were critical, they were obtained from the maxima or geometric center of each resonance for volume fractions of nortricyclene in carbon tetrachloride of approximately 1, 0.25, 0.06, 0.016, and extrapolating to infinite dilution.

1,3,4,5-Tetramethyl-2-methylene-bicyclo[3.1.0]hex-3-ene was obtained from Dr. L. deVries.[37] Two side bands from the vinyl peak were used to obtain the frequencies of the cyclopropyl peaks by interpolation, the chemical shift difference between the cyclopropyl hydrogens being 3.9 c.p.s. The chemical shift of the center of the cyclopropyl methylene quartet was measured by interpolation from side bands from tetramethylsilane for a 5% w./v. solution of the hydrocarbon in carbon tetrachloride and found to be 31.2 c.p.s.

2-Oxa-7,7-dichloronorcarane of b.p. 50–52° (1.6–1.9 mm.), $n^{25.7}$D 1.4981, was provided by Professor W. E. Parham.[38] The n.m.r. spectrum of a 5% w./v. solution of 2-oxa-7,7-dichloronorcarane in carbon tetrachloride showed two main groups of peaks, the larger group at high field being assigned to the methylene hydrogens at C-4, C-5, and the cyclopropyl methine hydrogen at C-6; and the smaller group at low field to the methylene hydrogens at C-3 and the cyclopropyl methine hydrogen at C-1. The latter gave a prominent unsymmetrical doublet on the low-field side of the lower group of peaks, due to *cis*-vicinal spin coupling with the cyclopropyl methine hydrogen at C-6. The frequencies of the peaks in this doublet were determined by side-band superposition from tetramethylsilane.

Dicyclopropylmethane was provided by Professor H. Hart.[39] The acyclic methylene resonance appeared as a broadened doublet near the cyclopropyl methine peaks. The chemical shift for the center of this doublet was obtained by extrapolation to infinite dilution and found to be 65.4 c.p.s. downfield from tetramethylsilane.

***trans*-3-(*trans*-2'-Carboxypropenyl)-2,2-dimethylcyclopropane-1-carboxylic acid** was the dextrorotatory enantiomer, m.p. 164–165°, obtained from Professor Y. Inouye.[40] The line positions were measured by superimposing side bands from chloroform.

Methyl *trans*-3-(*trans*-2'-carbomethoxypropenyl)-2,2-dimethylcyclopropane-1-carboxylate, m.p. 80°, was also provided by Professor Y. Inouye.

2,2-Dimethyl-*trans*-3-phenylcyclopropane-1-carboxylic acid was provided by Professor F. Sorm[41] and had m.p. 102°. Approximate chemical shifts (accurate to ±1 c.p.s.) were obtained for the methyl and cyclopropyl hydrogens by interpolation from a tetramethylsilane peak (internal reference) and the low-field cyclopropyl doublet, which has been accurately calibrated. The chemical shift differences were thus found to be 48 c.p.s. between the cyclopropyl hydrogens and 31 c.p.s. between the *gem*-dimethyl groups.

2,2-Dimethyl-*cis*-3-phenylcyclopropane-1-carboxylic acid was also provided by Professor Sorm and had m.p. 134°. The chemical shift between the cyclopropyl hydrogens was 39 c.p.s., and between the *gem*-dimethyl groups only 2 c.p.s.

2,2-Dimethyl-*trans*-3-phenylcyclopropane-1-carboxamide was obtained from Professor G. W. Perold.[42] The chemical shifts were approximately 55 c.p.s. between the cyclopropyl hydrogens and 27 c.p.s. between the *gem*-dimethyl groups.

Dimethyl 2,2-Dimethylcyclopropane-*trans*-1,2-dicarboxylate.—The parent diacid was obtained from Professors Y. Inouye and M. Matsui, who report m.p. 210–212° and 212–213°, respectively. The combined samples were esterified with excess diazomethane, and the product was microdistilled at 14 mm. with a bath at 125–130° and gave diester of n^{24}D 1.4434. The high-field cyclopropyl ^{13}C-satellite was a slightly unsymmetrical doublet. The resonances were calibrated by side-band superposition from the carbomethoxyl peak.

Dimethyl 1,2-dimethylcyclopropane-*cis*-1,2-dicarboxylate was provided by Professor L. L. McCoy and contained 7% of the *trans* isomer. Two side bands from the methyl peaks were placed on either side of the upfield cyclopropane doublet and the splitting determined by interpolation. The analysis of the cyclopropyl methylene quartet indicated that the chemical shift between the cyclopropyl hydrogens was 79.0 c.p.s.

Acknowledgment.—Besides the generous gifts of samples of cyclopropane derivatives mentioned above, we are deeply grateful to Drs. A. A. Bothner-By, J. D. Swalen, and Professor K. B. Wiberg for supplying us with program decks for the calculation and fitting of n.m.r. spectra for use with the IBM 7090 computer. Mr. K. Servis and Mr. L. Sloan provided extensive help with the computations.

(37) L. de Vries, *J. Am. Chem. Soc.*, **82**, 5242 (1960).
(38) E. E. Schweizer and W. E. Parham, *ibid.*, **82**, 4085 (1960).
(39) H. Hart and O. E. Curtis, *ibid.*, **78**, 112 (1956).
(40) Y. Inouye, *Bull. Inst. Chem. Res., Kyoto Univ.*, **35**, 49 (1957); *Chem. Abstr.*, **52**, 11759 (1958).
(41) J. Karkas, F. Kourim, and F. Sorm, *Chem. Listy*, **52**, 695 (1958); *Chem. Abstr.*, **52**, 13651 (1958).
(42) G. W. Perold, *J. S. African Chem. Inst.*, **10**, 11 (1957).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A., MEXICO D.F., MEXICO]

Spectra and Stereochemistry. VII.[1,2] Long-Range Shielding by Nitrile Groups

BY A. D. CROSS AND I. T. HARRISON

RECEIVED MAY 9, 1963

The long-range shielding of steroidal angular methyl protons by cyano groups has been calculated and compared with experimental values for the methyl proton resonance shifts. The importance of other factors which influence the methyl proton resonances is commented upon. Evidence is presented which suggests that in 5α-cyano-3-keto-steroids ring A is distorted from the chair form.

In recent years the utility of nuclear magnetic resonance (n.m.r.) spectra in steroid chemistry has developed rapidly. Shoolery and Rogers[3] in a classical opening study of steroid n.m.r. spectra demonstrated the close relation of the resonance frequency of angular methyl protons to the nature of, and orientation of, substituent groups on the steroid skeleton. Moreover, they observed the independent additivity of the frequency shifts of the angular methyl protons induced by several different functional groups. These concepts have been substantially extended,[1,4-16] though it has become apparent that where ring conformational changes occur, considerable caution must be exercised when considering the additivity of angular methyl proton frequency shifts, especially where long-range shielding effects are operative.[4,14]

In connection with some studies of 16,17-disubsti-

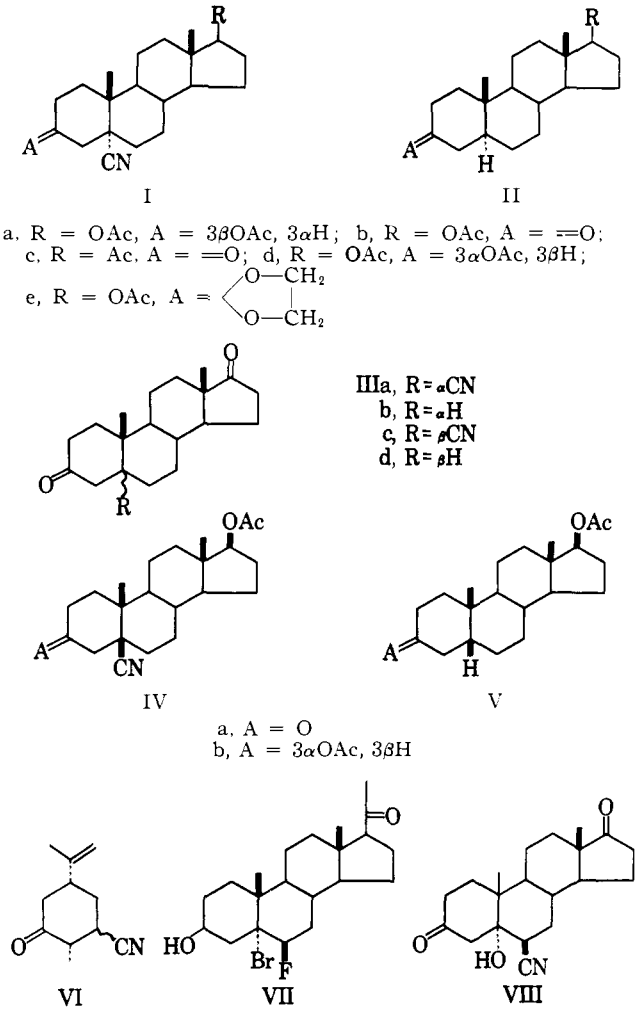
(1) Part VI: A. D. Cross, H. Carpio, and P. Crabbé, *J. Chem. Soc.*, in press.
(2) This paper constitutes Steroids. CCXXXVIII. For part CCXXXVII, see F. A. Kincl and A. F. Pi, *Ciencia Mex.*, **22**, 49 (1963).
(3) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).
(4) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961).
(5) G. Slomp and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959).
(6) L. L. Smith, M. Marx, J. J. Garbarini, T. Foell, V. E. Origoni, and J. J. Goodman, *ibid.*, **82**, 4616 (1960).
(7) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).
(8) J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960).
(9) B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschmann, and J. M. Chermeda, *J. Am. Chem. Soc.*, **82**, 3995 (1960).
(10) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963).
(11) J. Jacquesy, J. Lehn, and J. Levisalles, *Bull. soc. chim. France*, 2444 (1961).
(12) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamato, and K. Tsuda, *Chem. Pharm. Bull.*, **10**, 338 (1962).
(13) A. D. Cross, *J. Chem. Soc.*, 2817 (1961).
(14) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962), and unpublished observations.
(15) J. Iriarte, J. N. Shoolery, and C. Djerassi, *J. Org. Chem.*, **27**, 1139 (1962).
(16) E. Caspi, Th. A. Wittstruck, and P. K. Grover, *Chem. Ind.* (London) 1716 (1962).

tuted steroids,[17,18] it became necessary to assess the contribution of nitrile substituents to the shielding of angular methyl protons; n.m.r. spectra were therefore obtained for several cyano-steroids and the results are discussed here with particular reference to the long-range shielding effects of the C≡N triple bond, and to the effects of stereochemical changes upon the additivity of the nitrile shielding contribution.

Reddy, Goldstein, and Mandell[19] have shown that for acyclic nitriles the long-range shielding of a methyl group by the nitrile may be calculated in a manner similar to that used for the acetylenic triple bond. The applicability of this method to cyclic systems was therefore tested for steroids of known configuration. For each of the nine 5-cyano-steroids Ia–d,[20] Ie, IIIa, IIIc, IVa,[20] and IVb[21] the long-range shielding of the 19-angular methyl protons by the C≡N triple bond was calculated as follows. From Dreiding models[22] the distance r, in Å., between the center of the circle described by the protons of the freely rotating methyl group and the midpoint of the C≡N bond was measured, as was also the angle θ subtended by the line represented by r and the C≡N bond axis.[23,24] Limiting values ($\Delta\nu$) for the long-range shielding of the 19-methyl protons due to the anisotropy of the C≡N bond in the 5-cyano-steroids (Table I) were calculated by substitution of the measured values of θ and r in eq. 1,[25] where $\Delta\nu$, r, and θ are as defined above, and $\Delta\chi$ is

$$\Delta\nu = 1/3\,\frac{\Delta\chi(1 - 3\cos^2\theta)}{r^3} \qquad (1)$$

the anisotropy in the molecular magnetic susceptibility of the C≡N bond along its symmetry axis.[26] The calculated $\Delta\nu$ values (see Table I, column 4), were then compared with the observed shifts of the 19-angular methyl proton frequencies (Table I, column 8), the latter being derived from a comparison of n.m.r. spectra of the parent 5-H steroid and the 5-cyano derivative.[28] It is apparent that the observed resonance frequencies for the 5α-cyano-steroids show a substantial *increase* over those of the parent compounds, whereas, if long-range shielding by the C≡N triple bond were the sole new factor influencing the 19-proton resonance frequency, a substantial *decrease* is calculated. This discrepancy must be due principally to the anisotropy of the highly polar C_5–C≡N single bond which is also introduced into the molecule, and to the distortion of the magnetic environment of the methyl group by the C—C≡N dipole. Moreover, it is clear from the differences between the observed and calculated frequency shifts that the deshielding caused by these additional factors must be greater in magnitude than, and of opposite sign to, the long-range shielding due to the C≡N triple bond. This deshielding is given a numerical value in column 9 of Table I. It is of distinct interest that for the 5α-cyano-3-keto-steroids Ib, Ic, and IIIa, this value is of a similar order of magnitude to the recorded angular methyl proton shifts caused by other polar 5α-axial single bonds in 3-keto-steroids, *e.g.*, 5α-Br (+19 c.p.s.), 5α-Cl (+13 c.p.s.), and 5α-OH (+10 c.p.s.).[11,29] Levisalles and his co-workers in their detailed examination of numerous substituted 5α-cholestan-3-ones discussed the observed 19-proton frequency shifts solely in terms of the diamagnetic anisotropy of the polar 5α-σ-bond, and quote a figure of +7.5 c.p.s. for the additive shift caused by the 5α-cyano group.[11] It is now apparent that this figure gives an incomplete picture of the shielding effects of the 5α-cyano group



averages of six measurements, and calculations have been made for two values of θ, these being the limits within which all measured values fell. An accuracy of ±1° was usually obtainable.

(24) The center of the circle described by the angular methyl protons was chosen as a point approximation for the average of proton position in the measurement of r. It should be noted that from a consideration of the factor r^{-3}, which enters into eq. 1 for calculating the shielding effect, the proton nearest to the midpoint of the C≡N bond should experience a greater shielding effect than more remote ones. However, the calculation also involves a term containing $\cos^2\theta$ and, for this reason, the nearer proton could be the less favorably situated for shielding by the C≡N group. We believe our compromise to be a reasonable approximation.

(25) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

(26) The value of $\Delta\chi$ used in this work is that employed by Goldstein and his collaborators, multiplied by 3/2 to allow for the change to a 60 Mc./sec. oscillator frequency in our work from the 40 Mc./sec. instrument of the earlier investigators.[19] However, Professor Goldstein has very kindly informed us that a revision of $\Delta\chi$ to a higher value is indicated from subsequent work in his laboratories. Pople[27] has given a rough value (10 p.p.m.) for the diamagnetic shift of the acetylene proton, due to the triple bond anisotropy, which when substituted in eq. 1 leads to a value of $\Delta\chi$ substantially higher than that calculated later.[19] A correct value of $\Delta\chi$ is not critical for the calculations made in the current work since a larger value of $\Delta\chi$ would serve only to emphasize the disparity between the observed and calculated 19-H frequency shifts.

(27) J. A. Pople, *Proc. Roy. Soc.* (London), **A239**, 550 (1957).

(28) Positive values of $\Delta\nu$ indicate deshielding of angular methyl protons such that their chemical shifts, ν, are increased in magnitude relative to a tetramethylsilane (TMS) internal reference (0.0 c.p.s.). All chemical shifts described in this paper are for operation with a 60 Mc./sec. oscillator.

(29) It is pertinent to note that any increase of $\Delta\chi^{26}$ will raise the $\Delta\nu_{calcd}$ values (Table I, column 4) and $\Delta\nu_{obsd} - \Delta\nu_{calcd}$ values (Table I, column 9).

(17) P. Crabbé, L. M. Guerrero, J. Romo, and F. Sánchez-Viesca, *Tetrahedron*, **19**, 25 (1963).

(18) A. D. Cross and P. Crabbé, unpublished observations. A detailed account of the n.m.r. spectra of these compounds will appear shortly.

(19) G. S. Reddy, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.*, **83**, 1300 (1961).

(20) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961).

(21) A. Bowers, unpublished results, obtained this cyanosteroid some years ago by the same procedure as reported in the Experimental section.

(22) A. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(23) For each steroid three separate models were made and on each model r and θ were measured twice. Values of r used in the calculations are thus

TABLE I

CALCULATED AND OBSERVED RESONANCE FREQUENCIES FOR THE 19-PROTONS OF SOME 5-CYANO-STEROIDS,[28] IN COMPARISON WITH 5H-STEROIDS

1	2	3	4	5	6	7	8	9
Cyano-steroid	r, Å.	θ, deg.	Calcd. $\Delta\nu$ (c.p.s.) due to long-range shielding	Obsd. 19-H frequency, c.p.s.	Parent steroid	Obsd. 19-H frequency (c.p.s.) in parent steroid	Obsd. $\Delta\nu$, c.p.s.	$\Delta\nu_{obsd} - \Delta\nu_{calcd}$, c.p.s.
5α-CN					5α-H			
Ia	4.76	15–17	−6.9 – −7.1	60.2	IIa	49.6	+10.6	+17.5 – +17.7
Ib	4.80	15–18	−6.6 – −6.9	69.0	IIb	61.0	+8.0	+14.6 – +14.9
Ic	4.80	15–18	−6.6 – −6.9	68.5	IIc[a]	61.5	+7.0	+13.6 – +13.9
Id	4.76	15–17	−6.9 – −7.1	57.3	IId	48.1	+9.2	+16.1 – +16.3
Ie	4.72	17–19	−6.8 – −7.0	59.6	IIe	48.8	+11.8	+18.6 – +18.8
IIIa	4.76	18–20	−6.5 – −6.7	70.7	IIIb	63.2	+7.5	+14.0 – +14.2
5β-CN					5β-H			
IIIc	3.46	52–55	+0.2 – −1.1	77.8	IIId	62.9	+14.9	+14.7 – +16.0
IVa	3.45	51–54	−0.4 – −1.9	76.5	Va	62.3	+14.2	+14.6 – +16.1
IVb	3.44	50–54	−0.4 – −2.5	70.8	Vb	57.2	+13.6	+14.0 – +16.1

[a] This compound has been examined in three other independent investigations and the recorded values are 61.5,[3] 60.4,[4] and 61.5 c.p.s.[5] To convert the available n.m.r. information to values relative to a common internal reference (TMS) we have taken $\nu_{TMS} - \nu_{benzene}$ = 384 c.p.s. and $\nu_{TMS} - \nu_{H_2O}$ = 282 c.p.s. for a 60 Mc./sec. oscillator.

since their additivity shift value incorporates the diminution in the over-all frequency shift due to the long-range shielding by the C≡N triple bond.

A further complication exists. Of the six 5α-cyano-steroids studied the structure in which dipolar repulsion between the 5α-cyano and the substituent at C_3 is at a minimum is that (Ia) containing a 3β-acetate. In the other five compounds (Ib–Ie, IIIa) dipolar repulsion leading to ring A distortion is a possibility. A comparison of the observed shifts (Table I, column 8) for 5α-cyano-steroids carrying 3β-acetate (Ia) and 3-keto (Ib, Ic, IIIa) substituents reveals that for the former substituent the value of $\Delta\nu$ is consistently +3.0 ± 0.5 c.p.s. higher. Here, the contribution to $\Delta\nu$ of factors involving the polar 5α-single bond is actually no less than +17.5 c.p.s. (Table I, column 9). A plausible explanation of the higher value of $\Delta\nu$ in the 3β-acetate relative to the 3-ketone is that in the 5α-cyano-3-ketones ring A is distorted from its chair conformation (Fig. 1) in deuteriochloroform solvent by a mutual repulsion of the C=O and C—C≡N dipoles. This causes a shift in position of the 19-methyl protons either to a position nearer the cone of magnetic shielding (Fig. 2) or to a shielded position (Fig. 3). A net *decrease* in the deshielding experienced by the methyl protons results. Hence, considerable caution must be exercised when calculating additivity shifts due to nitrile where conformational distortion can occur.

The observed 19-methyl proton frequency shifts, $\Delta\nu$, for the 5α-cyano-3α-acetate Id, +9.2 c.p.s., and the 5α-cyano-3-ethylene ketal Ie, +11.8 c.p.s., relative to their parent 5α-H steroids, are close to the value, +10.6 c.p.s., found for the 5α-cyano-3β-acetate Ia. Having due regard to the possible magnitude of the experimental error in the measurement of chemical shifts (±1 c.p.s.), no firm conclusions may be arrived at concerning the possible distortion of ring A from the chair form in these compounds. Distortion may well occur in the 3α-acetate Id where, in contrast to the ketal Ie, a distortion toward the boat form does not introduce serious 1,3-nonbonded diaxial interactions. However, in the absence of a powerful long-range shielding group at C_3 the 19-H frequency is a much less sensitive indicator of the conformational change.

Cyclohexane ring distortion from the chair form in 3-cyano-2,3-dihydrocarvones (VI) where the cyano group is axially oriented (a structural analog of 5α-cyano-3-keto-steroids) has been considered briefly by Djerassi, Allinger, and their co-workers.[30] These authors were unable to estimate the contribution to observed dipole moments or rotatory dispersions by nonchair forms which arise from electrostatic repulsion between C=O and C≡N dipoles. However, they pointedly noted that in 3-cyano-2,3-dihydrocarvones

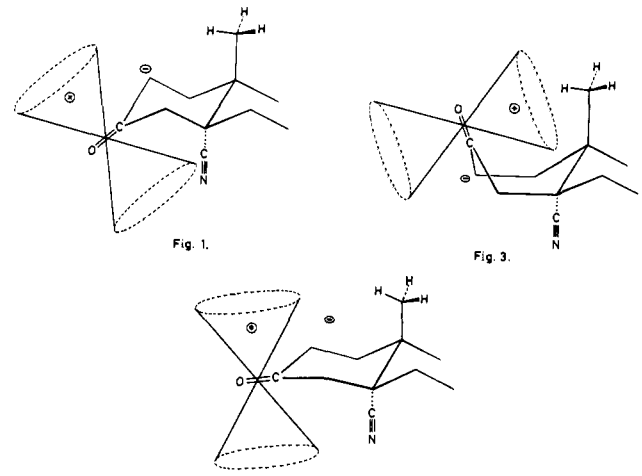


Fig. 1–3.—Position of 19-protons relative to carbonyl shielding cone for different ring A conformations.

the difference in molecular amplitude of the Cotton effect (Δa = 15) of the axially oriented cyano-ketone in methanol (a = +69) *vs.* isooctane (a = +54) is somewhat larger than the difference (practically no change) observed between these two solvents in the equatorial epimer. Their observation is compatible with some ring distortion through dipolar interaction. It may be noted also that in a single cyclohexane ring the strain induced by this interaction can be relieved by numerous bond angle distortions which can occur much less readily in a 5α-cyano-3-keto-steroid. In the latter a displacement of the carbonyl axis is thus more probable. Although the 5α-cyano-3-ketone (Ib) was insoluble in isooctane a comparison of the optical rotatory dispersion (O.R.D.) in methanol *vs.* dioxane was attempted (Fig. 4). Unfortunately the O.R.D.

(30) C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *J. Org. Chem.*, **28**, 1632 (1963). The authors are indebted to Prof. C. Djerassi for discussion, and for access to results prior to their publication.

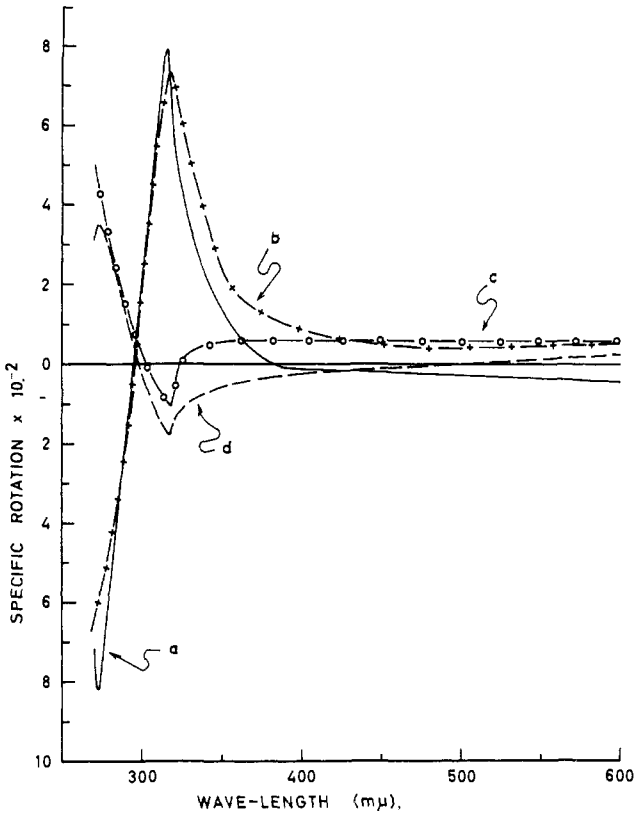


Fig. 4.—Optical rotatory dispersion curves of 5α-cyano-17β-hydroxy-androstan-3-one acetate: a, in methanol; b, in dioxane; of 5β-cyano-17β-hydroxy-androstan-3-one acetate: c, in dioxane; d, in methanol.

curve with dioxane solvent shows no trough down to 270 mμ. Hence, no valid comparison of amplitudes is possible.[31]

Djerassi and his co-workers have recently demonstrated that ring A of 5α-halo-3-ketones can be distorted from a chair conformation dependent upon the solvent used for the optical rotatory dispersion studies.[33] Therefore the additive frequency shift for 5α-bromine (19 c.p.s.), determined from an examination of 5α-bromo-3-*ketones*,[11] was checked for a 5α-bromo-3β-*alcohol*. Clearly, if a considerable discrepancy of calculated and observed resonance frequencies of the 19-methyl protons were discovered, then conformational distortion due to dipolar repulsion also exists in 5α-bromo-3-ketones. However, the calculated 19-proton resonance of 5α-bromo-6β-fluoro-3β-hydroxy-5α-pregnan-20-one,[34] 74.5 c.p.s.,[35] is in excellent agreement with the experimental value of 74.5 c.p.s.[36] Thus, for solvent deuteriochloroform the n.m.r. method indicates that ring A of 5α-bromo-3-ketones remains in the chair form. The apparent absence of ring A distortion for 5α-bromo-3-ketones in deuteriochloroform stands in contrast to the distortion demonstrated (*vide supra*) for the analogous 5α-cyano-3-ketones. The cause of this difference is very probably the greater dipole moment of C—C≡N as compared with C—Br,[38] leading to a stronger repulsion of the C_3-carbonyl dipole.

Boat or skew forms for ring A in various 3-keto-steroids have been proposed where nonbonded interactions render these forms more stable than the chair.[33,39,40] Allinger and DaRooge have demonstrated very recently that 2,2-dimethyl- and 4,4-dimethyl-3-keto-steroids do not exist as a regular chair or as a boat, but rather as a flattened chair structure.[41] From the n.m.r. data (Table I) it is not possible to calculate what form ring A of the 5α-cyano-3-keto-steroids assumes, since a reliable value for the anisotropy in the molecular magnetic susceptibility of the carbonyl group is not yet available. However, this anisotropy is likely to prove substantial enough so that relatively small changes in the angle θ (*vide supra*) may be expected to cause observable changes in the deshielding of the 19-angular methyl protons. Certainly a boat form ring A appears unlikely since in this form the 19-protons would be heavily shielded by the carbonyl (*cf.* Fig. 3) and deshielding by the 5α-nitrile would probably be cancelled out to an extent greater than has been observed.

When considering 5β-cyano-3-ketones a separate consideration of the stereochemistry has to be undertaken. Since the 3-carbonyl is more distant from the 19-methyl protons in 5β- than in 5α-steroids the long-range deshielding by carbonyl is weaker.[42] Dipolar repulsion of the 5β-C≡N and 3-C=O groups with distortion of ring A would move the 19-protons into a less *shielded* region of the carbonyl shielding cone. Thus, a change of the substituent at C_3 from carbonyl to equatorial 3α-acetate (negligible dipolar repulsion) in 5β-cyano-steroids should lead to a small *increase* in shielding, in contrast to the situation which exists in the isomeric 5α-cyano compounds (3-ketone to equatorial 3β-acetate).[43] Hence, observed $\Delta\nu$ values for 5β-cyano-3-keto-steroids should be higher than those for the corresponding 3α-acetates.

In the present work three 5β-cyano-steroids (IIIc, IVa, and IVb) were available for study. The observed $\Delta\nu$ values (Table I, column 8) are in agreement with the above predictions, but since the chemical shift (-1.0 ± 0.3 c.p.s.) on passing from 3-ketone (IIIc, IVa) to 3α-acetate IVb is within experimental error, these data cannot be regarded as proof of ring A distortion. Optical rotatory dispersion curves (Fig. 4) for 5β-cyano-17β-hydroxyandrostan-3-one acetate in methanol and dioxane were obtained, but, as discussed earlier for the 5α-cyano analogs, the absence of a well-defined extremum at lower wave lengths nullifies the value of the comparison.

Levisalles and his co-workers[11] also observed that a 6β-cyano group shifts the 19-proton resonance frequency downfield by 17 c.p.s. The calculated long-range shielding by C≡N as determined from molecular

(31) The O.R.D. data found for the various 5-cyano-3-keto-steroids described in this paper were kindly determined by Prof. W. Klyne, and agree well with data for other 5-cyano-3-keto-steroids.[32]

(32) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390 (1963).

(33) C. Djerassi, personal communication; *cf.* C. S. Barnes and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1962 (1962).

(34) A. Bowers, *ibid.*, **81**, 4107 (1959).

(35) 74.5 c.p.s. = 46.5 c.p.s. (5α-androstane)[4] + 0 c.p.s. (17β-acetyl)[4] + 2.5 c.p.s. (3β-OH)[4] + 19 c.p.s. (5α-Br)[11] + 6.5 c.p.s. (6β-F).[10]

(36) The C_{19}-methyl proton resonance appears as a doublet, $J_{H,F}$ 4.8 c.p.s., in accordance with earlier observations for 6β-fluorosteroids.[37]

(37) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736, 3784 (1962).

(38) L. Pauling, in "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd Edition, 1948, quotes the following dipole moments: C—Br, $\mu = 2.15 \times 10^{-18}$ (p. 154); C—C≡N, $\mu = 3.5 \times 10^{-18}$ (p. 75.)

(39) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962), has summarized the literature up to early 1961. Further publications dealing with boat form cyclohexanones have since appeared.[40]

(40) (a) J. Lehn, J. Levisalles, and G. Ourisson, *Tetrahedron Letters*, 682 (1961); (b) B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, and J. Levisalles, *Chem. Ind.* (London), 1667 (1961); (c) G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2725 (1961); (d) J. S. E. Holker and W. Whalley, *Proc. Chem. Soc.*, 464 (1961); (e) C. Djerassi, E. Lund, and A. A. Akrem, *J. Am. Chem. Soc.*, **84**, 1249 (1962).

(41) N. L. Allinger and M. A. DaRooge, *ibid.*, **84**, 4561 (1962).

(42) Zürcher[4] reported additive frequency shifts of 19-protons due to 3-carbonyl in 5α- and 5β-steroids as +14 c.p.s. and +6 c.p.s., respectively.

(43) The magnitude of the change is predictably smaller than that observed in the 5α-cyano-steroids since the 19-H-C_3 distance is considerably larger.

TABLE II

RESONANCE FREQUENCIES (C.P.S.) OF PROTONS, OTHER THAN 19-H, FOR SOME 5-CYANO- AND 5-H-STEROIDS[a]

Steroid	18-H	OAc	Other protons	Steroid	18-H	OAc	Other protons
5α-CN				5α-H			
Ia	47.1	122.0[b]		IIa	46.5	120.2[b]	
Ib	48.6	122.4		IIb	48.0	120.4	
Ic	38.6	...	125.8 (21-Me) 148.9 (C_4-protons)	IIc	39.2	...	127.9
Id	47.6	122.4 (17-OAc) 127.2 (3α-OAc)		IId	48.1	123.1[b]	
Ie	47.5	122.2	239.9 (ketal protons)	IIe	47.1	122.2	236.6 (ketal protons)
IIIa	53.8	...	152.2 (C_4-protons)	IIIb	53.7	...	
5β-CN				5β-H			
IIIc	54.5	...	134.3, 148.8, 175.2, 191 (C_4-protons) quartet, J = *ca.* 15 c.p.s.	IIId	53.7	...	
IVa	49.4	123.1	*ca.* 135, 150, 174.8, 190 (C_4-protons) quartet, J = *ca.* 15 c.p.s.	Va	48.8	122.7	*c*, 148, 164, 177 (C_4-protons), AB quartet, J = *ca.* 13 c.p.s.
IVb	47.1	122.7[b]		Vb	46.8	122.4[b]	

[a] All methyl proton resonances (C_{18}, C_{21}, and acetate esters) appear as singlets. The multiplicity of other resonances is considered in the Discussion. Only well-defined resonances are tabulated. [b] Two superimposed 3-proton singlets. [c] Obscured resonance.

models[22-24] and eq. 1[19,25] is +22.9 c.p.s. Therefore, in this orientation, long-range shielding by nitrile appears to be a major factor determining the methyl proton frequency shift. No ring A conformational change is anticipated in 6β-cyano-3-ketones since dipolar repulsions should be negligible. To test the reliability of the 6β-cyano frequency shift value (17 c.p.s.),[11] 6β-cyano-5α-hydroxy-androstane-3,17-dione (VIII)[44] was examined and the 18- and 19-proton resonances found to be at 56.0 and 89.7 c.p.s., respectively. The latter value agrees with the calculated 19-proton resonance (89 c.p.s.).[45]

In Table II the chemical shifts of other well-defined proton resonances of the nine 5-cyano-steroids are presented in comparison with their parent 5-H steroids. The introduction of cyano at C_5, either α- or β-oriented, has a negligible effect upon the 18-methyl proton frequency. Similarly, the proton resonance frequencies of 17β-acetate, 3β-acetate in the 5α-series, and 3α-acetate in the 5β-series remain unaffected. However, where the cyano group bears a 1,3-diaxial relation to an acetate group the anticipated shift is observed. Thus, in the n.m.r. spectrum of the 5α-cyano-3α-acetate Id the acetate protons resonate 4 c.p.s. to lower fields than in the parent compound IId, and thereby the stereochemistry at C_3 is defined. A conspicuous difference between the n.m.r. spectra of the 5β-cyano-3-ketones and 5α-cyano-3-ketones lies in the resonance patterns of the C_4-methylene protons, those of the 5β-cyano isomer constituting a well-resolved quartet in contrast to a broad singlet for the 5α-cyano isomer. Hence, a useful indicator of the stereochemistry at C_5 is available. The allocated data (Table II) offer convincing support for several structural assignments made earlier.[20]

Though ill-resolved, the multiplets due to the C_3-proton resonance offer an alternative path for the assignment of the stereochemistry at C_3. When compared with the parent 5-H steroids an axially-oriented C_3-proton resonance of a 5-cyano-steroid shows a downfield shift of *ca.* 30 c.p.s. In addition, this resonance multiplet has a half-band width of *ca.* 22 c.p.s., in contrast to the resonance of a C_3-equatorially-oriented proton, half-band width *ca.* 7 c.p.s.

The cyano-steroids used in this work were prepared by the procedures of Bowers, and by further elaborations using unexceptional methods (see Experimental section).

Experimental[46]

Addition of Cyanide to Testosterone.—To a solution of 15 g. of testosterone in 200 ml. of dimethylformamide were added, successively, solutions of 5.5 g. of potassium cyanide in 35 ml. of water and 3.3 g. of ammonium chloride in 35 ml. water. After being heated under reflux for 1 hr. the mixture was diluted by 200 ml. of water and the crystalline precipitate of 5α-cyano-17β-hydroxy-androstan-3-one (4.8 g.) was collected and stored. Extraction of the filtrate with ethyl acetate afforded the isomeric 5β-cyano-17β-hydroxy-androstan-3-one (4.0 g.), prisms, from ethyl acetate–methanol, m.p. 213–216°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.17; H, 9.22; N, 4.50.

The derived acetate had m.p. 195–197°, $[\alpha]_D$ +7° (lit. values[20] m.p. 195–197°, $[\alpha]_D$ +11°).

5α-Cyano-androstane-3,17-dione.—Jones reagent[47] (0.25 ml.) was added to a stirred solution of 100 mg. of 5α-cyano-17β-hydroxy-androstan-3-one in 15 ml. of acetone at 10°. After 10 min. had elapsed a small excess of aqueous sodium bisulfite was added and the mixture was poured into water. Extraction with methylene chloride, followed by the customary washings, drying and evaporation, led to 5α-cyano-androstane-3,17-dione, which was recrystallized from methylene chloride–hexane as colorless needles (85 mg.), m.p. 225–228°, $[\alpha]_D$ +114°. *Anal.* Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.28; H, 8.87; N, 4.60.

5β-Cyano-androstane-3,17-dione.—Oxidation of 5β-cyano-17β-hydroxy-androstan-3-one was carried out as described above to furnish the corresponding dione IIIc which, after recrystallization from methylene chloride–hexane, showed m.p. 228–230°, $[\alpha]_D$ +98°. *Anal.* Found: C, 76.59; H, 8.82; N, 4.61.

5β-Cyano-androstane-3α,17β-diol.—A solution of 300 mg. of sodium borohydride in 15 ml. of ethanol was added to 1.8 g. of 5β-cyano-17β-hydroxy-androstan-3-one[20] dissolved in a mixture of 60 ml. of ethanol and 10 ml. of ethyl acetate. Acetone (15 ml.) was added after 1 hr., followed by an excess of dilute hydrochloric acid, then water. Methylene dichloride extracts were washed with water, dried, and evaporated to afford 5β-cyano-

(44) A. Bowers, E. Denot, M. B. Sánchez, L. M. Sánchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5233 (1959).

(45) 89 c.p.s. = 46.5 c.p.s. (5α-androstane)[4] + 14 c.p.s. (3-C=O)[4] + 10 c.p.s. (5α-OH)[11] + 17 c.p.s. (6β-CN)[11] + 1.5 c.p.s. (17-C=O).[4]

(46) Rotations are for chloroform solutions. Melting points were taken on the Fisher–Johns apparatus and are uncorrected. Analyses were carried out by Mid-West Micro Laboratories, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mulheim (Ruhr), Germany. N.m.r. spectra are for 5–8% w./v. solutions in deuteriochloroform containing tetramethylsilane as an internal reference.

(47) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

androstane-3α-17β-diol, 1.3 g., after recrystallization from methanol. The analytical sample had m.p. 229–231°, $[\alpha]_D$ +16°. *Anal.* Calcd. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.55; H, 10.00; N, 4.52.

The derived diacetate crystallized from methylene chloride–hexane as prisms, m.p. 215–216°, $[\alpha]_D$ +8°. *Anal.* Calcd. for $C_{24}H_{35}NO_4$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.92; H, 8.82; N, 3.60.

Acknowledgments.—Thanks are due to the Universidad Nácional de Mexico for time on the Varian A-60 spectrometer.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO, CHICAGO 37, ILL.]

Conformations. IV. The Conformational Preference of the Phenyl Group in Cyclohexane

BY EDGAR W. GARBISCH, JR., AND DENNIS B. PATTERSON

RECEIVED JUNE 24, 1963

The thermodynamic parameters ΔH = 3.61 kcal./mole and ΔS = 2.09 e.u. have been determined for the equilibrium: *trans*-4-*tert*-butyl-1-phenylcyclohexane (III) ⇄ *cis*-4-*tert*-butyl-1-phenylcyclohexane (IV). Measurement of the n.m.r. spectrum of IV as a function of temperature demonstrated that an appreciable concentration of the boat form of IV is likely to be present at 25°. The conclusion that the phenyl group has a substantially greater preference for the equatorial position in cyclohexane than do the methyl, ethyl, and isopropyl groups is supported by the n.m.r. spectra of *cis*- and *trans*-4-methyl-1-phenylcyclohexanes.

Several estimations of the free energy difference between equatorial and axial phenyl groups in cyclohexane have been made recently. Eliel and Rerick have estimated this energy difference as roughly 2.6 kcal./mole (35°) by equilibrating *cis*- and *trans*-4-phenylcyclohexanol using a mixed lithium aluminum hydride–aluminum chloride reagent in the presence of the parent ketone.[1] More recently, Allinger and coworkers determined a value of 2.0 kcal./mole (25°) for this free energy difference by dipole moment measurement on 4-methyl-4-phenylcyclohexanone.[2] It appears from this latter result that the phenyl group enjoys about the same preference for the equatorial position in cyclohexane as do the methyl, ethyl, and isopropyl groups (*i.e.*, *ca.* 2 kcal./mole).[3] Since the two approaches used to estimate the conformational preference of the phenyl group in cyclohexane were somewhat indirect, it appeared desirable to determine this quantity by a more direct procedure. Consequently, we have investigated equilibrations between *trans*- and *cis*-4-*tert*-butyl-1-phenylcyclohexane (III and IV, respectively). In this paper, the results of these equilibrations together with results from other related work will be discussed.

Results

A mixture of stereoisomeric 4-*tert*-butyl-1-phenylcyclohexanols, obtained through reaction between phenylmagnesium bromide and 4-*tert*-butylcyclohexanone, was cleanly separated by chromatography on silica gel to roughly equal amounts of the two stereoisomers. The carbinol eluted first was considered to be *trans*-4-*tert*-butyl-1-phenylcyclohexanol (I) and that eluted last was considered to be the *cis* stereoisomer II.[4] This assignment is substantiated by the n.m.r. spectra of I and II which are shown in Fig. 1 and 2.[5] The higher chemical shift of 8.35 τ for the hydroxyl proton of I as compared with that of 8.09 τ for this proton of II suggests that II is slightly more hydrogen bonded than I.[6] The doublet at 7.48 τ for II appears to be a low field half of an AB spectrum with each component broadened through further unresolved coupling. The spectrum of the 2,2,6,6-tetradeuterio derivative (Fig. 2) shows that this doublet arises from the 2,6-protons of II and that the high field part of the AB spectrum, also the 2,6-protons, is centered at about 8.3 τ. The doublet at 7.48 τ is assigned to the equatorial protons on C_2 and C_6. The width at half-height of 7.2 c.p.s. for each part of this doublet leads to a value of J ($H_{2,6e}$, $H_{3,5a}$) ≅ 3.6 c.p.s. which is consistent with known couplings of this type.[7] The coupling of approximately 11.5 c.p.s. between $H_{2,6a}$ and $H_{2,6e}$ is also comparable with known methylene couplings in cyclohexane.[7] The chemical shift difference between $H_{2,6e}$ and $H_{2,6a}$ of about 0.82 p.p.m. is larger by about 0.2–0.3 p.p.m. than the chemical shift difference between axial and equatorial protons of other cyclohexane derivatives.[8] This is consistent with the phenyl group of II being confined largely to the rotational conformation shown in Fig. 2.[1,2] In this conformation the equatorial and axial protons on C_2 and C_6 are deshielded by the diamagnetic field of the benzene ring, and it can be calculated that the $C_{2,6}$ equatorial protons will be deshielded about 0.25 p.p.m. more than the $C_{2,6}$ axial protons.[9] From the spectrum of I, nothing can be said about preferred rotational conformations of the phenyl group in this compound, although it is reasonable to expect that the phenyl group is confined for the most part to the conformation shown in Fig. 1.[2]

The hydrogenolysis of the hydroxyl groups of the stereoisomeric 3-phenylcholestanols using Raney nickel is known to proceed with a high degree (>90%) of retention of configuration providing conditions are employed which minimize competing equilibration of the hydrocarbon products.[10] Using these controlled conditions for hydrogenolysis, compound I was converted to *trans*-4-*tert*-butyl-1-phenylcyclohexane (III, m.p. 42°) and II was converted to the *cis* stereoisomer IV (m.p. 24.5°). The n.m.r. spectrum of III shows the benzylic proton absorption at 7.63 τ (partially masked). The spectrum of 1-phenylcyclohexane has

(1) E. L. Eliel and M. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

(2) N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenberg, *J. Org. Chem.*, **27**, 4603 (1962).

(3) (a) N. L. Allinger and S. Hu, *ibid.*, **27**, 3417 (1962); (b) *J. Am. Chem. Soc.*, **84**, 370 (1962).

(4) Functions in the axial position of cyclohexane derivatives are known to be less strongly absorbed on silica gel or alumina than identical functions occupying the equatorial position. See J. A. Zderic, M. E. C. Rivera, and D. C. Limón, *J. Am. Chem. Soc.*, **82**, 6373 (1960); S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); and H. E. Zimmerman, *ibid.*, **79**, 6554 (1957).

(5) The n.m.r. spectrum of the acetate of I shows sharp absorptions for the phenyl and acetate protons at 2.79 and 8.07 τ, respectively. 1-Acetoxy-1-phenylcyclohexane, in which the acetate group probably exists almost exclusively in the axial position, shows identical chemical shifts for these absorptions. The spectrum of the acetate of II, however, shows a broad (28 c.p.s. at 56.4 Mc.) multiplet for the phenyl protons and an acetate proton absorption at 8.24 τ.

(6) J. A. Pople, W. G. Schneider, and H. S. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 15.

(7) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962); J. I. Musher, *J. Chem. Phys.*, **34**, 594 (1961); **37**, 2480 (1962).

(8) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

(9) The method of calculation is that described in paper III, *J. Am. Chem. Soc.*, **85**, 927 (1963).

(10) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 3363 (1962).