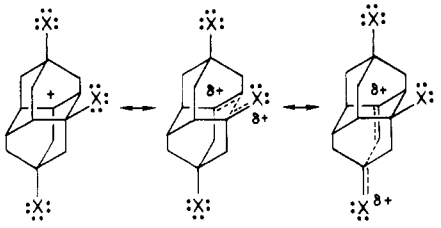
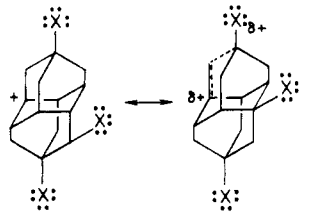
perconjugation as in 4. Such C–C hyperconjugative sta-



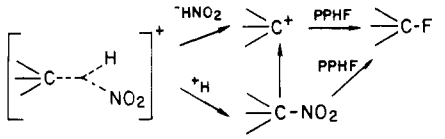
3



4

bilization in adamantyl and diamantyl cations under superacid conditions is well established.[15] Thus, the product observed in PPHF is the one with fluorine at C_7 position. In the quoted study[4] on ionic bromination, it is quite likely that the initially formed 1,4,7,9-tetrabromodiamantane in the presence of excess $AlBr_3$ rearranges to the more symmetrical and probably thermodynamically more stable 1,4,6,9-tetrabromodiamantane. This would explain that under the preparative conditions employed in the study[4] no 1,4,7,9-tetrabromodiamantane was detected.

Concerning the mechanism of the fluorinations, NO_2^+ is capable of bringing about bromide abstraction from the C–Br bonds followed by quenching of the bridgehead carbocations by fluoride from the pyridinium polyhydrogen fluoride reagent. This accounts for the S_N1 type fluorine exchange reaction of 1,4,9-tribromodiamantane. The nitronium ion is, however, also capable of attacking the tertiary bridgehead C–H bond at C_7. The transition state must involve 2e–3c interaction. No nitrodiamantane



products were, however, observed, indicating that even if nitration (competing with hyrogen abstraction) would take place, the tertiary bridgehead nitrocompounds would cleave to the same fluorinated product. Indeed electrophilic nitration of diamantane ith $NO_2^+BF_4^-$ can be carried out in solvent media other than PPHF and will be reported subsequently.

Experimental Section

1,4,9-Tribromodiamantane (1) was prepared from diamantane[16] with a literature procedure.[4] The compound gave satisfactory elemental and spectral analyses.

Reaction of 1,4,9-Trifluorodiamantane (1) with NO_2^+-BF_4^-/PPHF. To a solution of 5 g (38 mmol) of $NO_2^+BF_4^-$ in 100 mL of pyridinium polyhydrogen fluoride[2] (70%) in a 250-mL pressure reaction vessel at 0 °C was added 3.15 g (7.5 mmol) of 1,4,9-tribromodiamantane (1) with continuous stirring. After the addition the reaction mixture was stirred at 40–45 °C for 10 days. The mixture was poured into crushed ice and extracted with (2 × 100 mL) ether. The organic layer was washed successively with water, saturated $NaHCO_3$ solution, and finally with brine and dried over $MgSO_4$ and the solvent was distilled at low pressure. The 1,4,7,9-tetrafluorodiamantane (2) obtained was >90% pure and was further purified by chromatography on a silica gel column with hexane–chloroform as eluant. The yield of the purified product is 1.4 g (5.4 mmol, 72%). An analytical sample was prepared by sublimation over a steam bath at reduced pressure (~20 torr). It gave satisfactory elemental analysis (Found: C, 64.36; H, 6.15; F, 29.39. Calcd: C, 64.61; H, 6.20; F, 29.20.): mp 274–276 °C. The ^{13}C and ^{19}F NMR spectral data are given in Table I.

The ^{13}C NMR spectra were recorded in $CDCl_3$ (which also acts as the deuterium source for internal field-frequency lock) solution at room temperature on a Varian XL-200 superconducting NMR spectrometer at 50.3 MHz ^{13}C operating frequency with broadband proton noise decoupling. Chemical shifts are referenced to external Me_4Si, and the assignments are based on their position, carbon–fluorine coupling pattern, and magnitude, and proton multiplicites are obtained using APT (attached proton test)[6] experiment. The ^{19}F spectrum was recorded in $CDCl_3$ solution at room temperature on a Varian XL-200 NMR spectrometer at 188.2 MHz ^{19}F operating frequency. The chemical shifts are referenced to external $CFCl_3$ and are accurate to ±0.1 ppm.

Spin simulation and spectral fitting are based on standard Fortran program, LAME.[7,8] Initial guesses of $^nJ_{CF}$ and J_{FF} were made with the values reported earlier.[1] The values of $^nJ_{CF}$, J_{FF}, and $\Delta\delta_{FF}(^{13}C)$ were adjusted by trial to approach the experimental spectrum within 1–2 Hz. The coupling constants and the chemical shifts were then iterated to approach the given experimental spectrum. The iterations were continued until the root-mean-square (rms) frequency error reached a minimum. In general, rms frequency errors at the end of the iterations were <0.2 Hz with respect to the given experimental spectrum. The relative signs of the coupling constants were based on the initial assumption that $^2J_{CF}$ is positive.[17] The fluorine nearer to a ^{13}C isotope was always assumed to be more shielded compared to the one farther to ^{13}C.[13] In other words, $\Delta\delta_{FF}(^{13}C)$[12] was always assumed to be negative.

Acknowledgment. Support of our work by the U.S. Army Office of Research, Durham, NC, is gratefully acknowledged.

Registry No. 1, 32401-13-1; 2, 100466-62-4.

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The Conformational Preference of the Diphenylphosphinoyl Group in Cyclohexane[1]

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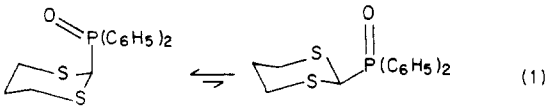
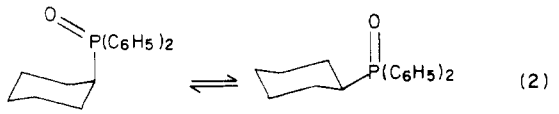
The discovery of a predominant *axial* conformation in [2-(1,3-dithianyl)]diphenylphosphine oxide (1, eq 1) was



1 axial 1 equatorial (1)

reported recently and attributed to an anomeric effect.[2] The steric repulsion present in the axial orientation (1-ax) was estimated from structural data, by means of the Hill equation,[3] to be ca. 1.25 kcal/mol.[4] However, a value for the anomeric effect in 1 could not be estimated since the conformational energy ($-\Delta G°$) of the diphenylphosphinoyl group was not known. This, coupled with the general paucity of conformational information available for phosphorus substituents, prompted this NMR study of the conformational preference exhibited by the diphenylphosphinoyl group[5,6] (eq 2).



2 axial 2 equatorial (2)

Results and Discussion

Accordingly, mobile and conformationally fixed compounds **2–6** were prepared as outlined in Schemes I and II. Table I contains the chemical shifts for the carbon atoms in **2–6** at 30 °C in $CDCl_3$. The assignments were based on anticipated shifts due to the inductive and field effects of the phosphinoyl moiety.[7] Spectroscopic comparison of **2** with anancomeric **5** and **6** by means of Eliel's equation[8] [$K = (\delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax})$] indicated the equilibrium **2**-ax ⇄ **2**-eq to be too highly biased, with a large predominance of the equatorial conformer. However, equilibrium constants closer to unity were observed for **3** and **4**, which incorporate counterpoise substituents,[9] and permitted a more precise calculation of $\Delta G°$.

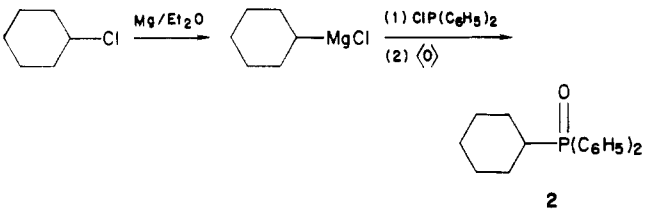
With **3**, the chemical shifts for the methyl group and C(1) offered the best signal spread and were convenient for incorporation into Eliel's equation, giving $-\Delta G°$ values of 2.72 and 2.60 kcal/mol, respectively.[10,11] In addition, the P-31 NMR spectra of **3**, **5**, and **6** were recorded, and the use of these data [δ(**3**) = 34.76 ppm; δ(**5**) = 36.35 ppm; δ(**6**) = 34.54 ppm] provided $-\Delta G°[P(O)Ph_2]$ = 2.91 kcal/mol. Similarly, with mobile **4**, C(1) chemical shift data afforded a $-\Delta G°$ value of 2.74 kcal/mol[12] using Eliel's equation. Therefore, an average $-\Delta G°[P(O)(C_6H_5)_2]$ = 2.74 ± 0.08 kcal/mol is obtained at room temperature.

Direct observation of the two conformers **4**-eq and **4**-ax was possible at low temperature (−80 °C), and the assignments for the aliphatic signals could be made easily by appropriate correlation (Scheme III). The equilibrium constant K(4-ax ⇄ 4-eq) was then readily obtained by measurement of signal intensities at low temperature, C(2,6) and C(4) being the most convenient signals to measure since they are well resolved from other peaks in the spectrum. In this way, the equilibrium constant for **4** was found to be 2.9, favoring equatorial phenyl; assuming additivity this implies $-\Delta G°[P(O)(C_6H_5)_2]$ = 2.46 kcal/mol.[12]

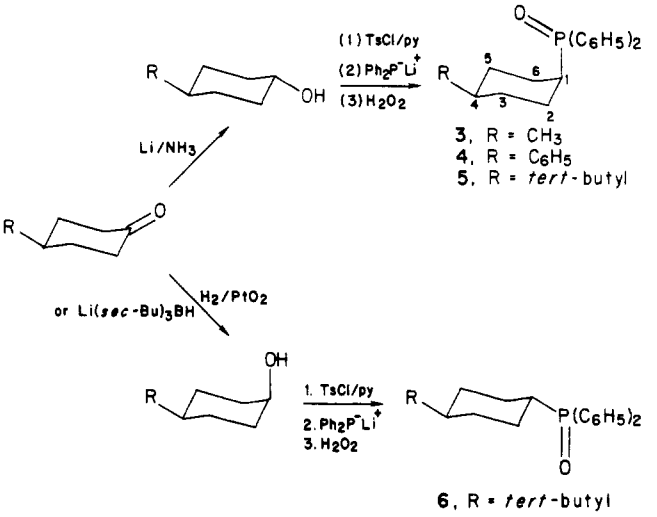
Because the $\Delta G°$ values obtained by Eliel's method are *all* substantially larger (vide supra), the value obtained at low temperature very likely reflects an entropy effect. There is considerable evidence that indicates that $\Delta S°$ for the phenyl group (in cyclohexane) is close to zero.[12,13] However, observation of Dreiding models suggests that an axial diphenylphosphinoyl group is conformationally constrained to rotamers with the P–O bond above the cyclohexane ring, whereas an equatorial diphenylphosphinoyl substituent is apparently free to fully rotate around the C–P bond. From the conformational free energy differences at room temperature (27 °C) and at −80 °C, a $\Delta S°$ = +2.6 Gibbs and $-\Delta H°$ = 1.96 kcal/mol are obtained.

The magnitude of anomeric effects is usually expressed as the difference of $\Delta G°$'s in cyclohexane and the system studied.[14] Accordingly, the anomeric effect present in

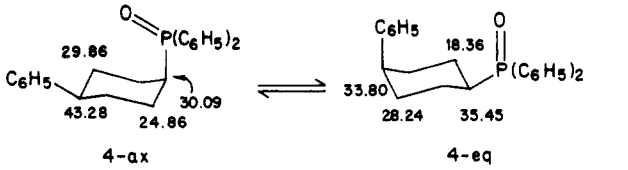
Scheme I



Scheme II



Scheme III



4-ax 4-eq

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(11) $-\Delta G°(CH_3)$ = 1.74 kcal/mol: Booth, H.; Everett, J. R.; *J. Chem. Soc., Chem. Commun.* **1976**, 278–279.

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Table I. ^{13}C NMR Chemical Shifts for 2–6 at 25.12 MHz[a]

compd	C(1)	C(2,6)	C(3,5)	C(4)	C(ipso)	C(ortho)	C(meta)	C(para)	other
2	37.16	24.78	26.32	25.75	132.06	130.86	128.32	131.18	
3	36.05	20.38	31.44	27.83	~132.4	130.68	128.27	131.09	b
4	33.34	24.76	30.47	42.42	133.40	130.72	128.23	131.16	c
5	31.79	25.91	23.75	47.53	133.45	130.55	128.25	130.89	d
6	37.08	26.83[e]	25.16[e]	47.15	132.65	130.74	128.36	130.74	f

[a] In ppm; at 30 °C, in $CDCl_3$. [b] CH_3: 18.29. [c] Phenyl substituent: C(ipso), 146.60; C(ortho), 127.26; C(meta), 128.77; C(para), 125.79. [d] $(CH_3)_3C$, 27.52; $(CH_3)_3C$, 32.48. [e] These assignments may have to be interchanged. [f] $(CH_3)_3C$, 27.27; $(CH_3)_3C$, 32.25.

2-(diphenylphosphinoyl)-1,3-dithiane[2] is thus estimated as ca. 3.74 kcal/mol. Of course, there is a well-recognized difficulty with evaluation of anomeric type effects in heterocyclic systems.[15] In the system at hand, the steric requirement of a group at the two position of the 1,3-dithiane is generally smaller (because of the long C–S bonds) to the steric requirement in a cyclohexane. Although no alternative way has become fashionable to "measure" anomeric effects, it would seem that theoretical estimation of the pure steric interactions in the axial and equatorial conformations of the heterocycle would provide the reference $\Delta G°$ (steric $\Delta G°$), from which to estimate the magnitude of the anomeric effect (eq 3).

$$\text{anomeric effect} = -\Delta G°_{\text{steric}} + \Delta G°_{\text{observed}} \quad (3)$$

For 2-(diphenylphosphinoyl)-1,3-dithiane a $\Delta G°_{\text{steric}} = -2.03$ kcal/mol may be calculated: $\Delta H° = -1.25$ kcal/mol[4] and $T\Delta S°_{298\,K} = 0.78$ kcal/mol (this work). The magnitude of the anomeric effect would then amount to ca. 3.03 kcal/mol.

Experimental Section[16]

Cyclohexyldiphenylphosphine Oxide (2). Magnesium (0.67 g, 0.028 g-atm), a crystal of iodine, and 15 mL of diethyl ether were placed in a 100-mL round-bottom flask provided with a condenser, addition, funnel, and a stirring bar. The cyclohexyl chloride (3 g, 25.1 mmol) dissolved in 15 mL of dry diethyl ether was added at such a rate as to maintain gentle reflux. A solution of chlorodiphenylphosphine (4.5 mL, 25.1 mmol) in 10 mL of ether was then added dropwise, and the reaction mixture was stirred for 1 h at room temperature. Quenching of the reaction was effected with saturated aqueous ammonium chloride. Extraction with ether and the usual workup procedure afforded the crude product, which was purified by flash column chromatography[18] [hexane/acetone (50:50)] and recrystallized from hexane/acetone (2:1) to afford 1.5 g (21% yield) of the pure product: mp 168–169 °C (lit.[19] mp 165 °C); ^1H NMR (90 MHz, CCl_4), δ 1.1–2.0 (m, 10 H, C(2–6)H, 2.07 (m, 1 H, C(1)H), 7.46 (m, 6 H, C(meta,para)H), 7.77 (m, 4 H, C(ortho)H); ^{13}C NMR in Table I; MS, m/e 284 (M^+).

Anal. Calcd for $C_{18}H_{21}OP$: C, 76.04; H, 7.44; Found: C, 75.91; H, 7.35.

(*cis*-4-Methylcyclohexyl)diphenylphosphine Oxide (3). Lithium metal (0.25 g, 0.036 mol) and 25 mL of dry THF were placed in a 250-mL round-bottom flask provided with condenser, addition funnel, and a magnetic bar, and the mixture was heated to reflux before the dropwise addition of 1.93 g (1.57 mL, 8.75 mmol) of chlorodiphenylphosphine in 50 mL of dry THF. The orange-red mixture was refluxed for 1 h, and then the excess lithium removed by transferring the solution via cannula, under positive pressure of nitrogen, to another flask capped with a rubber septum and submerged in a water–ice bath. *trans*-4-Methylcyclohexyl *p*-toluenesulfonate (1.005 g, 3.75 mmol; prepared from *trans*-4-methylcyclohexanol[20] according to the usual procedure[21]) in 50 mL of dry THF was then added, and when the addition was completed, the cooling bath was removed and the reaction mixture refluxed for 1 h. Quenching with saturated aqueous ammonium chloride, extraction with ethyl acetate, and the usual workup procedure yielded the crude phosphine precursor, which was dissolved in 25 mL of methylene chloride and stirred overnight at room temperature with 12.5 mL (large excesss) of aqueous 3% hydrogen peroxide. The organic layer was separated, dried ($MgSO_4$), and evaporated to afford the desired product (3), which was purified by flash chromatography[18] [ethyl acetate/hexane (70:30)]. Recrystallization from hexane/methylene chloride (2:1) provided 321 mg (28.9%) of 3: mp 144–146 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3 H, CH_3), 1.2–2.0 (m, 10 H, C(2–6)H), 2.20 (m, 1 H, C(1)H), 7.46 (m, 6 H, C(meta,para)H), 7.76 (m, 4 H, C(ortho)H); ^{13}C NMR in Table I; MS, m/e 298 (M^+).

Anal. Calcd for $C_{19}H_{23}OP$: C, 76.49; H, 7.77; Found: C, 76.52; H, 7.56.

(*cis*-4-Phenylcyclohexyl)diphenylphosphine oxide (4) was similarly prepared from *trans*-4-phenylcyclohexyl *p*-toluenesulfonate (1.24 g, 3.74 mmol; prepared from *trans*-4-phenylcyclohexanol[20] according to the usual procedure[21]). The desired product 4 was isolated as white crystals (40 mg, 3.0%): mp 219–220 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–2.9 (m, 10 H, C(1–6)H), 7.25 (m, 5 H, $C_6H_5C(1)$), 7.47 (m, 6 H, C(meta,para)H), 7.83 (m, 4 H, C(ortho)H); ^{13}C NMR in Table I; MS, m/e 360 (M^+).

Anal. Calcd for $C_{24}H_{25}OP$: C, 79.98; H, 6.99; Found: C, 79.94; H, 7.02.

(*cis*-4-*tert*-Butylcyclohexyl)diphenylphosphine oxide (5) was similarly prepared from *trans*-4-*tert*-butylcyclohexyl *p*-toluenesulfonate (2.33 g, 7.5 mmol; prepared from *trans*-4-*tert*-butylcyclohexanol[20] according to the usual procedure[21]). The desired product was isolated as white crystals (0.59 g, 26.5%): mp 194–195 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.87 (s, 9 H, *t*-Bu), 1.33–2.25 (m, 9 H, C(2,6)H), 2.50 (m, 1 H, C(1)H), 7.50 (m, 6 H, C(meta,para)H), 7.86 (m, 4 H, C(ortho)H); ^{13}C NMR in Table I; MS, m/e 340 (M^+).

Anal. Calcd for $C_{22}H_{29}OP$: C, 77.62; H, 8.59; Found: C, 77.84; H, 8.67.

(*trans*-4-*tert*-Butylcyclohexyl)diphenylphosphine oxide (6) was similarly prepared from *cis*-4-*tert*-butylcyclohexyl *p*-toluenesulfonate (0.58 g, 1.87 mmol; prepared from *cis*-4-*tert*-butylcyclohexanol[22] according to the usual procedure[21]). The

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(16) Melting points, determined with a Mel-Temp or an Electrothermal apparatus, are uncorrected. Infrared (IR) spectra were recorded with a Pye Unicam SP 1000 or a Nicolet MX-1-FT spectrometer calibrated against the 1601-cm^{-1} band of styrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian EM-360 or EM-390 spectrometer and are reported in ppm from internal tetramethylsilane (Me_4Si) on the δ scale. Data are reported as follows: chemical shift, multiplicity, coupling constants (Hz), integration, assignment. Carbon-13 NMR spectra were recorded on Varian XL-100 (25.12 MHz) or JEOL FX-90Q (22.49 MHz) instruments operated in pulsed Fourier transform mode and locked on solvent deuterium. The low-temperature ^{13}C NMR spectra were recorded on Bruker WM-250 spectrometer at 62.9 MHz using deuterated dichloromethane as solvent. Phosphorus-31 NMR spectra were recorded on a JEOL FX-90Q instrument operated in pulsed Fourier transform mode and locked on solvent deuterium. Data are reported in ppm from external phosphoric acid. Mass data were obtained on a Hewlett-Packard 5985-A spectrometer. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.[17]

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(23) Eliel, E. L.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5992–5994.

desired product was isolated as white crystals (0.19 g, 30.5%): mp 177-178 °C; ^{1}H NMR (90 MHz, CCl_4) δ 0.83 (s, 9 H, *t*-Bu), 0.90-2.05 (m, 9 H, C(2,6)H), 2.1 (m, 1 H, C(1)H), 7.46 (m, 6 H, C(meta,para)H), 7.77 (m, 4 H, C(ortho)H); ^{13}C NMR in Table I; MS, *m/e* 340 (M^+).

Anal. Found: C, 78.12; H, 8.61.

Acknowledgment. We are grateful to J. Espiñeira and G. Uribe for recording the C-13 NMR spectra and to Mr. H. Pastrana for some preliminary experiments. Partial financial support from CONACYT (No. 140105G 203-035) and NSF INT-8312711 is gratefully acknowledged.

Registry No. **2**, 13689-20-8; **3**, 100702-02-1; **4**, 100702-03-2; **5**, 100702-04-3; **6**, 100702-05-4; cyclohexyl chloride, 542-18-7; chlorodiphenylphosphine, 1079-66-9; *trans*-4-methycyclohexyl *p*-toluenesulfonate, 34866-36-9; *trans*-4-phenylcyclohexyl *p*-toluenesulfonate, 100702-06-5; *trans*-4-*tert*-butylcyclohexyl *p*-toluenesulfonate, 7453-04-5; *cis*-4-*tert*-butylcyclohexyl *p*-toluenesulfonate, 7453-05-6.

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Reaction of 16-Bromo-17-oxo Steroids with Potassium Cyanide

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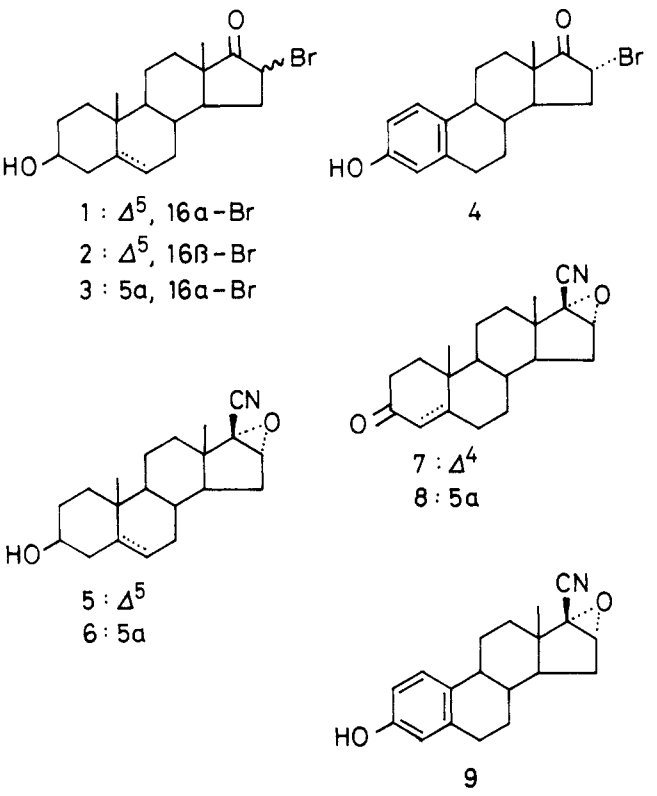
Recent studies on the reaction of 16-bromo-17-oxo steroids with nucleophiles indicated that equilibration between 16α- and 16β-bromo ketones precedes displacement of bromine with hydroxide ion and morpholine, with the ture intermediate being the 16β isomer, that 16α-substituted 17-oxo compounds are formed by S_N2 displacement of the 16β-bromo ketone (Scheme I, path a),[1] and that direct S_N2 displacement of bromine by sulfur nucleophiles is possible in the case of the α-bromo ketone without prior epimerization of the bromo ketones (path b).[2]

On the other hand, reaction of the 16-bromo ketone with methoxide ion[3] and hydrazine[4] produces the 16α-hydroxy derivatives probably by attack of the nucleophiles at the 17-carbonyl function via three-membered ring (epoxide) intermediates (path c). However, the presumed epoxide intermediates have not yet been isolated.

In conjunction with our investigation of the reaction of 16-bromo-17-oxo steroids with the nucleophiles, we explored the reaction of 16α- and 16β-bromo ketones 1 and 2 with potassium cyanide. The reaction produced 17β-cyano-16α,17α-epoxy derivative **5** by a mechanism that is stereochemically equivalent to an S_N2 displacement.

Chart I



Results and Discussion

Reaction of 16α- and 16β-bromo-3β-hydroxy-5-androsten-17-ones (**1**, **2**) with 2 equiv of potassium cyanide was carried out under controlled conditions (aqueous pyridine,[1a,b] room temperature, 24 h). Both **1** and **2** gave in high yield[5] the same product, 17β-cyano-16α,17α-epoxide derivative **5**, whose total structure was unambiguously determined by X-ray crystallography.[6] When **1** and **2** were separately treated with the nucleophile in a similar way for a shorter time (3 h), they were recovered in ca. 70% as an equilibrated mixture of **1** and **2** in the ratio of 1:1.2, which is consistent with the previously reported results,[1a,b] along with product **5** in ca. 30% yield.[7] Similar treatment of **1** and **2** in D_2O-pyridine (2 equiv, 24 h) gave **5**-*16-d* (more than 97 atom %). Moreover, when **1**-*16-d* and **2**-*16-d*, obtained by treatment of **1** with NaOD under controlled conditions, were separately subjected to reaction with cyanide (2 equiv, 24 h), the product **5** isolated did not retain deuterium at all.

The results indicated that equilibration between the 16α- and 16β-bromo ketones precedes the formation of the epoxy nitrile, in which the true intermediate is the 16β-bromo isomer and not the 16α-isomer in analogy with the reaction[1] of the bromo ketones with hydroxide ion and morpholine. Hence, the formation of the epoxy nitrile can be best rationalized as in Scheme II. Cyanide ion is considered to eject the bromide by internal displacement,

(1) (a) Numazawa, M.; Osawa, Y. *J. Am. Chem. Soc.* **1980**, *102*, 5402. (b) Numazawa, M.; Nagaoka, M.; Osawa, Y. *J. Org. Chem.* **1982**, *47*, 4024. (c) Numazawa, M.; Kimura, K.; Nagaoka, M. *Steroids* **1981**, *38*, 557. (d) Numazawa, M.; Nagaoka, M. *Steroids* **1982**, *39*, 345. (e) Numazawa, M.; Nagaoka, M.; Tsuji, M.; Osawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1983**, 121.

(2) Numazawa, M.; Madarame, M.; Ogata, M.; Kimura, K. *J. Org. Chem.* **1984**, *49*, 3231.

(3) Hassner, A.; Catsoulacos, P. *J. Org. Chem.* **1966**, *31*, 3149.

(4) Catsoulacos, P.; Hassner, A. *J. Org. Chem.* **1967**, *32*, 3723.

(5) The production of the 16α-hydroxy-17-oxo derivative (ca. 5%) was observed by TLC analysis of the reaction mixture.

(6) Swenson, D. C.; Duax, W. L.; Numazawa, M.; Osawa, Y. *Cryst. Struct. Commun.* **1982**, *11*, 617.

(7) The ^{1}H NMR spectra of **1**, **2**, and **5** proved useful for the quantitative analysis of the mixtures without isolation. The signals at δ 0.90 (s, 3 H) and 4.57 (m, 1 H) for **1**, δ 1.09 (s, 3 H) and 4.37 (t, 1 H) for **2**, and δ 0.98 (s, 3 H) and 3.83 (s, 1 H) for **5** correspond to the H at the C-18 angular methyl and the H at C-16, respectively.

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