

tions of *t*-butylferrocene and ferrocene (see below) were used in the calculations for the noncompetitive case. Obviously this approach assumes that the proportions of 1'- and 3-acetyl-*t*-butylferrocenes formed in the competition experiment were identical with isomer distributions in the noncompetitive runs.

The results for the site reactivities obtained in all of the noncompetitive runs are listed in Table I.

Competitive Acetylations of Alkylferrocenes.—A mixture of 5.00 mmoles of the alkylferrocene and 5.00 mmoles of ferrocene was acetylated competitively. The general procedure was identical with that described for the noncompetitive experiments.

Analysis of the products by v.p.c. revealed the presence of unreacted ferrocene and alkylferrocene in every instance. There were no products indicative of diacylation. However, the v.p.c. chromatograms indicated only poor resolution between acetylferrocene and the isomeric acetylalkylferrocenes. Hence, each competitive run was reduced quantitatively with a lithium aluminum hydride-aluminum chloride combination. This resulted in a mixture of ethylferrocene and the isomeric ethylalkylferrocenes which could be resolved by v.p.c. (Apiezon L, 16-ft. column, 230°).

In the case of the competitive experiment between methylferrocene and ferrocene, for example, the peak area of ethylferrocene was measured as 315, while the total ethylmethylferrocene peak area was 722. Table II lists the relative site reactivities obtained in these competitive experiments.

Thermal Conductivity Correction Factors.—The thermal conductivities of ethylferrocene *vs.* 1'-methylethylferrocene, 1,2-diethylferrocene, 1'-isopropylethylferrocene, and 1-*t*-butyl-3-ethylferrocene were checked. In every case, the peak areas per mole of sample injected were so close that no correction factor for differences in thermal conductivity was deemed necessary.

Kinetic Experiments.—The glacial acetic acid used was Baker and Adamson reagent grade. This was distilled and a fraction

boiling at 117–118° was collected. This cut was further purified by refluxing it with 7.8 ml. of acetic anhydride per 100 ml. of acid. A middle cut of this material was collected by distillation through a 2-ft. column packed with glass helices (b.p. 117–118°). This was stored under dry nitrogen.

The hydrochloric acid (Baker and Adamson, C.P. product) was used without further purification. The concentration of hydrogen chloride was determined with a potentiometric titrimeter.

General Kinetic Procedure.—The cleaving media were prepared at desired concentrations by mixing appropriate amounts of glacial acetic acid, hydrochloric acid, and, if necessary, deionized water. Carefully weighed samples of the silane (about 100 mg.) and an internal standard (about 80 mg. of octadecane, Matheson Coleman and Bell, reagent grade, m.p. 27–28.5°) were placed in a 50-ml. volumetric flask containing about 20 ml. of glacial acetic acid and immersed in a constant-temperature bath held at $25 \pm 0.02^\circ$. At zero time, the cleaving medium was added to the volumetric flask, which was then shaken vigorously, and the liquid volume brought quickly to 50 ml. with additional acetic acid. Aliquots were withdrawn periodically and poured into a sodium hydroxide solution to quench the reaction. The products were extracted twice with petroleum ether (b.p. 35–37°) and the solvent was then removed by evaporation. The residual liquid was analyzed by v.p.c.

Table III lists the data collected for the cleavage of 1'-methyltriethylsilylferrocene and is indicative of the calculations made. Since the reactions were pseudo-first order (carried out in a large excess of water) the following rate equation was used: $2.303 \log a - 2.303 \log (a - x) = k_1 t$. A plot of t *vs.* $\log (a - x)$ gave very satisfactory straight lines in all cases. The rate constants (k_1) were calculated by a least square treatment of the line slopes in each case. Duplicate and triplicate runs were made in all cases. A summary of the rate results are listed in Table IV.

[CONTRIBUTION FROM SHIONOGI RESEARCH LABORATORY, SHIONOGI & CO., LTD., FUKUSHIMA-KU, OSAKA, JAPAN]

Steric Effect on Deshielding of the Aromatic C₄-Proton by a C₅-Proton in an Octahydrophenanthrene Series¹

BY WATARU NAGATA, TADAO TERASAWA, AND KAZUO TORI

RECEIVED APRIL 15, 1964

An n.m.r. study of an A-ring-aromatic octahydrophenanthrene series revealed strong deshielding of the aromatic C₄-proton owing to the steric effect of an equatorial C₅-proton. The degree of this deshielding, which is represented by the difference in the chemical shifts between the C₁- and C₄-protons, is elucidated to be correlated to the van der Waals compression between the C₄- and C₅-hydrogens, which is represented by the interatomic distance between them. Dreiding models show that the distance is closely related to both B/C ring juncture and conformation. A large number of compounds of this series are exemplified to explain this correlation, which is believed to be very useful for estimation of the spatial structure of an analogous compound.

In nuclear magnetic resonance (n.m.r.) studies of steroids, there is considerable evidence that a proton is deshielded by steric effects of other proximate hydrogen atoms.^{2,3} Earlier studies on n.m.r. spectra of phenanthrene and 7,8-dihydrophenanthrene suggested that the steric effect may play a role in marked deshielding of the C₄- and C₆-protons besides the ring-current effect.^{4,5} In A-ring-aromatic octahydrophenanthrenes,

(1) Studies on Total Syntheses of Steroids. XV; part XIV: W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Letters*, No. 14, 869 (1963).

(2) (a) The signal shift due to deshielding of the 19-methyl group in steroids by a 6 β -methyl group was found to be about 0.10 p.p.m. [G. Slomp and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959)]. (b) Signal shifts to lower fields of the 18- and 19-methyl groups owing to introduction of an 8 β -methyl group were observed to be about 0.06 and 0.10 p.p.m., respectively [K. Tori, T. Tomita, H. Itazaki, M. Narisada, and W. Nagata, *Chem. Pharm. Bull. (Tokyo)*, **11**, 956 (1963)]. (c) In spectra of estra-1,3,5(10)-triene derivatives, a 1-methyl signal appears at about 7.6 τ because of a probable interaction with the 11-methylene, whereas a 4-methyl signal appears at about 7.8 τ in the absence of the interaction [E. Caspi, Th. A. Wittstruck, and P. K. Grover, *Chem. Ind. (London)*, 1716 (1962)]. (d) A downfield shift of 0.27 p.p.m. was observed in the C₁-proton signal due to introduction of an 11 α -methyl group into a $\Delta^{1,4}$ -3-keto steroid [K. Tori, unpublished result].

(3) R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963).

a similar deshielding of the C₄-proton can be anticipated to be caused likewise by the steric effect of the C₅-equatorial proton, at least when the B/C juncture is *trans*. However, no study has been hitherto reported on this point. In the course of a totally synthetic study of steroids we have examined the n.m.r. spectra of a number of derivatives of 2-methoxy- or 2-hydroxy-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (I),⁶ and found that remarkable deshielding ascribable to the steric effect actually exists and the degree of this deshielding is closely related to the distance between the C₄- and C₅-protons.

Inspection of molecular models (Dreiding) of various octahydrophenanthrene derivatives of formula I shows

(4) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 253.

(5) C. Reid, *J. Mol. Spectry.*, **1**, 18 (1957).

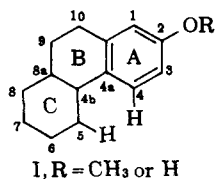
(6) The spatial structures of the new hydrophenanthrene derivatives examined in this study have been elucidated in our laboratory (see W. Nagata, T. Terasawa, and T. Aoki to be published; I. Kikkawa, K. Kawata and W. Nagata, to be published).

TABLE I
N.M.R. SPECTRAL DATA

Type	Compd.	Chemical shift, τ					$\Delta\tau_{1,4}$, p.p.m. ^a
		H ₁	H ₃	H ₄	OCH ₃	Other protons	
Type A ($c = 0.6$) ^b B/C- <i>trans</i> juncture	II	3.43	3.37	3.04	6.27		0.39
	III	3.37	3.28	2.77	6.23		.60
	IV	3.36	3.27	2.78	6.23		.58
	V	3.38	3.28	2.78	6.25	7.75 (COCH ₃)	.60
	VI	3.42	3.32	2.84	6.26	8.84 (4b-CH ₃) 9.06 (8-CH ₃)	.58
	VII	3.45	3.35	2.88	6.28	8.80 (4b-CH ₃) 8.96, 9.08 (8-CH ₃)	.57
	VIII ^c	3.43	3.31	2.83	6.25	8.74 (4b-CH ₃) 9.00 (8-CH ₃)	.60
	IX	3.41	3.31	2.85	6.24	9.17 (CH ₃)	.56
	X	3.36	3.27	2.77	6.23	8.95 (CH ₃)	.59
	XI	3.38	3.27	2.79	6.24	8.65 (CH ₃)	.59
	XII	3.39	3.31	2.79	6.25	8.97 (CH ₃)	.60
	XIII	3.35	3.28	2.78	6.23	4.11 (olefinic H)	.57
	XIV	3.37	3.27	2.78	6.23	4.13 (olefinic H)	.59
	XV	3.42	3.34	2.81		7.87 (COCH ₃) 9.10 (CH ₃)	.61
	XVI	3.44	3.37	2.86		7.85 (COCH ₃) 9.34 (CH ₃)	.58
XVII	3.36	3.28	2.80	6.23	9.10 (CH ₃)	.56	
XVIII	3.37	3.29	2.78	6.24	9.22 (CH ₃)	.59	
Type B ($c = 0.6$) ^b B/C- <i>cis</i> juncture	XIX ^d	3.44	3.35	2.86	6.26	8.87 (4b-CH ₃) 9.08 (8 β -CH ₃), 9.62 (8 α -CH ₃)	.58
Type C ($c = -0.3$) ^b B/C- <i>cis</i> juncture	XX ^e	3.40	3.31	3.01	6.25	8.69 (CH ₃)	.39
	XXI	3.37	3.29	2.98	6.24	4.07 (olefinic H)	.39
Type D ($c = 0.3-0.4$) ^b B/C- <i>cis</i> juncture	XXII ^f	3.35	3.27	2.88	6.23	8.80 (CH ₃)	.47
	XXIII ^f	3.34	3.27	2.84	6.22	9.60 (CH ₃)	.50
Type E	XXIV	3.36	3.27	2.88	6.24		.48
	XXV	3.38	3.29	2.94	6.24		.44
	XXVI	3.37	3.29	2.93	6.23	7.78 (COCH ₃)	.44
	XXVII	3.38	3.28	2.88	6.24	8.74 (CH ₃)	.50
	XXVIII	3.38	3.30	2.89	6.24	9.05 (CH ₃)	.49
	XXIX	3.39	3.31	2.87	6.23	9.07, 9.18 (CH ₃)	.52

^a Difference in chemical shifts between the C₁- and C₄-protons. ^b The van der Waals compression factor estimated from Dreiding models. ^c We thank Dr. A. Tawara of the Institute of Physical and Chemical Research (Tokyo) for supplying us with the sample of this compound. ^d See ref. 10. ^e See ref. 12. ^f See ref. 13.

that the distance between the C₄- and C₅-protons, which in this paper is suitably represented by the van der Waals compression factor c ,⁷ varies greatly with both



B/C ring juncture and conformations. Thus all the B/C-*trans* hydrophenanthrenes (type A) which are inherently of a rigid system have a c value of 0.6 as shown in Fig. 1. On the other hand, compounds having the B/C-*cis* juncture usually equilibrate between the two canonical conformers, types B and C (see Fig. 1), owing to their flexible nature. In such a case, no c -value can be estimated directly from molecular models, but it is believed to be smaller than that for type A. However, in special cases where the molecules are fixed,⁸

(7) The "compression factor c " is the difference in Å. between the sum of the van der Waals radii (2.4 Å.) and the measured interatomic distance of the relevant C₄- and C₅-hydrogen atoms [see D. M. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962)].

(8) For instance, the molecules of the compounds XX, XXI, and XXX are fixed, in spite of their B/C-*cis* juncture, by fusion with an additional ring or bridged system and that of the compound XIX probably by avoiding a 1,3-diaxial interaction of the two bulky methyl groups (see ref. 10-13).

they can take a single form, either types B or C. No interaction between the C₄- and C₅-hydrogen atoms can be expected for compounds of type C, whereas com-

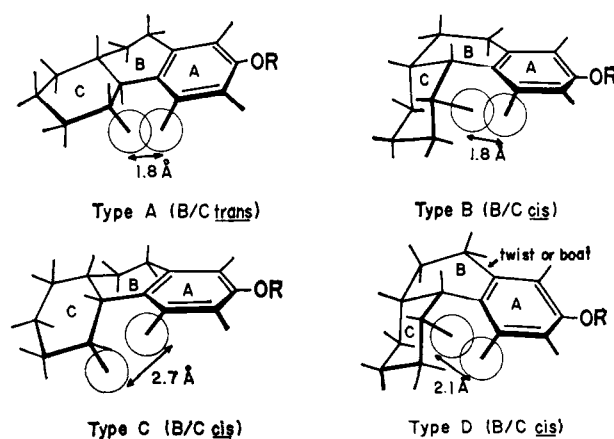
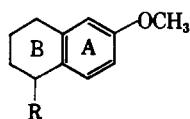
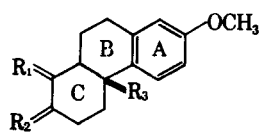


Figure 1.

pounds of type B have the same c -values as estimated for type A. In addition, a few compounds in which the B-ring is of a twist or a boat conformation were treated as type D (see Fig. 1). Compounds of this type have a c -value of 0.3-0.4. We assumed that deshielding, if any, would occur only when both C₄- and



- II, R = H
 XXVII, R = CH₂
 XXVIII, R = C₂H₅
 XXIX, R = CH(CH₃)₂



B/C *trans*

- III, R₁ = H₂, R₂ = O, R₃ = H
 IV, R₁ = O, R₂ = H₂, R₃ = H

- V, R₁ = $\begin{cases} \text{H} \\ \text{CH}_2\text{COCH}_3 \end{cases}$, R₂ = O, R₃ = H

- VI, R₁ = $\begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$, R₂ = H₂, R₃ = CH₃

- VII, R₁ = $\begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$, R₂ = $\begin{matrix} \text{O} \\ \diagup \quad \diagdown \\ \text{ } \end{matrix}$, R₃ = CH₃

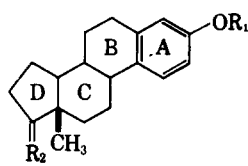
- VIII, R₁ = $\begin{cases} \text{COOCH}_3 \\ \text{CH}_3 \end{cases}$, R₂ = H₂, R₃ = CH₃

B/C *cis*

- XXIV, R₁ = H₂, R₂ = O, R₃ = H
 XXV, R₁ = O, R₂ = H₂, R₃ = H

- XXVI, R₁ = $\begin{cases} \text{CH}_2\text{COCH}_3 \\ \text{H} \end{cases}$, R₂ = O, R₃ = H

- XIX, R₁ = $\begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$, R₂ = H₂, R₃ = CH₃



B/C/D *trans-anti-cis*

- XV, R₁ = H, R₂ = $\begin{cases} \text{COCH}_3 \\ \text{H} \end{cases}$

B/C/D *trans-anti-trans*

- XVI, R₁ = H, R₂ = $\begin{cases} \text{COCH}_3 \\ \text{H} \end{cases}$

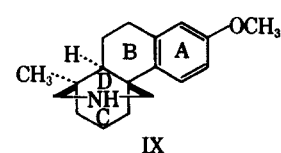
- XVII, R₁ = CH₃, R₂ = O

- XVIII, R₁ = CH₃, R₂ = $\begin{cases} \text{OH} \\ \text{H} \end{cases}$

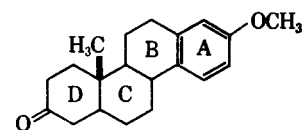
C₅-hydrogen atoms enter in a range of their van der Waals interaction (2.4 Å.), that is, the ρ -value is greater than zero, and moreover that the degree of the deshielding may increase with increasing ρ -values.

The signals of aromatic protons of the compounds examined appear as an ABK-type pattern, as is well known. We treated the signal patterns as an ABX system by the quasi-first-order approximation. Table I lists the examined compounds classified under each type and their n.m.r. spectral data. We chose 2-methoxy-5,6,7,8-tetrahydronaphthalene (II) as a reference compound because this molecule has no hydrogen atom capable of interaction with the C₄-proton. As shown in Table I, the chemical shifts of the C₁- and C₃-protons in all the compounds fall in a narrow range of about 0.1 p.p.m. On the other hand, the C₄-proton signal in compounds of types other than type C, particularly of type A, is shifted downfield in comparison with that in II, whereas the chemical shift of this proton in the compounds of type C changes slightly. It is reasonable to assume that both the steric effect of the C₅-hydrogen atom and diamagnetic anisotropies of the additional C-ring, particularly those of the C_{4b}-C₅, C₅-C₆, and C₅-H bonds, are reflected in the deshielding of the C₄-proton in compounds of types other than type C.

In order to correlate more exactly this deshielding to the ρ -value, we take the difference in the chemical shifts between the C₁- and C₄-protons, $\Delta\tau_{1,4}$, as an index to the deshielding of the C₄-proton. This treatment is

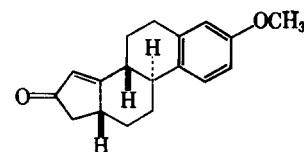


IX

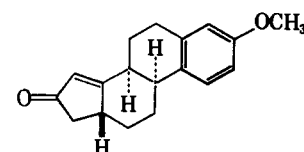


B/C/D

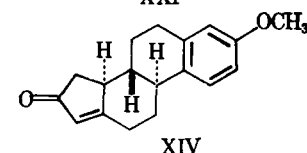
- X, *trans-anti-cis*
 XI, *trans-syn-cis*
 XII, *trans-anti-trans*
 XX, *cis-anti-cis*
 XXII, *cis-syn-cis*
 XXIII, *cis-anti-trans*



XIII



XXI



XIV

amply justified by the following reasons. Anisotropies of the additional C-ring moiety on passing from II to a hydrophenanthrene can slightly affect the C₁- and C₃-protons, as can be seen from Table I. However, substituents possessing strong anisotropies, such as a carbonyl or a double bond, even though situated at the far C₇- and/or C₈-positions, exert long-range shielding effects on the protons in the A-ring, as the signals of the C₁- and C₃-protons of the compounds having such a group are actually somewhat shifted downfield (see Table I). This long-range effect is believed to be exerted to an almost equal extent on both C₁- and C₄-protons as long as the substituent is situated at the C₇- and C₈-positions.⁹ Therefore, we can almost exclude the other effects by taking the differential chemical shift, $\Delta\tau_{1,4}$. Thus, the last column of Table I shows a successful attempt to correlated $\Delta\tau_{1,4}$ values to the ρ -value in a series of derivatives of I. The $\Delta\tau_{1,4}$ value was observed to be about 0.6 p.p.m. for the hydrophenanthrenes classified under types A and B.¹⁰ This value is large in comparison with the value of 0.39 p.p.m. for the reference compound II, implying that deshielding of the C₄-protons of the

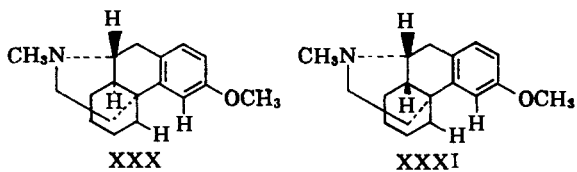
(9) In fact, substituents, such as a cyano or a carbonyl group or a double bond, at more proximate positions than the C-7 and C-8 were ascertained experimentally to exert significant effects upon the chemical shift of the C₁- and/or C₄-protons in several compounds. These compounds are, therefore, not used in the present study.

(10) The compound XIX has proved to be of type B from the fact that the 8 α -methyl signal appears at 9.62 τ under a marked shielding effect of the benzene ring⁴ (see Table I). However, this compound may not be considered strictly as a typical example for type B, because it has a C_{6b}-methyl group which, although to a minor extent, may affect the C₄-proton (*vide infra*).

compounds in these classes is significant.¹¹ The $\Delta\tau_{1,4}$ value of 0.39 p.p.m. for the compounds¹² of type C, which is the same as that obtained for II, indicates that no deshielding of the C₄-proton is caused in accordance with the negative c -value. The fairly large c -value of the compounds¹³ of type D reasonably corresponds to the observed $\Delta\tau_{1,4}$ value of about 0.5 p.p.m. The B/C-*cis* compounds with flexible conformations (XXIV-XXVI) and 2-methoxy-5-alkyl-5,6,7,8-tetrahydronaphthalenes (XXVII-XXIX), which are also examined and probably have the B-ring with a distorted half-chair conformation, are classified under type E. As expected, the compounds of this type exhibit a $\Delta\tau_{1,4}$ value (0.44-0.52 p.p.m.) intermediate between those for types B and C. As a result, this correlation will evidently provide useful information on the configurations and conformations of compounds of such a series.

One possible reason why different shielding effects are exerted on the C₄-protons in compounds in each type shown in Table I is the diamagnetic anisotropies of C-C and C-H bonds of the C-ring, which have so far been used to explain such difference in the chemical shifts of the axial and equatorial protons as observed for cyclohexane.¹⁴ However, an attempt to explain the difference in the $\Delta\tau_{1,4}$ values by bond anisotropies was unsuccessful. Our calculations showed that magnitudes of the bond-anisotropic effects of the C-ring on the C₄-protons are about 0.01 p.p.m. and about 0.02 p.p.m. of upfield shifts for compounds of type A and of type C, respectively, when the geometries estimated from Dreiding models¹⁵ and a value of -5.5×10^{-30} cm.³/molecule for the anisotropy of a C-C bond are employed as usual.¹⁴ This result implies that the anisotropy cannot explain the marked deshielding of the C₄-proton

(11) Another good example favorable to the present study is given by 3-methoxy-N-methylmorphinan (XXX) and isomeric 3-methoxy-N-methylisomorphinan (XXXI). Since the former belongs to type B and the latter to type A, the same $\Delta\tau_{1,4}$ values of 0.24 p.p.m. were obtained as expected, in spite of their different B/C ring junctures.



(12) An n.m.r. evidence for the conformation of the compound XX is that the 8 β -methyl signal appears at a relatively lower field (8.69 τ). If this compound were of type B or C, the methyl signal should appear at about 9.6 τ (see the n.m.r. data on XIX and XXIII).

(13) The half-twist or the half-boat conformation is apparently preferable for the B-rings of both compounds XXI and XXII on the grounds of the appropriate energy evaluation and of their n.m.r. data.⁴

(14) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 112.

(15) The possible distortion of the molecules arising from the van der Waals interaction was not taken into account in the present calculations.

of compounds of type A. Further, the magnitude of the anisotropic effect for compound XIX (type B) was calculated to be 0.18 p.p.m. of an upfield shift. Also for type D, a somewhat larger value than that for type B may be estimated.¹⁶ These values are indeed large and may not be ignored. However, it is suggested that differential anisotropies of the additional rings may not play a significant role in view of the fact that the same value of $\Delta\tau_{1,4}$ is actually obtained for both epimeric compounds XXX (type B) and XXXI (type A),¹¹ although they should show different $\Delta\tau_{1,4}$ values owing to the differential anisotropic effect of the C₅-C₆ bonds (0.12 p.p.m. according to our calculations). The same $\Delta\tau_{1,4}$ value of 0.58 p.p.m. observed for VI and XIX can be rationalized in the same way. Consequently, the anisotropic effects of the C-ring can not provide a satisfactory explanation for the deshielding of the C₄-proton.

On the above bases, we conclude that the van der Waals interaction between the C₄- and C₅-hydrogen atoms plays a principal role in deshielding of the C₄-proton in the hydrophenanthrenes examined, and that the deshielding increases with increasing van der Waals interaction (c -value), as anticipated earlier. From a recent n.m.r. study of simple molecules in gas states, it was proposed that the van der Waals interaction affects chemical shifts.¹⁷ This result was applied by Abraham and Holker³ to explain deshielding of the 2 β -proton due to 1,3-diaxial interaction of the 4 β -methyl group of 2 α -bromolanost-8-en-3-one. Although the nature of the deshielding mechanism by this interaction is not very apparent at present, we suppose that a hydrogen atom in an S-state might be distorted by a van der Waals interaction owing to steric hindrance of another hydrogen atom or other atoms, and this distortion can cause dedeshielding of the affected proton.¹⁸

Experimental

The n.m.r. spectra were taken with a Varian A-60 spectrometer on 2-5% (w./v.) solutions of the samples in deuteriochloroform containing tetramethylsilane as an internal reference at room temperature. Calibration of the spectrometer was checked according to Tiers and Hotchkiss.¹⁹ Chemical shifts are expressed in τ -values. Accuracy limits of the measurements are about $\pm 0.02 \tau$.

Acknowledgment.—We thank Dr. Y. Sawa of this laboratory for the data on morphinanes and Dr. I. Kikkawa of this laboratory for providing us with several samples used.

(16) The indefinite conformation of the B-ring made the calculation difficult.

(17) W. T. Raynes, A. D. Buckingham, and H. J. Bernstein, *J. Chem. Phys.*, **36**, 3481 (1962).

(18) An atom in an S-state distorted by a uniform electric field is known to be deshielded [see A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960)].

(19) G. V. D. Tiers and D. R. Hotchkiss, *J. Phys. Chem.*, **66**, 560 (1962).