Bromination of 1-Methylestradiol (VI).—When a solution of 55 mg. of 1-methylestradiol (VI)² in 1.4 cc. of glacial acetic acid was warmed with 63 mg. of pyridine hydrobromide perbromide for ca. thirty seconds, decolorization resulted with evolution of hydrogen bromide. After standing for a few minutes, the product was precipitated by the addition of water, filtered, and acetylated as in (a) to give 60 mg. (70% over-all yield) of the diacetate of m. p. 188–192°. Further recrystallization led to crystals melting at 193–194.5°, $[\alpha]^{25}_D + 125^\circ$, which gave no depression in m. p. when mixed with a sample prepared according to (a). The ultraviolet absorption spectrum was also practically identical with that shown for the above sample (method a), maximum at 272.5 m μ , log $E = 2.70$, minimum at 257.5 m μ , log $E = 2.54$.

1-Methyl-2-bromoestradiol (Va).—Sixty milligrams of the diacetate Vb on saponification with methanolic potassium hydroxide gave 40 mg. of 1-methyl-2-bromoestradiol (Va) of m. p. 166–167.5°. Recrystallization from hexane or dilute ethanol raised the m. p. to 167.5–169°, $[\alpha]^{24}_D + 189^\circ$, 185°, maximum at 288.5 m μ , log $E = 3.42$, minimum at 257 m μ , log $E = 2.70$ (Fig. 2). The same material was obtained from samples of the diacetate prepared according to (a) and (b) above.

Anal. Calcd. for $C_{19}H_{26}O_2Br$: C, 62.47; H, 6.90; Br, 21.88. Found: C, 62.81; H, 7.05; Br, 21.63.

The authors are greatly indebted to Jean Rogers and Helen Dudek for assistance in the experimental work.

Summary

It has been shown that while the bromination of Δ^1 -androst-17-ol-3-one 17-hexahydrobenzoate (I) proceeded rapidly with the formation of the corresponding Δ^1 -2-bromo-3-ketone II, the latter reacted only slowly with bromine to form Δ^1 -2,4-dibromoandrost-17-ol-3-one 17-hexahydrobenzoate (III). The dibromo compound was dehydrobrominated with collidine yielding a 2-bromo-1,4-dienone IV, which underwent the dienone-phenol rearrangement to 1-methyl-2-bromoestradiol (V). The latter was also obtained on direct bromination of 1-methylestradiol (VI), thus establishing a link between the two series.

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Optical Activity of the 4,5-Phenanthrene Type: 4-(1-Methylbenzo[c]phenanthryl)-acetic Acid and 1-Methylbenzo[c]phenanthrene¹

By MELVIN S. NEWMAN AND WILLIAM B. WHEATLEY²

The theoretical considerations leading to the prediction of optical activity in compounds of the 4,5-dimethylphenanthrene type have been presented.³ The structural feature necessary for this type of optical isomerism (called optical activity of the 4,5-phenanthrene type) involves the substitution in the 4 and 5 positions of phenanthrene of groups large enough to prevent their existence in the same plane as that of the aromatic rings. The preparation and resolution of one compound of this type, 4,5,8-trimethyl-1-phenanthrylacetic acid, have been described.^{3b,c} In order to obtain an additional example of compounds exhibiting this type of optical activity we undertook the synthesis and resolution of 4-(1-methylbenzo[c]phenanthryl)-acetic acid, I. This has been successfully

accomplished and is herein reported. We have also synthesized 1-methylbenzo[c]phenanthrene, II, the last monomethyl derivative of the parent hydrocarbon which remained to be prepared.⁴ This compound is to be tested for carcinogenic activity.

The optical activity in I is undoubtedly due to the fact that the methyl group is forced out of the plane of the aromatic rings.^{3c} The hydrocarbon, II, should also be capable of resolution but no suitable resolving agent for hydrocarbons is known. We hope to prepare such a resolving agent in the future. We are also planning to synthesize compounds with larger interfering groups so that more accurate studies on the rates of racemization can be made.

The synthetic methods used are outlined in the chart.

The mixture of unsaturated esters resulting from the Reformatsky reaction of ketone III and ethyl α -bromopropionate was dehydrogenated

(1) The material herein presented was taken from the Ph.D. Thesis of W. B. W., The Ohio State University, June, 1947, and was presented before the Division of Organic Chemistry of the ACS, New York, September, 1947.

(2) Present address, Bristol Laboratories, Inc., Syracuse, New York.

(3) (a) Newman, *THIS JOURNAL*, **62**, 2295 (1940); (b) Newman and Hussey, *ibid.*, **69**, 978 (1947); (c) Newman and Hussey, **69**, 8023 (1947).

(4) 2-, 3- and 4-isomers, Hewett, *J. Chem. Soc.*, 1286 (1938); 5 isomer, Hewett, *ibid.*, 596 (1936); 6-isomer, Hewett, *ibid.*, 293 (1940).