Preparations and Properties of Higher [2^n]Paracyclophanes, Cyclic Oligomers of *p*-Xylylene

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Syntheses and some properties of [2.2.···2]paracyclophanes [cyclic *n*-mer of *p*-xylylene, abbreviated as [2^n]paracyclophane or *n*°-PCP (*n* = 3, 4, 5, 6, and 8)] are described. At room temperature, NMR spectra of these compounds showed two singlets of benzene and ethylene proton resonances. At low temperature, however, broadening of signals of the ethylene protons were observed, while the shape of a benzene singlet was not remarkably changed. This broadening was due to the internal rotation (axial–equatorial exchange) of the ethylene protons. Based on temperature-dependent NMR spectra, energy barrier of this conformation change was concluded to be in the interesting order, 4°-PCP ([2.2.2.2]paracyclophane or [2^4]paracyclophane; similar abbreviations are used throughout this paper) > 5°-PCP > 6°-PCP > 3°-PCP. The activation energy of this conformation change for 4°-PCP was evaluated to be 3.8 kcal/mol.

In earlier papers we have described the chemistry of [2.2.2]paracyclophane (3°-PCP) and [2.2.2.2]paracyclophane (4°-PCP) where the planarity of benzene rings was concluded on spectroscopic ground to be satisfactorily retained.[1,2] In this article, we wish to report the preparations and some properties of higher [2^n]-paracyclophanes (*n*°-PCPs), cyclic oligomers of *p*-xylylene, in connection with conformation problems which may be very important in their inclusion.[3]

Preparations of 5°-PCP, 6°-PCP, and 8°-PCP were successful by the modified Wurtz condensation[4,5] of *p*-xylylene chloride,[6] and each paracyclophane was isolated by means of column chromatography coupled with fractional crystallization. 6°-PCP and 8°-PCP were also prepared by the modified Wurtz condensation of *p,p'*-di(chloromethyl)-1,2-diphenylethane.[7] Table I shows some physical properties of *n*°-PCPs. Some irregular changes in melting points of present *n*°-PCPs are similar to those of reported [2^n]metacyclophanes.[8]

Table I
Physical Properties of *n*°-PCPs

n°-PCP	Mp, °C	Recrystn solvent	Crystal form	Ref
2°-PCP[a]	285–287	Acetic acid	Needle	*b*
3°-PCP	168	*n*-Hexane	Feather	*c*
4°-PCP	185	*n*-Hexane–benzene	Prism	*d*
5°-PCP	170–172	*n*-Hexane–benzene	Prism	*e*
6°-PCP	200–202	*n*-Hexane–benzene	Plate	*e*
8°-PCP	273–275	*n*-Hexane–benzene	Scale	*e*

[a] [2.2]Paracyclophane. [b] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, 73, 5691 (1951). [c] Reference 1. [d] Reference 2. [e] This work.

NMR Spectra of *n*°-PCPs. At room temperature, each paracyclophane showed two singlet NMR absorptions due to aromatic and aliphatic protons. The aromatic δ value showed the presence of a considerable shielding effect, the magnitude of which decreased with increase of macrocyclic ring size (Table II). These observations suggest that benzene rings predominantly (in a statistical sense) take the "face" conformation[9] where the aromatic protons are shielded by other benzene rings and the magnitude of shielding effect diminishes with increase in the transannular distance of a paracyclophane. In order to investigate the conformation problem of these paracyclophanes, the NMR spectra of 3°-PCP, 4°-PCP, 5°-PCP, and 6°-PCP were measured in $CDCl_3$–CH_2Cl_2 or CS_2 solution at low temperature. The results at −75° in $CDCl_3$–CH_2Cl_2 solution are

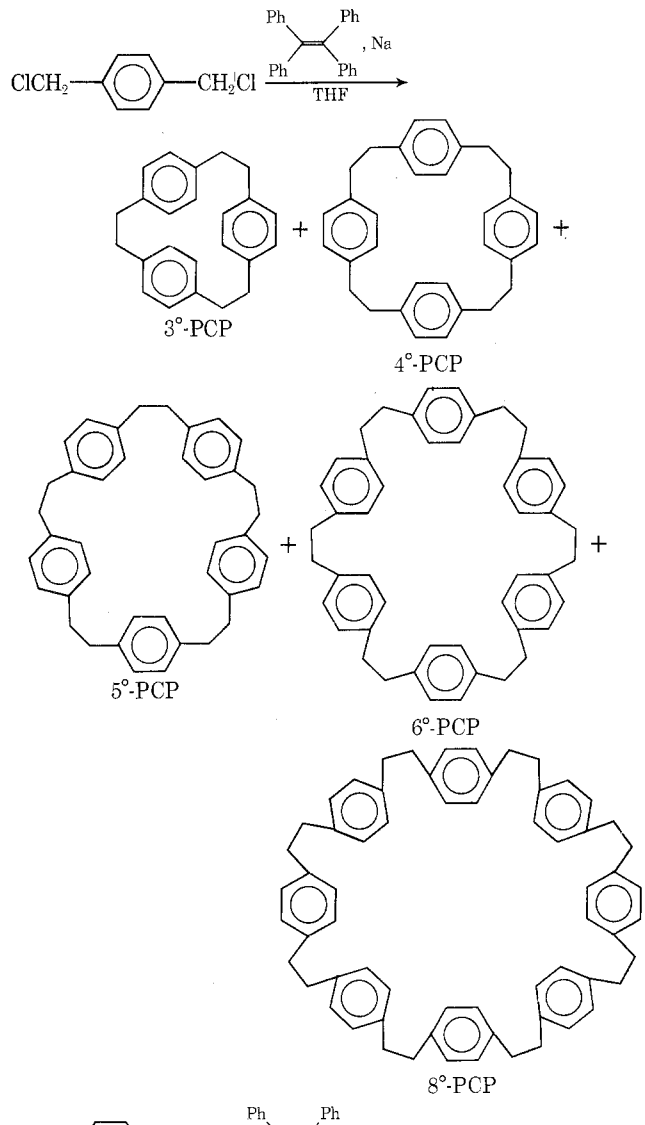

Table II
δ Values and Line Broadening[a] of n°-PCPs

Compd	δ (room temp, CCl_4, Me_4Si) CH_2	Arom	Ref	Line broadening[a] (−75°, $CDCl_3$–CH_2Cl_2) CH_2	Arom
p,p'-Dimethylbibenzyl	2.80	6.94	*b*		
2°-PCP	3.04	6.30	*c*		
3°-PCP	2.93	6.62	*d*	4.9/2.0	3.1/2.0
4°-PCP	2.84	6.65	*e*	*f*	2.8/1.8
5°-PCP	2.76	6.68	*g*	7.5/1.8	2.5/1.8
6°-PCP	2.84	6.75	*g*	7.5/3.3	3.0/3.3
8°-PCP	2.84	6.82	*g*		

[a] Relative half-width in hertz (half-width of protons of paracyclophanes compared with that of added CH_2Cl_2). [b] F. A. Bovey, "NMR Data Tables for Organic Compounds", Vol. 1, Wiley, New York, N.Y., 1967, p 426. [c] D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Am. Chem. Soc.*, **82**, 6302 (1960). [d] Reference 1. [e] Reference 2. [f] Below the coalescence temperature. [g] This work.

Table III
Uv Spectra of n°-PCPs[a] and *p*-Xylene[b]

Compd	λ_1, mμ (log ε)	λ_2, mμ (log ε)	λ_3, mμ (log ε)	λ_4, mμ (log ε)
p-Xylene[c]	274 (2.85)	269 (2.75)	266 (2.73)	260 (2.60)
2°-PCP[d]	302 sh (2.19)		285 (2.41)	
3°-PCP	276 (2.89)	269 sh (2.88)	267 (2.95)	262 (2.83)
4°-PCP	274 (3.13)	267 sh (3.16)	265 (3.20)	260 (3.09)
5°-PCP	274 (3.24)	267.5 sh (3.22)	265.5 (3.28)	260 (3.15)
6°-PCP	273.5	267 sh	265	260
8°-PCP	274	267.5 sh	265.5	260

[a] In hexane. [b] In heptane. [c] "UV Atlas of Organic Compounds", Vol. III. [d] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, 73, 5691 (1951).

listed in Table II together with δ values at room temperature. Under the condition investigated and among the compounds investigated, only ethylene protons of 4°-PCP coalesced at −71° in $CDCl_3$–CH_2Cl_2 or −85° in CS_2 ($\Delta G^{\ddagger}_{-85°}$ = 9.1 kcal/mol in CS_2). During the temperature change, the signal of ethylene protons changed from singlet to AB quartet as shown in Figure 1. This indicates that the conformation change including ethylene proton (such as axial–equatorial exchange) begins to freeze at low temperature. The peak separations of ethylene protons of 4°-PCP at various temperatures are listed in Table III. The chemical shift difference ($\Delta\delta$, $\nu_A - \nu_B$) for frozen 4°-PCP was estimated to be 51 Hz by means of computation analysis so as to give the largest correlation coefficient for the linear relationship between $1/T$ and log $2\pi(\nu_A - \nu_B)\tau$ where $\frac{1}{2}\tau$ was the rate of exchange of nuclei (Figure 2). Thus, the activation energy (E_a) of this conformation change was estimated to be 3.8 kcal/mol and the frequency factor, k_0, to be 3.0×10^6 Hz. The ethylene protons of the other paracyclophanes did not separate until −111° in CS_2 but line broadening was observed, the magnitude of which was in the order, 5°-PCP ≃ 6°-PCP > 3°-PCP. Therefore, the observed barrier ($\Delta G^{\ddagger}$) of the conformation change of ethylene protons of these paracyclophanes is concluded to be in the interesting order 4°-PCP > 5°-PCP ≃ 6°-PCP > 3°-PCP. On the other hand, aromatic protons of each paracyclophane showed only small line broadening, which indicated

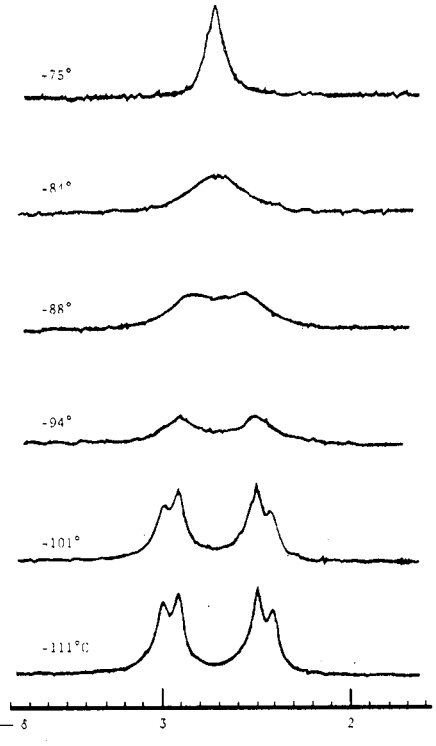

Figure 1. ^1H NMR spectra of ethylene protons in 4°-PCP at several temperatures, 100 MHz, Me_4Si, in CS_2.

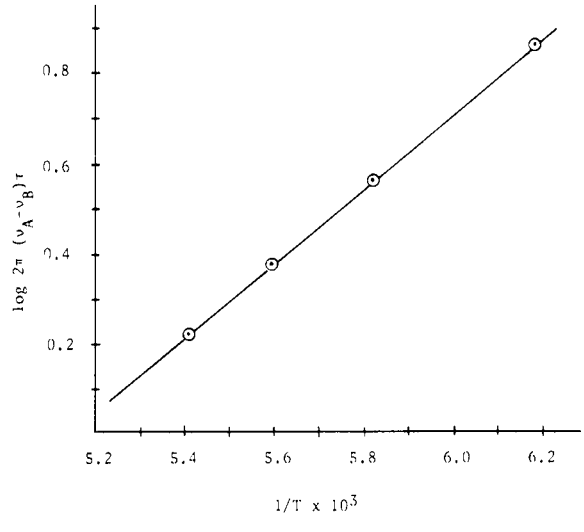

Figure 2. Temperature dependence of the rate of exchange of nuclei of ethylene protons of 4°-PCP.

that motions of benzene rings were not remarkably restricted under the condition investigated (vide infra).

The conformation change for 4°-PCP (Figure 3) is understood as the axial–equatorial change from the following considerations.

(1) Ethylene protons of 4°-PCP were frozen to two kinds of protons at low temperature (Figure 2) and the chemical shift difference ($\Delta\delta$) for the two different protons was estimated to be 0.51 ppm. This value was reasonably ascribed to the axial–equatorial difference based on the following reason. The shift difference between the axial and equatorial benzyl protons by the shielding effect from benzene rings for an "all face" [9] conformation (benzenes are perpendicular to the hypothetical molecular plane) was calculated, as an extreme, by computer with Johnson's equation[10] to be ca. 1.0 ppm, while for an "all lateral" conformation (benzenes are on the plane) as an opposite extreme (Figure

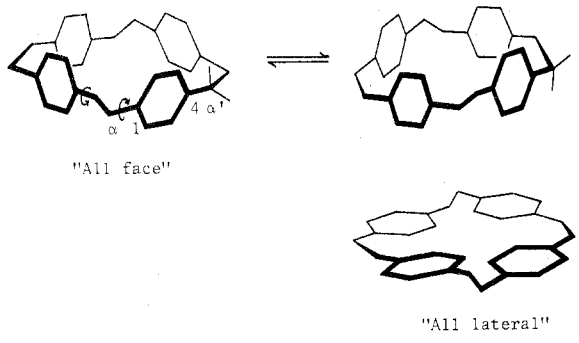

Figure 3. The axial–equatorial exchange of ethylene protons of 4°-PCP.

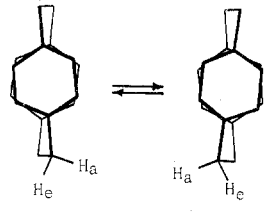

Figure 4. Conformation change of 2°-PCP.

3), $\Delta\delta$ was 0 ppm, and for freely rotating benzene rings, $\Delta\delta$ was ca. 0.12 ppm. The present observed value (0.51 ppm) suggests that the benzene rings still vibrate or rotate (around a C_α–C_1–C_4–$C_{\alpha'}$ axis) to produce a statistically averaged shielding effect; however, "face" conformation is much favored in a statistical sense under the condition investigated. This is consistent with the fact that aromatic protons showed only small line broadening.

(2) E_a of the axial–equatorial change was estimated to be 3.8 kcal/mol for 4°-PCP and this value suggests a reasonable connection between present barrier and the usual ethane barrier.[11]

The smaller $\Delta G^\ddagger$ value of 5°-PCP or 6°-PCP than 4°-PCP may be due to greater flexibility of 5°-PCP or 6°-PCP than 4°-PCP, but the unexpectedly small $\Delta G^\ddagger$ value of 3°-PCP is interesting to note. According to our calculation of energy of 3°-PCP by means of π approximation (VI/1 method[12]), the transannular distance of 3°-PCP seems to be somewhat in a slightly repulsive region.[13] This forces benzene rings to be apart, making the conformation nearly eclipsed and raising the bottom of the energy surface (the gauche conformation). Actually, 2°-PCP, where much larger π–π repulsion is involved, was reported to have a very low transition region, at near 55 K, from the measurement of heat capacity of crystals and the ΔH of the transition to be only 51 cal/mol.[14] This transition was presumed to be due to the conformational exchange of H_a and H_e as shown in Figure 4. X-Ray analysis of 2°-PCP at 93 K also indicated that this conformation change did take place even at this very low temperature.[15] This small energy barrier of the axial–equatorial change of 2°-PCP may be ascribed to the increasing π–π repulsion in the gauche conformation. This situation seems to be similar to that in 3°-PCP. Therefore, the expected order of the activation energy for the conformation change of n°-PCPs is 4°-PCP > 5°-PCP $\simeq$ 6°-PCP > 3°-PCP > 2°-PCP, just consistent with the observed order.

Other Spectral Properties of n°-PCPs. Table III shows the uv spectra of n°-PCPs together with that of p-xylene. A considerable bathochromic shift for 2°-PCP is reported where benzene rings are not planar as shown by X-ray analysis. However, uv spectra of higher paracyclophanes were very similar to that of p-xylene. Therefore, it should be concluded that benzene rings of these paracyclophanes, except 2°-PCP, are "normal" (i.e., not appreciably distorted).

In the region from 400 to 1000 cm^{-1} of ir spectra, p-xylene showed only two sharp absorptions at 796 and 482 cm^{-1}. Every paracyclophane showed an additional sharp absorption at near 600 cm^{-1} and near 800 and 500 cm^{-1} (Table IV). This may be characteristic of paracyclophane, although details are not yet known.

Table IV
Moderately Intense Absorptions of Ir Spectra of n°-PCPs at Near 800, 600, and 500 cm^{-1} [a]

2°-PCP	3°-PCP	4°-PCP	5°-PCP	6°-PCP	8°-PCP
807	804, 787	822, 813	816, 806	819	829
623	588	587, 569	594	595	576
509	469	459,[b] 452[b]	537[b]	546,[b] 463[b]	546,[b] 506[b]

[a] KBr, cm^{-1}. [b] Moderately weak absorption.

Experimental Section

Materials. 3°-PCP and 4°-PCP were prepared by the modified Wurtz condensation of p-xylylene chloride in the presence of a catalytic amount of tetraphenylethylene as described elsewhere.[1,2] Combined mixture of several reactions, from which 3°-PCP 4°-PCP had been already separated,[1,2] were chromatographed on silica gel. Early elution product with 15% benzene–n-hexane solution mainly consisted of 5°-PCP. Repeated fractional crystallizations from benzene–n-hexane gave pure 5°-PCP as colorless prisms in about 2% yield, based on p-xylylene chloride used: mp 170–172° (from benzene–n-hexane); mass spectrum m/e (rel intensity) 520 (M^+, 0.37), 168 (13), 167 (100), 165 (19), 152 (13); ir (KBr) 3075, 3040, 2995, 2915, 2845, 1511, 1438, 1415, 1310, 1200, 1142, 1093, 1022, 920, 905, 816, 806, 594, 537 cm^{-1}. Anal. Calcd for $C_{40}H_{40}$: C, 92.26; H, 7.74. Found: C, 92.02; H, 7.72.

Further elution with 15% benzene–n-hexane solution contained 6°-PCP mainly, which was purified by means of repeated fractional crystallizations. Thus 6°-PCP was obtained as white plates in about 2% yield based on p-xylylene chloride: mp 200–202° (from benzene–n-hexane); mass spectrum m/e (rel intensity) 624 (M^+, small), 168 (14), 167 (100), 165 (20), 152 (14); ir (KBr) 3070, 3025, 2995, 2845, 1510, 1440, 1415, 1338, 1200, 1096, 1021, 920, 819, 595 cm^{-1}. Anal. Calcd for $C_{48}H_{48}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 7.64.

Then elution with 50% benzene–n-hexane gave mainly 8°-PCP, which was purified similarly. 8°-PCP was obtained as scale-like crystals and melted at 273–275° (from benzene–n-hexane): mass spectrum m/e (rel intensity) 832 (M^+, very small), 415 (13), 311 (18), 156 (31), 119 (41), 118 (18), 117 (25), 103 (95), 102 (100); ir (KB) 3080, 3030, 3010, 2990, 2915, 2835, 1512, 1438, 1414, 1341, 1200, 1142, 1094, 1023, 924, 825, 576, 546, 506 cm^{-1}. Anal. Calcd for $C_{64}H_{64}$: C, 92.26; H, 7.74. Found: C, 92.36; H, 7.73.

6°-PCP and 8°-PCP were also prepared by the modified Wurtz condensation of p,p'-di(chloromethyl)-1,2-diphenylethane using a catalytic amount of tetraphenylethylene.

Measurements. NMR spectra were measured by using Varian T-60 and HA-100 spectrometers. Temperature was determined by the NMR chemical shift difference between hydroxyl and methyl protons of methanol.

Uv spectra were measured with a Hitachi Model EPS-3T spectrophotometer in hexane.

Ir spectra were measured with a Hitachi Model 285 ir spectrophotometer.

The activation energy of the conformation change of 4°-PCP was calculated from the slope of the plots of log $*2\pi(\nu_A - \nu_B)\tau$ vs. $1/T$ according to the reported procedure,[16] where ν_A and ν_B are corresponding separate chemical shifts of protons A and B and $\frac{1}{2}\tau$ is the exchange rate between A and B (cf. Figure 2).

Registry No.—2°-PCP, 1633-22-3; 3°-PCP, 283-80-7; 4°-PCP, 283-81-8; 5°-PCP, 43082-13-9; 6°-PCP, 43082-14-0; 8°-PCP, 54823-92-6; tetraphenylethylene, 632-51-9; p-xylylene chloride, 623-25-6; p,p'-di(chloromethyl)-1,2-diphenylethane, 38058-86-5.

References and Notes

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Stereochemistry of Deuteron Attack on the 3α,5α-Cycloandrost-6-ene System[1]

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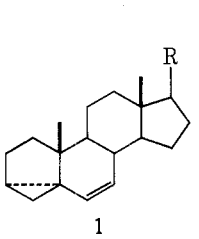
Acid-catalyzed hydration of the 3α,5α-cycloandrost-6-ene system gives the 3β-hydroxyandrost-5-ene system in high yield. In the presence of D_2O, irreversible deuteron attack at the 7 position occurs equally from the α and β faces of the steroid. Elimination of methanol from 7β-deuterio-6β-methoxy-3α,5α-cycloandrostan-17β-ol occurs by pyrolysis with 70% loss of the 7β-deuterium (cis elimination), by alumina catalysis with 48% loss of the 7β-deuterium, and by electron impact in the mass spectrometer with no loss of the 7β-deuterium.

Although it had been observed in 1946[2] that acid-catalyzed hydration of 3α,5α-cyclocholest-6-ene (**1**, R = C_8H_{17}) gives rise to cholesterol, no further study of this reaction had been reported. Acid-catalyzed rearrangements of related vinyl cyclopropanes have, however, been examined in considerable depth.[3,4] Since this hydration appeared to offer a useful method for the introduction of deuterium at the 7 position of the biologically important 3β-hydroxy-Δ^5-steroids, we have determined the direction of addition of the proton (deuteron) to the 3α,5α-cyclo-Δ^6 system.



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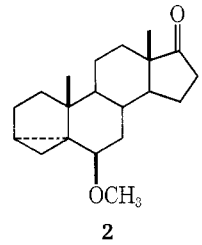

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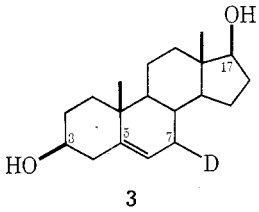

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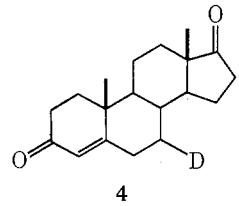

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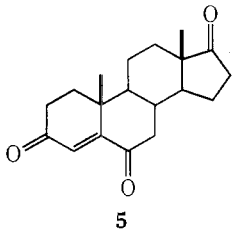

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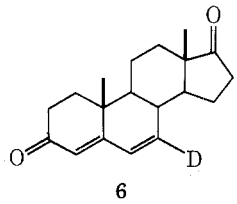

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3α,5α-Cycloandrost-6-en-17-one[5] (**1**, R = O) was prepared by the standard procedure of converting 3β-hydroxyandrost-5-en-17-one *p*-toluenesulfonate to 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**), which on treatment with alumina in refluxing xylene gave **1**, R = O, in 14% yield. Attempts to convert the 3-*p*-toluenesulfonate directly to the 3α,5α-cycloandrost-6-ene system with potassium *tert*-butoxide in *tert*-butyl alcohol, or treatment with alumina or barium oxide in refluxing xylene, led instead to the formation of the 3,5-diene.

Hydration of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O) with D_2SO_4 and D_2O in dimethyl sulfoxide at 90°, followed by acid-catalyzed exchange of the 16-deuterium, gave 3β-hydroxyandrost-5-en-17-one with incorporation of 94% of one nonexchangeable deuterium atom per molecule.

With bis(2-methoxyethyl) ether (diglyme) which had been distilled from a mixture with D_2O, 3α,5α-cycloandrost-6-en-17β-ol (**1**, R = OH) was converted by D_2SO_4–D_2O to androst-5-ene-3β,17β-diol (**3**, 87% d_1, 13% d_2), which crystallized on cooling the sealed tube. Chromium trioxide oxidation[6] and isomerization with dilute hydrochloric acid gave androst-4-ene-3,17-dione (**4**, 100% d_1, 0% d_2). Unlabeled androst-5-ene-3β,17β-diol was recovered essentially unlabeled after treatment with D_2SO_4–D_2O–diglyme under the conditions of the hydration reaction, and in experiments in which 3α,5α-cycloandrost-6-en-17β-ol was recovered, it too was unlabeled. The additional 13% of deuterium is therefore incorporated at positions 2, 3, 4, or 6 during the ring-opening hydration reactions.

That the deuteron attack on the vinyl cyclopropane (**1**, R = OH) had occurred at the 7 position was established since no loss of label occurred from the derived androst-4-ene-3,17-dione (100% d_1) under conditions (D_2SO_4–D_2O–diglyme) which caused incorporation of five deuterium atoms into testosterone at carbons 2, 2, 4, 6, and 6. A by-product in the chromium trioxide oxidation of deuterated androst-5-ene-3β,17β-diol (**3**) is androst-4-ene-3,6,17-trione (**5**).