The Metabolic Fate of Tolbutamide in Man and in the Rat

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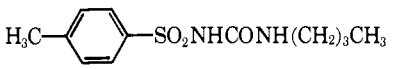
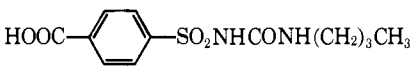
Tritium-labeled tolbutamide was found to be metabolized by man to 1-butyl-3-(*p*-hydroxymethyl)phenylsulfonylurea as well as to the generally recognized metabolite, 1-butyl 3-(*p*-carboxy)phenylsulfonylurea. These two metabolites were the only drug-related materials detected in urine and together comprised 85% of an orally administered dose of tolbutamide. Both metabolites were isolated from urine in crystalline form and characterized. The carboxy metabolite accounted for 67% and the hydroxymethyl metabolite 33% of urinary radioactivity as determined by quantitative paper and thin layer chromatography. In the rat, 80% of an orally administered dose of tritium-labeled tolbutamide was excreted in urine, predominantly as 1-butyl-3-(*p*-hydroxymethyl)phenylsulfonylurea, which was isolated in crystalline form and characterized. Small amounts of 1-butyl-3-(*p*-carboxy)-phenylsulfonylurea and *p*-tolylsulfonylurea (together approximately 5% of drug-related material excreted in urine) were also detected by paper chromatography.

The metabolism of tolbutamide (1-butyl-3-*p*-tolylsulfonylurea, I), an orally active hypoglycemic agent,



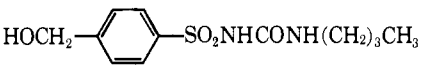
I

has been extensively studied.[1] The literature, although occasionally in conflict, indicates pronounced species differences. The major metabolite of tolbutamide in man has been isolated and identified as 1-butyl-3-*p*-carboxyphenylsulfonylurea[1a-c] (carboxy metabolite, II),



II

although Wittenhagen, *et al.*,[1d] on the basis of paper chromatography, reported that 1-butyl-3-*p*-hydroxymethylphenylsulfonylurea (hydroxymethyl metabolite, III) is also produced in small amounts. The dog is



III

reported[1d,e] to excrete *p*-tolylsulfonamide and *p*-tolylsulfonylurea following oral administration of tolbutamide. Larsen and Madsen[1f] mention III as the primary metabolite of tolbutamide in the cat, but do not elaborate on its identification. Wittenhagen, *et al.*,[1d] however, state that preliminary paper chromatographic results indicated that the cat metabolizes tolbutamide in a manner similar to the dog. Miller, *et al.*,[1g] employing paper chromatography, found that the rat converts S^{35}-labeled tolbutamide to a major and two minor metabolites. One of the minor metabolites appeared to be II, but the others, including the major metabolite, were not identified. Wittenhagen, *et al.*,[1d] in the light of their own work, stated that the unidentified excretion products are III and unchanged tolbutamide. Inspection of Miller's results, however, shows that no unchanged tolbutamide is excreted by the rat. Wittenhagen, *et al.*,[1d] also report that tolbutamide is converted to II by rats, guinea pigs, and rabbits. In each case a minor amount of III was detected in the animal's urine.

In each case that has implicated III as a metabolite of tolbutamide, identification has been by paper chromatography in a single solvent system; crystalline material has not been isolated and subjected to analysis. Although III has been reported as a metabolite of tolbutamide in man, there has been no investigation of its quantitative importance relative to II. Previous efforts to quantify II in urine have involved either its direct precipitation from urine[1h,i] or use[1j-n] of an assay[2] which, as will be discussed, also responds to III.

The present work, employing tritium-labeled tolbutamide, was conducted to clarify both qualitatively and quantitatively the metabolism of this drug in man and in the rat.

Experimental Section

Radioactivity Measurements.—All counting was performed with a Tri-Carb[3] Model 314X or 314EX-2A liquid scintillation spectrometer at −8° under conditions suitable for measuring tritium. Appropriate aliquots of samples were dissolved in 15 ml of Diotol scintillation solvent [toluene–dioxane–methanol (350:350:210 by vol) containing 73 g of naphthalene, 4.6 g of 2,5-diphenyloxazole, and 0.080 g of 1,4-bis-2-(5-phenyloxazolyl)-benzene/l.]. The absolute counting efficiency for each sample was determined by addition of an internal standard of tritium-labeled toluene and results then were converted to microcuries or disintegrations per minute.

Paper and Thin Layer Chromatography.—Paper chromatography was carried out in a 1-butanol–piperidine–water (81:2:17 by vol) system on Whatman No. 1 paper. Dried chromatograms were routinely examined under short wavelength ultraviolet light with an ultraviolet scanner[4] to locate standards and metabolites, when possible, by fluorescence quenching. Radioactive zones were located by cutting the developed paper

(1) L. H. Louis, S. S. Fajans, J. W. Conn, W. A. Struck, J. B. Wright, and J. L. Johnson, *J. Am. Chem. Soc.*, **78**, 5701 (1956); (b) G. Wittenhagen and G. Mohnike, *Deut. Med. Wochschr.*, **81**, 887 (1956); (c) T. Dorfmüller, *ibid* **82**, 888 (1956); (d) G. Wittenhagen, G. Mohnike, and W. Langenbeck, *Z. Physiol. Chem.*, **316**, 157 (1959); (e) G. Mohnike, G. Wittenhagen, and W. Langenbeck, *Naturwiss.*, **45**, 13 (1958); (f) J. A. Larsen and J. Madsen, *Proc. Soc. Exptl. Biol. Med.*, **109**, 120 (1962); (g) W. L. Miller, Jr., J. J. Krake, M. J. VanderBrook, and L. M. Reineke, *Ann. N. Y. Acad. Sci.*, **71**, 118 (1957); (h) S. S. Fajans, L. H. Louis, H. S. Seltzer, R. D. Johnson, R. D. Gittler, A. R. Hennes, B. L. Wajchenberg, I. P. Ackerman, and J. W. Conn, *Metab. Clin. Exptl.*, **5**, 820 (1956); (i) G. Mohnike and G. Wittenhagen, *Deut. Med. Wochschr.*, **82**, 1556 (1957); (j) R. U. Lemieux, K. F. Sporek, I. O'Reilly, and E. Nelson, *Biochem. Pharmacol.*, **7**, 31 (1961); (k) E. Nelson and I. O'Reilly, *J. Pharmacol. Exptl. Therap.*, **132**, 103 (1961); (l) E. Nelson, *Nature*, **193**, 76 (1962); (m) E. Nelson, S. Long, and J. G. Wagner, *J. Pharm. Sci.*, **53**, 1224 (1962); (n) B. E. Ballard and E. Nelson, *Arch. Intern. Pharmacodyn.*, **133**, 206 (1961).

(2) E. Nelson, I. O'Reilly, and T. Chulski, *Clin. Chim. Acta*, **5**, 774 (1960).

(3) Packard Instrument Co., Inc., Downers Grove, Ill.

(4) N. A. Drake, W. J. Haines, R. E. Knauff, and E. D. Nielson, *Anal. Chem.*, **28**, 2036 (1956).

strip into sequential 1.25- or 2.5-cm segments (depending on the resolution desired) and counting the segments in individual counting vials in the usual manner.

Thin layer chromatography was carried out in a chloroform–formic acid (92:8 by vol) system or in a chloroform–methanol–formic acid (95:4:1 by vol) system on silica gel GF.[5] The fluorescence quenching of standards and, when possible, metabolites was detected by viewing the dried chromatograms under short-wavelength ultraviolet light. Radioactive zones were located by transferring sequential 0.62- or 1.25-cm segments (depending on the resolution desired) of the developed chromatogram into individual counting vials and counting in the usual manner.

Rat Experiments.—Tolbutamide was suspended in water and then dissolved by addition of a slight excess of NH_4OH. The pH of the solution was adjusted to approximately 7.5 and then diluted so as to contain 68 mg of tolbutamide/ml. Tritium-labeled tolbutamide was made up in an identical manner. The preparation of the labeled material by exposure to tritium gas has been reported.[6]

Female Sprague–Dawley rats each weighing approximately 250 g were housed in individual metabolism cages designed for the separation and collection of urine and feces. The animals were allowed food and water *ad libitum*.

In a preliminary experiment three rats were each dosed by stomach tube with 68 mg of tritium-labeled tolbutamide containing 150 μcuries of tritium. Daily urine collections were made for 3 days. The recovery of urinary radioactivity is presented in Table I.

TABLE I

URINARY EXCRETION OF RADIOACTIVITY FOLLOWING ORAL DOSE OF TRITIUM-LABELED TOLBUTAMIDE TO RATS

Collection period, hr	% of administered dose			
	Rat 1	Rat 2	Rat 3	Av
0–24	70	65	56	64
24–48	6.2	13.2	24.2	14.5
48–72	0.86	1.66	1.70	1.41
Total	77	80	82	80

Several series of experiments were carried out in which rats were given 20 successive 68-mg doses of tolbutamide by stomach tube every other day. In a typical series 2 rats each received an initial radioactive dose (150 μcuries) followed by 18 nonradioactive doses and finally a terminal radioactive dose. Urine collections were made at daily intervals. Each of the urine samples (0–48-hr collections) following administration of the tritium-labeled drug were kept separate while the urine collections following administration of nonradioactive tolbutamide were combined. Paper chromatography of both the initial and terminal radioactive urine samples revealed a single radioactive zone in each case, having an R_f value of 0.63, corresponding to that of III.[7] Tolbutamide, *p*-tolylsulfonylurea, and II, chromatographed at the same time, had R_f values of 0.74, 0.49, and 0.22 respectively.

The radioactive urine samples were then combined with the nonradioactive samples for isolation of the tolbutamide metabolite. The composite urine (approximately 1 l.) was saturated with $(NH_4)_2SO_4$ and extracted five times with 1-l. portions of diethyl ether–ethanol (6:1 by vol). The extract was evaporated to dryness *in vacuo* and the residue was taken up in water and extracted into ether. Approximately 80% of the radioactivity initially present in the urine was removed in the final ether extract. Paper chromatography of the ether extract at a level of radioactivity considerably higher than was possible with whole urine revealed, in addition to the major radioactive zone, two minor zones of radioactivity at R_f values of 0.22 and 0.49, together comprising approximately 5% of the radioactivity chromatographed. The compound at R_f 0.22 corresponds chromatographically to II and that at R_f 0.49 to *p*-tolylsulfonylurea. The distribution coefficient of radioactivity in the ether extract was determined as a function of pH in chloroform–0.05 *M* buffer systems and found to be unity at pH 5.1. The residue from one-half the ether extract was applied to the first two tubes of a 200-tube, 10 ml/phase, Craig countercurrent distribution apparatus. The system chloroform–0.05 *M* pH 5.1 phosphate buffer was then used for 152 transfers. An aliquot from the $CHCl_3$ phase of every other tube was analyzed for radioactivity. The major radioactive peak (approximately 95% of the radioactivity applied to the apparatus) was split into three fractions by combining appropriate tube contents, acidifying, and extracting into the chloroform phase. In each case an oily residue was obtained upon removal of the $CHCl_3$ *in vacuo*. One fraction was lost in an unsuccessful attempt at purification by sublimation. The other two fractions were recrystallized from acetone–water and ethanol–water, respectively, to yield 400 mg of white crystalline material; mp 110–110.5° (capillary, uncorrected; authentic III had the same melting point). The ultraviolet and infrared spectra were identical with those of standard III. Paper and thin layer chromatography in the previously mentioned systems revealed single fluorescence quenching and radioactive zones corresponding to III. The nmr spectrum of the product was consistent with that expected for the proposed structure; the singlet at δ 2.43 (in dimethylformamide-d_7) attributable to the aromatic methyl group of tolbutamide was replaced by a new singlet at δ 4.72 attributable to an aromatic hydroxymethyl group.

Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.40; H, 6.34; N, 9.77; S, 11.20. Found: C, 50.31; H, 6.28; N, 9.87; S, 11.32.

Human Experiments.—One gram of finely powdered tolbutamide containing 104 μcuries of tritium was administered orally to each of eight normal male subjects. Urine, feces, and blood samples were taken at appropriate intervals over a period of 7 days. An average of 85% of the administered tritium was excreted in the urine. Over 99% of this was excreted during the first 48 hr. Details of this study and a kinetic interpretation of the dynamics of absorption, metabolism, and excretion will be reported later.

Paper and thin layer chromatography of urine samples from the eight subjects (during period of peak urinary excretion of radioactivity) revealed two radioactive zones in each case corresponding to II and III, which were run on the same chromatograms as standards. The relative amounts of the two metabolites are presented in Table II. A similar analysis was made of the 0–48-hr urine samples from four of the subjects by paper chromatography only. These results are presented in Table III.

TABLE II

RELATIVE DISTRIBUTION OF TOLBUTAMIDE METABOLITES IN URINE OF HUMAN SUBJECTS DURING PERIOD OF PEAK EXCRETION OF RADIOACTIVITY

Subject	Collection period, hr	% hydroxymethyl metabolite[a]		
		Thin layer	Paper chromatog	Av
1	5–7	34	33	33
2	3–5	37	42	39
3	7–9	32	32	32
4	3–5	28	23	25
5	3–5	40	44	42
6	5–7	37	31	34
7	5–7	34	28	31
8	5–7	33	29	31
Av		34	33	33
Range		28–40	23–44	25–42

[a] Remainder is carboxy metabolite.

TABLE III

RELATIVE DISTRIBUTION OF TOLBUTAMIDE METABOLITES IN 0–48-HR URINE COLLECTIONS OF HUMAN SUBJECTS

Subject	Hydroxymethyl metabolite, %[a]
1	30
3	32
5	34
8	34
Av	33
Range	30–34

[a] Remainder is carboxy metabolite. Analysis by paper chromatography only.

(5) Brinkmann Instruments, Inc., Great Neck, N. Y.

(6) R. C. Thomas and G. J. Ikeda, *J. Pharm. Sci.*, **55**, 12 (1966).

(7) An authentic sample of 1-butyl-3-*p*-hydroxymethylphenylsulfonylurea was generously supplied by the late Dr. E. Nelson, State University of New York at Buffalo.

The 0–48-hr urine collections from the eight subjects were combined and, after being acidified to pH 2, were extracted in 1.5-l. batches with one 1.5-l. and two 1.0-l. portions of acetone–chloroform (1:1 by vol). A fourth extraction of each batch was made with 1 l. of chloroform. The extracts were combined and evaporated *in vacuo* to a damp residue. The residue was suspended in 500 ml of 1 *M* phosphate buffer at pH 5 and the suspension was extracted six times with 500-ml portions of $CHCl_3$. After shaking the suspension with the first portion of chloroform, a precipitate was removed by filtering the two phases. The following distribution of tritium resulted from this extraction procedure: chloroform phase, 26%; precipitate (6.23 g), 63%; aqueous phase, 11%.

The precipitate was recrystallized once from acetone (with charcoaling) and once from ethanol–water to yield 3.30 g of pure II. Infrared and ultraviolet spectra of the compound were the same as those of authentic II. Thin layer and paper chromatography revealed in each case a single ultraviolet-absorbing and radioactive zone corresponding to standard II.

Anal. Calcd for $C_{12}H_{16}N_2O_5S$: C, 48.04; H, 5.38; N, 9.34; S, 10.69. Found: C, 47.98; H, 5.54; N, 9.50; S, 10.97.

Evaporation of the previously mentioned $CHCl_3$ extract produced a dark, oily residue. Attempts to crystallize this material directly were not successful. The bulk of the oily residue was taken up in 100 ml of 0.1 *M* phosphate buffer at pH 5 and extracted with five 100-ml portions of chloroform. The following distribution of radioactivity resulted: extract 1, 63%; extracts 2–5, 19%; aqueous phase, 18%. Evaporation of extract 1 resulted in a dark, oily residue which could not be crystallized. The residue from extracts 2–5 was lighter in color and semisolid. This was recrystallized twice from ethanol–water and once from acetone–water (with charcoaling) to yield 18 mg of crystalline III. Infrared and ultraviolet spectra of the compound were the same as those of authentic III. Thin layer and paper chromatography revealed in each case a single ultraviolet-absorbing and radioactive zone corresponding to standard III. Mass spectroscopy of the compound revealed a molecular ion peak at 286 mass numbers (mol wt of III, 286) and a fragmentation pattern in all respects consistent with the proposed structure.

Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.4; H, 6.34; N, 9.77. Found: C, 50.0; H, 6.55; N, 9.88.

Results and Discussion

It was surprising to find III such a quantitatively important metabolite of tolbutamide in man. As shown in Tables II and III, it accounted for 33% of drug-related material excreted in urine following oral administration of tolbutamide. The only other detectable metabolite was II. Together, the two metabolites accounted for 85% of an orally administered dose. Most (9%) of the remaining radioactivity was excreted in feces and was not identified. The report by Wittenhagen, *et al.*,[1d] is the only one which mentions a human metabolite of this drug other than II. Their identification of III was by paper chromatography in a single solvent system and they did not quantify this metabolite relative to II or to the administered drug. They did, however, say that a small amount of it was found in urine together with a large excess of II. The use of radioactive tolbutamide in the present work permitted not only quantification of III but assisted in its isolation in crystalline form for characterization.

Previous efforts to quantify tolbutamide metabolites in urine have involved either direct precipitation by acidification[1h,i] or use of an assay[1j–n] capable of differentiating between tolbutamide and II. The former approach depends on the low solubility of II (0.06 g/l. at pH 2 or lower),[8] permitting direct gravimetric determination (usually following an oral dose of at least 3 g of tolbutamide). Recoveries of II have ranged up to 80% of the administered drug. This approach would not have included III since its solubility is 2.6 g/l. at a pH of 2 or below.[9]

More recently Nelson, *et al.*,[2] have reported a method for determination of II based on a modification of the Spingler[10] assay for tolbutamide. The proposed specificity of this method involves removal of interfering tolbutamide by extraction from urine at pH 5.5 prior to assaying for II. Using tritium-labeled compounds, we confirmed this quantitative separation in that 99% of tolbutamide and only 1% of II were extracted at pH 5.5; however, only 20% of III was removed in this way. Furthermore, we found that the responses of II and III in the colorimetric assay were equivalent. Therefore, determination of urinary tolbutamide metabolites by this method would include all of II and 80% of III, thus yielding an apparently nearly quantitative excretion of II.

The major urinary metabolite of tolbutamide, following oral administration of the tritium-labeled drug to the rat, has been shown by paper and thin layer chromatography, as well as by isolation in crystalline form and characterization, to be III. Traces of II and *p*-tolylsulfonylurea (approximately 5% of drug-related material in the urine) were the only other detectable metabolites. These three metabolites account for 80% of an oral dose of tolbutamide (Table I). The remainder, presumably excreted in the feces, was not identified. Wittenhagen, *et al.*,[1d] report that II is the primary metabolite of tolbutamide in the rat following intraperitoneal administration in contrast to our results and those of Miller, *et al.*,[1g] following oral administration. We therefore dosed each of two rats intraperitoneally with 10 mg of tolbutamide containing 10 μcuries of tritium and collected 48-hr urine samples. Paper chromatography of the urine revealed a single radioactive zone in each case corresponding to III.

Chronic administration (20 doses over a 40-day period) of tolbutamide to the rat did not reveal adaptation insofar as the distribution of metabolites is concerned; there was no appreciable increase in the relative amounts of II and *p*-tolylsulfonylurea formed and excreted. The effect of chronic administration of the drug on its rate of metabolism was not investigated. Remmer, *et al.*,[11] however, have reported that, even though tolbutamide is a strong inducer of microsomal enzymes in the rat, it is not metabolized by these enzymes in this species and thus does not stimulate its own metabolism. No studies involving the effect of chronic administration of tolbutamide on the relative distribution of its metabolites in man were carried out in the present investigation. Südhof, *et al.*,[12] have reported a slight apparent adaptation to tolbutamide in diabetic subjects in that the half-life of the drug decreased 20% following several months' treatment. They did not feel that this change is sufficient to influence the results of antidiabetic therapy, however.

The limited supply and great solubility of III prevented determination of its solubility above pH 5.4 (10 g/l. at 37°). Extrapolation of the pH–solubility curve, however, indicates a solubility of at least 30

(8) A. A. Forist and T. Chulski, *Metab. Clin. Exptl.*, **5**, 807 (1956).

(9) A. A. Forist, personal communication.

(10) H. Spingler, *Klin. Wochschr.*, **35**, 533 (1957).

(11) (a) H. Remmer and H. J. Merker, *Ann. N. Y. Acad. Sci.*, **123**, 79 (1965); (b) H. Remmer, M. Siegert, and H. J. Merker, *Arch. Exptl. Pathol. Pharmakol.*, **249**, 71 (1964).

(12) H. Südhof, S. Altenburg, and E. Sander, *Klin. Wochschr.*, **36**, 585 (1958).

g/l. at pH 6.[9] Thus, this metabolite of tolbutamide, as well as the carboxy metabolite, is very soluble at normal urinary pH values. Both II[1h] and III[13] have been reported to have no hypoglycemic activity.

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(13) H. Ruschig, G. Korger, W. Aumüller, H. Wagner, R. Weyer, A. Bänder, and J. Scholz, *Arzneimittel-Forsch.*, **8**, 448 (1958).

The Preparation and Chemistry of 9α,10α-Oxidoestra-4-en-3-ones

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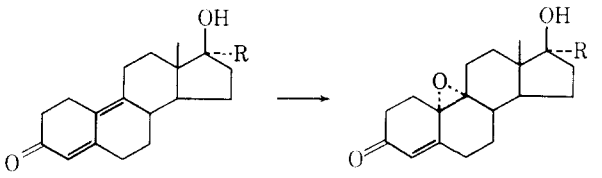
The reaction of estra-4,9(10)-dien-3-ones with peracid affords 9α,10α-oxido compounds in high yield. Upon treatment of the oxides with base or acid, $\Delta^{9(11)}$-estradiols or ethers of these diols, respectively, are obtained. With pyrrolidine the oxides rearranged to yield 3-pyrrolidinoestra-1,3,5(10)-trien-9α-ols and 3-pyrrolidinoestra-1,3,5(10),9(11)-tetraenes. The pharmacology of these compounds is summarized.

The reaction of various estra-4,9(10)-dien-3-ones[1] with peracids results in the preparation of monoepoxides in high yield. Because of the importance of several estrenes or 19-nor steroids in various biological areas, including anabolic[2] and ovulation inhibition,[3] an investigation of the structure, the chemistry, and the pharmacology of these epoxides was undertaken.

The epoxidation of double bonds in a variety of different positions in the steroid nucleus gives oxides whose resultant stereochemistry is frequently attributed to steric factors alone. The epoxidation of the 5(10) double bond of estrenes results in almost exclusive formation of 5β,10β-epoxides.[4] On the other hand, the 9(11) double bond of a number of steroids on epoxidation affords 9α,11α-oxides. A recent example of epoxidation of a possible incipient 9(10) double bond of an estrene was found to yield a 9β,10β-epoxide.[5] This case, however, was not clearly an epoxidation of a 9(10) double bond and could also be the result of β-face attack of peracid at C-10. The reaction of a 9(10) double bond with peracid could then be an indication of the steric factors operating in this system.



Ia, R = H
b, R = CH_3
c, R = C≡CH

IIa, R = H
b, R = CH_3
c, R = C≡CH

The epoxides in this report, which were obtained by reaction of the estra-4,9(10)-dien-3-ones and *m*-chloroperbenzoic acid in about 80% yield, were found to possess 9α,10α stereochemistry indicating α-face attack by the peracid.[6] This epoxidation was carried out with the compounds indicated.

The stereochemistry of the epoxides was not readily apparent using the available physicochemical methods. While the compounds II gave ORD curves similar to that of 10α-testosterone,[7] the effect of oxides at this position in relation to the absorbing chromophore was not known. Further, the conformational mobility of the A ring could also interfere with interpretations of these spectra. The nmr spectra were similarly equivocal showing a broadened 4-vinyl proton[8] with no pronounced shifts of the positions of the 18-methyl protons when compared to the spectrum of the appropriate 19-nortestosterone. Thus, chemical transformations were necessary in order to complete the stereochemical assignment.

Compound IIa was treated with excess lithium aluminum hydride, and the resultant product in turn was treated with manganese dioxide to reoxidize the allylic hydroxyl grouping. The substituted 19-nortestosterone compound obtained was an α,β-unsaturated ketone as evidenced by its ultraviolet spectrum. Examination of its ORD spectrum indicated stereochemistry identical with that of 19-nortestosterone, namely 9α,10β. It has been demonstrated that the 10β-hydroxy grouping does not alter the shape and direction of the ORD curve[4] and similar behavior would be expected for the C-9 hydroxyl substitution.

The known estra-4-ene-10β,17β-diol-3-one[4] was prepared. Although this gave a similar ORD curve, its physical constants differed considerably. Thus IIIa must have the alternate estra-4-ene-9α,17β-diol-3-

(1) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(2) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953).

(3) O. V. St. Whitelock, *Ann. N. Y. Acad. Sci.*, **71**, 479 (1958).

(4) J. P. Ruelas, J. Iriarte, F. A. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(5) H. Hasegawa and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 473 (1964).

(6) After our work was completed some related studies were reported by D. Hartley and H. Smith, *J. Chem. Soc.*, 4492 (1964). Only a few portions of the two studies overlap.

(7) (a) R. Wenger, H. Dutler, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 1096 (1963). (b) E. Farkas, unpublished results. A similar spectrum was obtained for 10α-19-nortestosterone.

(8) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).