very well while azulene is ineffective. The results of a run using filtered light (see Experimental Section) are summarized in Table II.

TABLE II
PHOTOISOMERIZATION OF QUADRICYCLANES

Compound[a]	Sensitizer	Result[b]
Quadricyclane[c]	Pyrene	3.7% conversion to norbornadiene
Quadricyclane	Anthracene	9.4% conversion to norbornadiene
2,3-Dicyanoquadricyclane	Pyrene	No detectable reaction
2,3-Dicyanoquadricyclane	Anthracene	No detectable reaction[d]
2,3-Dicyanonorbornadiene	Pyrene	Trace of 2
2,3-Dicyanonorbornadiene	Anthracene	Trace of 2

[a] Concentration = 50 mg/0.3 ml of CD_3CN. Degassed and sealed in nmr tubes. [b] Quadricyclane and norbornadiene concentrations determined by glpc. Concentrations of 1 and 2 determined by nmr. [c] Kindly supplied by Dr. C. D. Smith. [d] Excluding the dimerization of anthracene.

We conclude that under conditions where the sensitized isomerization of quadricyclane to norbornadiene takes place, there is no evidence for a similar sensitization of 2,3-dicyanoquadricyclane. We cannot rule out the possibility, however, that some sensitized isomerization does take place. The isomerization of 1 to 2 is always observed under all conditions tried and if the sensitized isomerization of 2 to 1 is extremely slow compared to the isomerization of 1 to 2, then any 1 formed will be converted back to 2. This could lead to an undetectable concentration of 1.

Experimental Section[12]

2,3-Dicyanoquadricyclane.—2,3-Dicyanonorbornadiene[7] (500 mg) dissolved in 20 ml of oxygen-free ether was irradiated for 18 hr at 32° in a cylindrical photoreactor.[13] The solution was then filtered to remove a trace of insoluble residue, diluted with petroleum ether (bp 60°), and cooled in a Dry Ice chest. The resulting slurry was filtered to give 370 mg of analytically pure leaflets melting at 74–76°. One recrystallization from ether gave 2,3-dicyanoquadricyclane melting at 76.5–77°.

Anal. Calcd for $C_9H_6N_2$: C, 76.12; H, 4.20. Found: C 75.97; H, 4.37.

Kinetic Runs.—A 15% solution of 2,3-dicyanoquadricyclane in deuterioacetonitrile was sealed in thin-walled nmr tubes. The nmr spectra of the solutions were recorded and integrated on a Varian A-60 spectrometer. The tubes were then submerged in constant-temperature baths (±0.1°), removed after a given time, and cooled with ice water. The nmr spectra were determined as soon as possible and the per cent of 2,3-dicyanoquadricyclane was calculated from the integration. The tubes were protected from light as much as possible and the total product area remained constant within experimental error as determined by comparison with the solvent peak in the deuterioacetonitrile.

Solutions of quadricyclane in deuterioacetonitrile (~15%) were sealed in melting point capillary tubes. The tubes were immersed in a constant-temperature bath and then withdrawn at various intervals, cooled, and analyzed by glpc (Dow 200 silicone oil on 60–80 Chromosorb W at room temperature). The per cent of quadricyclane was calculated from the peak areas.

Photoisomerizations.—Solutions were prepared for photolysis by placing 50 mg of the appropriate acceptor (see Table II), 5 mg of sensitizer, and 0.3 ml of deuterioacetonitrile in thin-walled, Pyrex nmr tubes. The tubes were degassed by three freeze–thaw cycles and then sealed. Three tubes, one containing 2,3-dicyanoquadricyclane, one 2,3-dicyanonorbornadiene, and one quadricyclane, were irradiated with a sensitizer for 18 hr with a 450-w Hanovia high-pressure lamp using a cupric sulfate pentahydrate solution (400 g/600 ml) and Corning 7-39 filter between the tubes and the light source. This combination of sensitizer, light source, and filters gave the smallest conversion of 2,3-dicyanonorbornadiene to 2,3-dicyanoquadricyclane of any tried, while still effecting the isomerization of quadricyclane to norbornadiene.

(12) Melting points are corrected and were taken on a Mel-Temp apparatus.

(13) Rayonet Srinivasan-Griffin photochemical reactor equipped with 16 F8T5 BLB bulbs.

Registry No.—2, 13283-33-5.

Acknowledgments.—The author is indebted to Mr. P. Baiocco for the nmr determinations, to Dr. R. S. H. Liu for photochemical advice, and to Drs. H. E. Simmons, H. K. Hall, and Professor D. Applequist for discussing the data.

Steroids. CCCV.[1] Synthesis of 11-Hydroxy-1-methyl-19-norretrotestosterone[2]

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With few exceptions,[3] most retro (9β,10α) steroids have so far been obtained by photochemical reactions.[4] In this note, the chemical synthesis is reported of a retro steroid presenting the *anti,cis,anti,trans* stereochemistry at the ring junctions. Reduction of the aromatic ring of estrone methyl ether with metals in amines, followed by subsequent mild acid treatment, is known[5] to afford 19-nortestosterone, with the "natural" 9α,10β stereochemistry. However, examination of molecular models and conformational considerations suggested that an analogous reduction of ring A aromatic steroids with the 9β-H configuration should lead, after acid treatment, to 19-nor-Δ^4-3-keto steroids with the 9β,10α (retro) stereochemistry.

Aromatization of prednisone acetate (I) by the method of Bailey, *et al.*,[6] afforded the $\Delta^{9(11)}$-aromatic

(1) Part CCCIV: I. T. Harrison and S. Harrison, *Chem. Commun.*, No. 20, 752 (1966).

(2) A preliminary communication of this work has already appeared; see J. A. Edwards, P. Crabbé, and A. Bowers, *J. Am. Chem. Soc.*, **85**, 3313 (1963).

(3) (a) L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and J. Tessier, *Compt. Rend.*, **252**, 3903 (1961); L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965); L. Velluz, J. Mathieu, and G. Nominé, *Tetrahedron Suppl.*, **8**, Part II, 495 (1966), and references therein; (b) J. A. Edwards, H. Carpio, and A. D. Cross, *Tetrahedron Letters*, 3299 (1964); (c) J. M. H. Graves, G. A. Hughes, T. Y. Jen, and H. Smith, *J. Chem. Soc.*, 5488 (1964).

(4) (a) The classical work of Windaus, Heilbron, and their collaborators on the irradiation of ergosterol is summarized by L. F. Fieser and M. Fieser in "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 136, and in "Topics in Natural Products," Reinhold Publishing Corp., New York, N. Y., 1963, p 231; (b) J. Castells, E. R. H. Jones, G. D. Meakins, and R. W. J. Williams, *J. Chem. Soc.*, 1159 (1959), and related papers; (c) W. G. Dauben and C. J. Fonken, *J. Am. Chem. Soc.*, **81**, 4060 (1959); (d) E. H. Reerink, H. F. L. Schöler, P. Westerhof, A. Querido, A. A. H. Kassenaar, E. Dickfalusy, and K. C. Tillinger, *Nature*, **186**, 168 (1960); M. P. Rappoldt and P. Westerhof, *Rec. Trav. Chim.*, **80**, 43 (1961); (e) R. van Moorselaar, Ph.D. Thesis, University of Leiden, Holland, 1962; (f) P. Westerhof, J. Hartog, and S. J. Halkes, *Rec. Trav. Chim.*, **84**, 863 (1965).

(5) (a) A. J. Birch, *J. Chem. Soc.*, 367 (1950); (b) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); (c) see also H. Smith in "Chemistry in Nonaqueous Ionizing Solvents," Part 2, G. Jander, Ed., Interscience Publishers, Inc., New York, N. Y., 1963.

(6) E. J. Bailey, J. Elks, J. F. Oughton, and L. Stephenson, *J. Chem. Soc.*, 4535 (1961); see also, E. Caspi, P. K. Grover, and Y. Shimizu, *J. Am. Chem. Soc.*, **86**, 2463 (1964), and related papers.

steroid II in the crystalline form. Alkaline treatment[2,6] of II, followed by acetylation, provided a mixture of 9β-IIIb and 9α-IV isomers, which were easily separated by chromatography. When II was treated with sodium methoxide and then methylated at C-3 with dimethyl sulfate and acetylated at C-21, the 3-methoxy-21-acetate (IIId) was obtained. In the 9β-H compounds (IIIa–d), the nonbonded interactions between the 1-methyl group and the 11-ketone are substantially reduced, as compared to the 9α-H isomers (*e.g.*, steroid IV), thus explaining the facile isomerization.[7] Worthy of mention is the intense positive Cotton effect[8] associated with the 9β-H-11-keto compounds (IIIa–d). The strong optical activity exhibited by the homoconjugated chromophore in these compounds is due to the prevalence of a conformation in which the orientation of π electrons of the benzene ring relative to electrons of the carbonyl group is geometrically favorable to enhancement.[9]

Further insight into the conformation of these derivatives was obtained from their nuclear magnetic resonance (nmr) spectra. The three-proton signal corresponding to the C-1 methyl group is deshielded by *ca.* 5 cps in going from IV (119 cps) to IIIb (124 cps).[10] Furthermore, the epimerization of IV to IIIb is accompanied by substantial deshielding of the 18-methyl protons by the 11-carbonyl group, *i.e.*, from 41 cps in the former to 59 cps in the latter. These data strongly support the hypothesis that ring C flips from a chair conformation in the 9α epimer (IV) to a boat conformation in the 9β isomer (IIIb).

Since diborane reduction[11] of IIIb gave the pentol V cleanly, compound IIId was treated with a stream of diborane[11] and the side chain of the crude product was directly oxidized with sodium periodate[12] to provide the 9β-substituted estratriene derivative VI. The 11β configuration is assigned to the hydroxyl group on the basis of the probable approach of the reducing agent from the less hindered α face. This assignment of configuration is supported by the signal associated with the 18-methyl protons in the nuclear magnetic resonance spectrum. Indeed, the 18-proton frequency (73 cps) minus the calculated value[13] for the 11,17-dione (58 cps) gives $\Delta\nu_{C=O\rightarrow CHOH} \cong +15$ cps. This value is close to the value expected for the extra shielding due to 11β-OH compared with 11-ketone for a chair conformation in ring C. Moreover, since the value is quite different from the shielding change predicted if the 11-ketone were reduced to 11α-OH ($\Delta\nu$ *ca.* 5 cps), one can conclude that the configuration is β at C-11 in steroid VI.

Lithium and ammonia reduction[5] of VI, followed by mild acid treatment, gave the 1-methyl 19-nor retrosteroid (VII). The positive multiple Cotton effect, associated with the n–π^* transition of the Δ^4-3-keto chromophore, supports[8] the retro (9β,10α) configuration. The optical properties of 11ξ,20β-dihydroxy-9β,10α-19-norpregn-4-en-3-one,[2] retrotestosterone,[4,8] 19-norretrotestosterone,[3,8,14] lumist-4-en-3-one,[15] and 11β-hydroxy 1ξ-methyl-9β,10α-19-nortestosterone (VII) are opposite in sign when compared to that of 19-nortestosterone.[5b] These data are compatible with the 9β,10α configuration proposed for the nor steroid (VII)[2] (Scheme I).

Experimental Section[16]

1-Methyl-3,11β,17α,21-tetrahydroxy-19-norpregna-1,3,5(10),-9(11)-tetraen-20-one Tetracetate (II).—Prednisone acetate (I) (30 g) was dissolved in 750 ml of freshly distilled acetic anhydride; a cooled solution (0°) of 150 ml of acetic anhydride containing 1.5 ml of 70% perchloric acid was slowly added. The reaction mixture was stirred at room temperature for 6 hr. After that time a solution of 2 kg of $NaHCO_3$ in 8 l. of water was slowly added under vigorous stirring. The compound was extracted with ethyl acetate. The organic layer was washed with 10% sodium bicarbonate and then with water until neutral pH. After drying over anhydrous sodium sulfate, the solution was filtered and concentrated *in vacuo*. The crude oily material which was obtained (41.4 g) was chromatographed on 1.5 kg of Florisil. Elution with hexane–benzene (1:1) afforded 39 g of the enol acetate (II), which was recrystallized from benzene–hexane to give the analytical sample of II:[17] mp 90–93°; $[\alpha]_D$ −64° (*c* 1, $CHCl_3$); ultraviolet, λ_{max}^{EtOH} 242 mμ (log ε 4.1); infrared λ_{max}^{KBr} 5.65, 5.72–5, 8.07 μ.

Anal. Calcd for $C_{29}H_{34}O_9$: C, 66.14; H, 6.51; O, 27.35. Found: C, 65.95; H, 6.48; O, 27.52.

1-Methyl-3,17α,21-trihydroxy-19-nor-9β-pregna-1,3,5(10)-triene-11,20-dione 3,21-Diacetate (IIIb) and Its 9α Isomer (IV).—Treatment of II under the conditions described by Bailey, *et al.*[5] (sodium methoxide), followed by acetylation afforded a mixture of IIIb (30%) and IV (15%), which were separated by partition chromatography. The analytical sample of IIIb exhibited:[6] mp 191–192°; $[\alpha]_D$ +108° (*c* 1, $CHCl_3$); ORD (*c* 0.029, methanol), $[\Phi]_{700}$ +526°, $[\Phi]_{589}$ + 725°, $[\Phi]_{312.5}$ +18387°, $[\Phi]_{280}$ −1916° (!); CD (*c* 0.14, dioxane), $[\theta]_{296}$ +26730;[18] infrared λ_{max}^{KBr} 2.96, 5.66, 5.71, 5.78, 5.91 μ; nmr 59 cps (18-Me), 124 (1-Me), 128 (21-OAc), 135 (3-OAc), 287–292 (21-CH_2).

The pure sample of IV[6] showed, after crystallization from chloroform–hexane: mp 227–229°; $[\alpha]_D$ +262° (*c* 1, $CHCl_3$); ORD (*c* 0.052, methanol), $[\Phi]_{700}$ +460°, $[\Phi]_{589}$ +778°, $[\Phi]_{311}$ +15,116°, $[\Phi]_{275}$ +2695°; CD (*c* 0.13, dioxane), $[\theta]_{296-300}$ +16,240;[18] nmr 41 cps (18-Me), 119 (1-Me), 129 (21-OAc), 135 (3-OAc), 287–298 (21-CH_2).

1-Methyl-3,17α,21-trihydroxy-19-nor-9β-pregna-1,3,5(10)-triene-11,20-dione 21-Acetate (IIIc).—In one experiment, when the acetylation was performed for too short a period of time, apart

(7) A similar situation is encountered in the isomerization of the triterpene chaparrol to isochaparrol; see, T. R. Hollands, P. de Mayo, M. Nisbet, and P. Crabbé, *Can. J. Chem.*, **43**, 3008 (1965).

(8) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965.

(9) P. Crabbé, *Vietnamica Chim. Acta*, 1 (1966); see also ref 8, pp 238 and 239, and references therein.

(10) See, for example, E. Caspi, Th. A. Wittstruck, and P. K. Grover, *Chem. Ind.* (London), 1716 (1962).

(11) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(12) See, for example, G. J. Buist, C. A. Bunton, and J. Lomas, *J. Chem. Soc. Sect. B*, 1094, 1099 (1966), and references therein.

(13) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(14) (a) M. Legrand and R. Viennet, *Compt. Rend.*, **254**, 322 (1962); (b) J. A. Edwards, H. Carpio, and A. D. Cross, *Tetrahedron Letters*, No. 45, 3299 (1964).

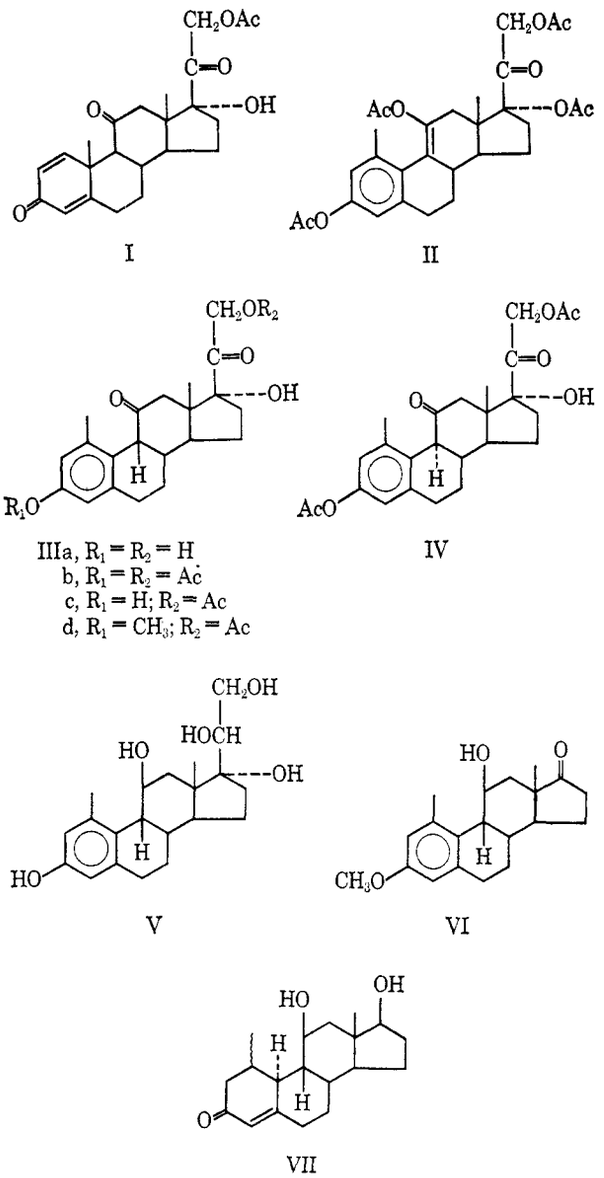
(15) The rotatory dispersion curve of lumist-4-en-3-one (reproduced in ref 8) was obtained through the kindness of Professor C. Djerassi and Professor E. R. H. Jones; see J. Castells, G. A. Fletcher, E. R. H. Jones, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 2627 (1960).

(16) Microanalyses were performed by Dr. A. Bernhardt, Max Planck Institut, Mühlheim, Germany. Melting points were determined in capillary tubes with a Mel-temp apparatus. They are corrected. Rotations were taken between 16 and 22° with a 1-dm tube at sodium D-light (589 mμ). Infrared spectra were taken with a Perkin-Elmer Model 21, NaCl prism. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU (EtOH refers to 95% ethyl alcohol). The optical rotatory dispersion (ORD) curves were measured with a Rudolph photoelectric spectropolarimeter. The circular dichroism (CD) curves were obtained with a Roussel-Jouan dichrograph at the University of Strasbourg, through the courtesy of Professor G. Ourisson. The nuclear magnetic resonance spectra (nmr) were recorded at 60 Mcps, using 5–8% w/v solution of the steroid in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies, ν, are quoted as cycles per second downfield from TMS reference (0.0 cps) and are accurate to ±0.5 cps.

(17) Bailey, *et al.*,[5] reported on oil: ultraviolet, λ_{max} 242 mμ ($E_{1\,cm}^{1\%}$ 248); infrared, ν_{max}^{Nujol} 1754 and 1210 cm^{-1} (aromatic OAc), 1734 and 1234 cm^{-1} (OAc), 840 cm^{-1} (*meta* type).

(18) P. Crabbé, *Tetrahedron*, **20**, 1211 (1964).

SCHEME I



from the mixture of diacetates (IIIb) and (IV), a small amount of 21-monoacetate (IIIc) could be isolated by direct crystallization from the reaction mixture obtained after work-up. The analytical sample of IIIc was obtained by crystallization from acetone, giving dimorphic crystals: mp 179–180, 224–226° dec; $[\alpha]_D$ +116° (*c* 0.4, $CHCl_3$); ORD (*c* 0.022, methanol), $[\Phi]_{600}$ +260°, $[\Phi]_{312.5}$ +24,220°, $[\Phi]_{295}$ +1080°; ultraviolet, λ_{max}^{EtOH} 282–284 mμ (log ε 3.22); in alkaline medium, λ_{max} 242–244 mμ (log ε 4.0), 296–298 mμ (log ε 3.5); infrared, λ_{max}^{KBr} 2.95, 5.72, 5.81, 5.93, 8.15 μ; positive triphenyl tetrazolium chloride and ferric chloride tests.

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; mol wt, 400.4. Found: C, 69.31; H, 7.07; mol wt (Rast), 404.

The strong postive Cotton effect was indicative of the 9β configuration; this was confirmed when further acetylation of IIIc gave IIIb.

1-Methyl-3,17α,21-trihydroxy-19-nor-9β-pregna-1,3,5(10)-triene-11,20-dione 3-methyl Ether 21-Acetate (IIId).—Treatment of II with sodium methoxide as described by Bailey, *et al.*,[6] gave the crude triol (IIIa) contaminated with some of its 9α isomer. Direct methylation of 14 g of this mixture with dimethyl sulfate (18 ml) in 500 ml of acetone containing 34 g of anhydrous potassium carbonate, at reflux temperature for 24 hr, followed by extraction, did not afford a crystalline product. However, when the methylated compound was acetylated at room temperature in pyridine solution (40 ml) with acetic anhydride (20 ml), followed by usual extraction procedure, the crude acetate (IIId) was obtained. Direct crystallization from benzene provided 2 g of IIId. Chromatography of the mother liquors over neutral alumina (500 g) gave, by elution with benzene–chloroform (8:2), an additional 1.1 g of 3-methoxy-21-acetoxy derivative (IIId). Recrystallization from benzene solution provided the analytical sample of IIId with the following properties: dimorphic crystals, mp 124–127, 173.5–174°; $[\alpha]_D$ +126° (*c* 1, $CHCl_3$); ORD (*c* 0.029, methanol), $[\Phi]_{700}$ +145°, $[\Phi]_{589}$ +497°; $[\Phi]_{310}$ +20,783°, $[\Phi]_{290}$ +8330°; ultraviolet, λ_{max}^{EtOH} 278 mμ (log ε 3.13); infrared, λ_{max}^{KBr} 2.98, 5.72, 5.78, 5.95, and 8.14 μ; nmr, 58 cps (18-Me), 123 (1-Me), 128 (21-OAc), 188 (9β-H), 224 (O-CH_3), 287–293 (21-CH_2).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30; O, 23.16. Found: C, 69.64; H, 7.34; O, 23.14.

1-Methyl-3,11β,17α,20β,21-pentahydroxy-19-nor-9β-pregna-1,3,5(10)-triene (V).—Diacetate (IIIb) (500 mg) was dissolved in 60 ml of anhydrous tetrahydrofuran. A stream of diborane (generated from $NaBH_4$ and BF_3 etherate)[11] was allowed to pass through the solution for a period of 2 hr. The reaction mixture was left overnight at room temperature. When cooling (ice bath), water was carefully added. After extraction with ethyl acetate, washing with water, drying over anhydrous sodium sulfate, filtration, and evaporation, a crude product was obtained. Treatment of the amorphous material (0.9 g) in tetrahydrofuran solution (10 ml) with 10% NaOH–H_2O (10 ml) and 10% H_2O_2 (10 ml), followed by usual extraction procedure, afforded the crystalline pentol (V) (350 mg). Recrystallization from methanol–water furnished the analytical sample of V: mp 237–240°; $[\alpha]_D$ −50° (*c* 1, MeOH); ultraviolet, λ_{max}^{EtOH} 282–284 mμ (log ε 3.14); in alkaline medium, λ_{max} 246 mμ (log ε 4.01), 296 (log ε 3.35); infrared, λ_{max}^{KBr} 2.9 μ (strong), 6.0, and 6.19.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.55; H, 8.38.

3,11β-Dihydroxy-1-methyl-9β-estra-1,3,5(10)-trien-17-one 3-Methyl Ether (VI).—Compound IIId (300 mg) was dissolved in 20 ml of anhydrous tetrahydrofuran. A stream of diborane (generated from $NaBH_4$ and BF_3 etherate)[11] was allowed to pass through the above solution for 1 hr. The reaction mixture was then left overnight at room temperature. When cooling at 0°, the excess of diborane was carefully destroyed with water. After extraction with ethyl acetate followed by usual work-up, the crude product was directly treated with 10 ml of 10% NaOH–H_2O and 20 ml of 10% H_2O_2 at 0° for 90 min. The ethyl acetate extract was then washed with water until neutral, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the crude 11β,17α,20β,21-tetrahydroxylated steroid. This product was not isolated but immediately dissolved in 50 ml of methanol and oxidized with 500 mg of $NaIO_4$ in 50 ml of water. The reaction mixture was abandoned overnight and then extracted with ethyl acetate. After evaporation of the solvent, the crude 17-ketone (VI) was chromatographed on 15 g of neutral alumina. Elution of the column with benzene–10% chloroform afforded a crystalline material. After purification by crystallization from acetone–hexane, 19% of analytical VI was obtained: mp 139–141°; $[\alpha]_D$ +18° (*c* 1, $CHCl_3$); ultraviolet, λ_{max} 283 mμ (log ε 3.23); infrared, λ_{max}^{KBr} 2.86, 5.76, 6.23, 6.31 μ; nmr 73 cps (18-Me), 143 (1-Me), 228 (3-OCH_3).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.33; H, 8.10.

11β-Hydroxy-1-methyl-19-nor-9β,10α-testosterone (VII).—Compound VI (200 mg) dissolved in 15 ml of tetrahydrofuran was added to 100 ml of liquid ammonia. Then 100 mg of lithium was introduced and the reaction mixture was stirred magnetically until deep blue. The reaction was allowed to proceed for 90 min. Methanol was then slowly added and the ammonia allowed to evaporate slowly. Water and 10% HCl solution were added and extraction was performed with ethyl acetate. After washing the organic layer to neutral pH followed by evaporation of the solvent, the residue was dissolved in 10 ml of methanol. To this solution a few drops of 10% HCl were added and the mixture was allowed to reflux gently for 15 min. Usual extraction procedure was followed by chromatography on 5 g of neutral alumina. Elution of the column with benzene–chloroform (1:1) afforded 85 mg of crystalline material. Recrystallization from acetone–hexane furnished the analytical sample of retro steroid (VII): long and fine needles, mp 200–201°; $[\alpha]_D$ −33° (*c* 0.5, $CHCl_3$); ORD (*c* 0.018, dioxane), $[\Phi]_{600}$ +243°, $[\Phi]_{365}$ +2280°, $[\Phi]_{277.5}$ −9363°, $[\Phi]_{270}$ −8810;[19] CD (*c* 0.05, dioxane), $[\theta]_{346}$

(19) This optical rotary dispersion curve was obtained on a Bellingham and Stanley–Bendix–Ericsson spectropolarimeter at the University of London, through the courtesy of Professor W. Klyne.

+5000, $[\theta]_{333}$ +52,500, $[\theta]_{324}$ +4970; ultraviolet, λ_{max}^{EtOH} 244–246 mμ (log ε 4.11), 300–304 (log ε 2.18); infrared, λ_{max}^{KBr} 2.82, 6.0, and 6.19 μ.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.94; H, 9.73.

Registry No.—II, 13396-30-0; IIIb, 13341-86-1; IIIc, 13341-87-2; IIId, 13341-88-3; IV, 13319-96-5; V, 13341-89-4; VI, 13396-31-1; VII, 13428-11-0.

Acknowledgments.—We wish to express our gratitude to Dr. A. D. Cross for his help and advice in the interpretation of the nmr spectra.

The Structure of Resistomycin

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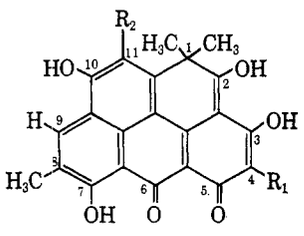
Resistomycin was isolated by Brockmann and Schmidt-Kastner[1] from *Streptomyces resistomycificus* in 1951. The partial structure of this gram-positive antibiotic was established by Brockmann and coworkers[2-5] as a methyl-2,3,7,10-tetrahydroxy-1,1-dimethyl-6H-benzo[*c*,*d*]pyrene-5(1H),6-dione. Only the position of the aromatic methyl group remains to be determined.

The nuclear magnetic resonance (nmr) spectrum of resistomycin (Figure 1, in concentrated deuteriosulfuric acid) is entirely consistent with the proposed structure (see structure **1**). The C-1 *gem*-dimethyl group exhibits two superposed 3-proton singlets at 131.5 cps. Superposition of these signals establishes that the methyl groups are equidistant from the plane of the ring and confirms the expectation of a highly aromatic ring system. The unassigned aromatic methyl group shows a 3-proton singlet at 204 cps. Three 1-proton singlets at 438, 466, and 475.5 cps are attributed to the aromatic protons. The absence of coupling between the latter protons locates the aromatic methyl group (204 cps) at position 8 or 9 (structure **1**). After 20 hr



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = Cl$
3, $R_1 = Br$; $R_2 = H$

in deuteriosulfuric acid, the protons exhibiting signals at 475.5 and 438 cps underwent complete deuterium exchange, while the 466-cps signal was essentially unchanged. Deuterium exchange of the 438-cps proton occurs at two to three times the rate observed for that of the 475.5-cps proton.

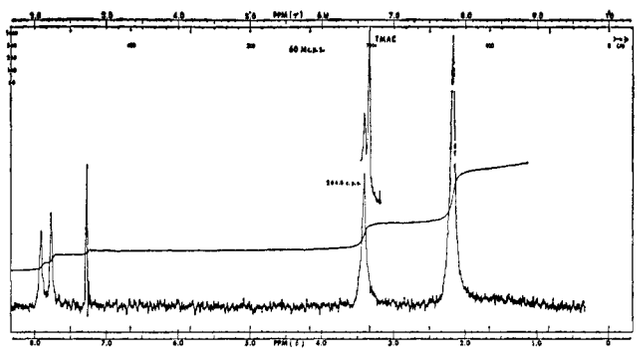


Figure 1.—Nmr spectrum of resistomycin (10% in concentrated deuteriosulfuric acid) after 5 min in solution with tetramethylammonium chloride as internal standard.

Since acid catalyzed deuterium exchange of aromatic protons was observed to follow electrophilic substitution,[6] the exchange-resistant 466-cps signal is assigned to a proton at the 9 position. This position is a *meta* position relative to both the C-7 and C-10 phenolic hydroxyl groups and would not be expected to undergo electrophilic substitution or, consequently, deuterium exchange. The aromatic methyl substituent of resistomycin must, therefore, be assigned to the 8 position.

Halogenation of resistomycin verifies the presence of only two aromatic protons susceptible to electrophilic substitution. Only a dichloro derivative (**2**) was obtained, whose aromatic proton (a 1-proton singlet at 476 cps, 10% in deuteriosulfuric acid) did not undergo perceptible deuterium exchange and whose C-1 methyl groups were deshielded by 20 cps (a 6-proton singlet at 152 cps). A paramagnetic shift of this magnitude can only be explained by chlorination at the 11 position, which results in a close spatial relationship of the C-1 methyl protons with the chlorine atom. The second chlorine substituent must be assigned to the 4 position by logical elimination of the 8 and 9 positions. Bromination yielded only a monobromo derivative (**3**) which exhibited an exchangeable 1-proton singlet at 475.5 cps and a second unexchangeable 1-proton singlet at 468.5 cps. The bromine substituent had no effect on the chemical shift of the C-1 methyl groups (132 cps) and was therefore assigned to the 4 position. Molecular models demonstrate that bromine would encounter considerably more steric hindrance from the C-1 methyl groups than would chlorine during substitution at the 11 position. These data corroborate the assignment of the 466-cps signal in the nmr spectrum of resistomycin to a proton at the 9 position and enable the 438- and 475.5-cps signals to be assigned to protons at positions 4 and 11, respectively.

Brockmann,[5] on the basis of unspecified reflection on the biogenesis of resistomycin, has tentatively assigned the aromatic methyl group to the 9 position. Deuterium exchange of the aromatic protons, nmr spectra, and the failure to derive a perchlororesistomycin dictate assignment of the aromatic methyl group of resistomycin to the 8 position (**1**).

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(6) A. I. Shatenshtein, *Kernenergie*, **5**, 335 (1962).