

Infrared Spectral Study of Some Epimeric Alcohols

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Abstract: Infrared data have been recorded of the hydroxyl stretching band for a series of epimeric cyclohexanols and piperidinols in dilute carbon tetrachloride solution. In general, the band of the axial alcohol occurs at a higher frequency and has a greater absorption coefficient, smaller half-band width, and greater symmetry than its equatorial epimer. Little or no difference was found in the integrated band areas, especially for members of an epimeric pair. The results are interpreted in terms of rotational conformations of the hydroxyl group. The application of these spectral criteria represents a useful method for stereochemical assignment of the hydroxyl group, especially for vicinally unsubstituted alcohols. The scope and limitations of the method are discussed. The application of spectral data to the conformational analysis of some azabicyclo[3.3.1]nonanol systems is presented. The synthesis of the epimeric 1-azabicyclo[3.3.1]nonan-3-ols is reported.

Earlier, we reported¹ on the direct conformational assignment of the hydroxyl group in a six-membered ring, based on the shape of the fundamental free O-H stretching band. We now report a more detailed infrared spectral study of a larger number of compounds in order to better define the utility and limitations of the method.

Results

Table I presents the free ν_{OH} spectral data recorded for pairs of epimeric alcohols, broadly viewed as substituted cyclohexanol and piperidinol systems, and

convenience of the organization of these data, the possibility that an individual OH group may exist in other than an equatorial or axial conformation (as a result of the existence of nonchair forms) is ignored. However, this point is considered with regard to pertinent compounds (2 and 4) in a following section. For each compound, the band maximum (ν_{max}), half-band width ($\Delta\nu_{1/2}$), apparent molecular absorption coefficient (ϵ), apparent integrated band area (B), and band symmetry value (α/β) are given. The latter is expressed as the ratio of the segments of the half-band width on the high- (α) and low- (β) frequency sides of the band max-

Table I. Infrared Spectral Data of the Free O-H Stretching Band of Epimeric Alcohols in Dilute CCl₄

Structure	Equatorial hydroxyl epimer							Axial hydroxyl epimer						
	Compd no.	Con-fig	ν_{max} , cm ⁻¹	$\Delta\nu_{1/2}$	ϵ	B	α/β	Compd no.	Config	ν_{max} , cm ⁻¹	$\Delta\nu_{1/2}$	ϵ	B	α/β
1-Azabicyclo[3.3.1]nonan-3-ol	1	<i>exo</i>	3624	22	45	2950 ^a	0.76	2	<i>endo</i>	3623	16	65	2800 ^a	0.94
3-Granatanol	3	β	3620	26.5	46	2850 ^b	0.58	4	α	3625	18	62	3200	0.80
3-Tropanol	5	β	3621	26	49	3400	0.53	6	α	3626	16	70	3200	1.0
2-Tropanol	7	α	3627	20	66	3550	0.90	8	β	3472 ^c				
7-Indolizidinol	9	<i>cis</i> -7,9-H	3624	21.5	52	2900 ^a	0.65	10	<i>trans</i> -7,9-H	3627	15.5	71	3300	0.94
2-Quinolizidinol	11	<i>cis</i> -2,10-H	3625	23	58	3000	0.61	12	<i>trans</i> -2,10-H	3628	16	67	3050	0.97
3-Quinolizidinol	13	<i>t</i> -3,10-H	3625	24	58	3300	0.77	14	<i>cis</i> -3,10-H	3527 ^c				
Scopine ^d								15	α	3624	15	73	2750	1.0
3-Cholestanol	16	β	3624	18	69	3350	0.60	17	α	3627	15	67	3200	1.0
5 α -Androstan-3-ol-17-one	18	3 β	3623	18	64	3200	0.85	19	3 α	3627	15.5	69	3150	1.0
2-Methylcyclohexanol	20	<i>trans</i>	3631	29	41	3100	0.57	21 ^e	<i>cis</i>	3632.5	22.5	52	3250	0.88
2-Ethylcyclohexanol	22	<i>trans</i>	3628	32.5	43	3300	0.74	23 ^e	<i>cis</i>	3632	20.5	59	3350	0.91
2-Isopropylcyclohexanol	24	<i>trans</i>	3628	33	42	3200	0.56	25 ^e	<i>cis</i>	3630.5	19	61	3200	0.95
2- <i>t</i> -Butylcyclohexanol	26	<i>trans</i>	3617	20.5	52	3000	1.1	27	<i>cis</i>	3626	18	51	3150	1.18
3-Methylcyclohexanol	28	<i>cis</i>	3624	18	50	3100	0.60	29 ^e	<i>trans</i>	3627	16.5	61	3250	0.94
4- <i>t</i> -Butylcyclohexanol	30	<i>trans</i>	3624	17	64	3300	0.70	31	<i>cis</i>	3628.5	17	63	3350	1.0
2-Isopropyl-5-methylcyclohexanol	32	Menthol	3628	33	43	3400	0.60	33	Neomenthol	3630	18.5	56	3100	0.95

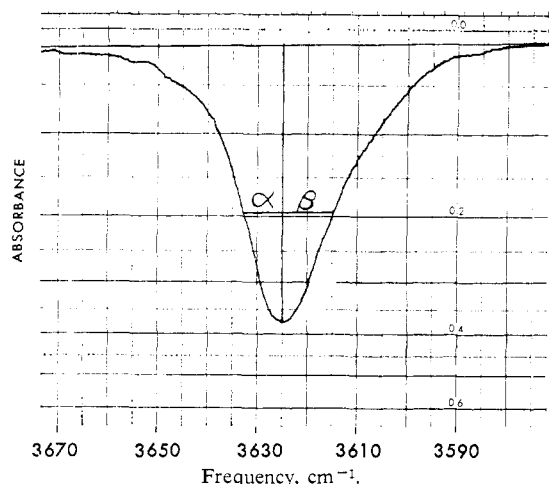
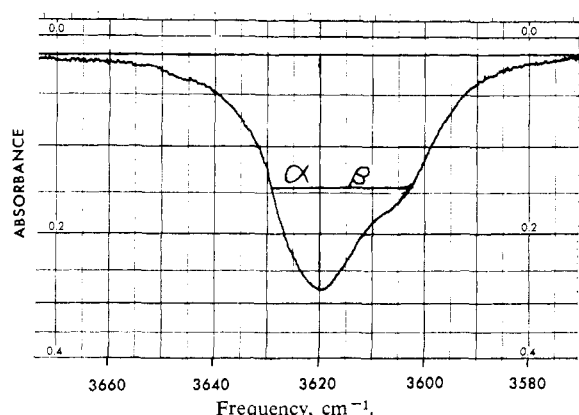
^a Low due to presence of persistent absorption (presumably dimer) at ~ 3225 cm⁻¹. ^b Low due to presence of 11% intramolecularly bonded (boat) conformation, ν 3380 cm⁻¹. ^c 100% intramolecularly hydrogen-bonded band. ^d Pseudoscorpine not available to us. ^e Calculated for 21, 23, and 29 to be 85%, for 25, 93%, in the axial conformation, respectively, at 25°, using indicated $-\Delta G^\circ$ values for hydroxyl (0.7), methyl (1.7), ethyl (1.7), and isopropyl (2.2) taken from ref 11a, p 436 ff.

grouped according to the configuration or (for the mobile cyclohexanols) conformational preference of the hydroxyl group. For the conformationally heterogeneous systems 21, 23, 25, and 29, the calculated percentages of the dominant conformations are given in the footnotes to the table. In addition, for the

imum. The other terms are defined in the Experimental Section. Spectral bands of an axial (4) and two equatorial (3 and 9) hydroxyl types are given in Figures 1-3.

A review of the data for Table I reveals that, in general, the O-H stretching band of each axial alcohol occurs at a higher frequency, and has a greater absorption coefficient, smaller half-band width, and greater

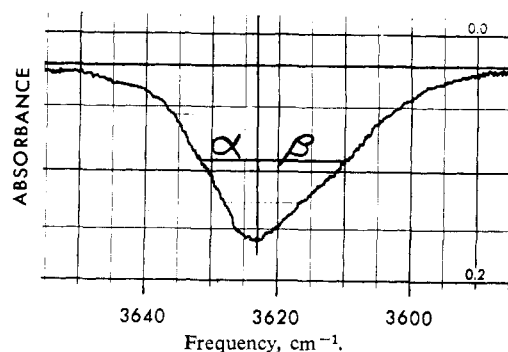
(1) H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, **85**, 3046 (1963).

Figure 1. Expanded O-H stretching band of α -granatanol (4).Figure 2. Expanded O-H stretching band of β -granatanol (3).

symmetry than that of its equatorial epimer. Furthermore, there appears to be little difference (within experimental error) in the integrated band areas of the secondary alcohols that we have examined, especially for members of an epimeric pair.

The greater apparent molecular absorption coefficient and smaller half-band width that we have found for axial hydroxyl epimers appear not to have been noted previously. The higher frequency of the axial band maximum has been reported by Cole and co-workers, who observed a 5- to 10- cm^{-1} difference between epimers.² In the present study, however, a smaller difference (2 to 5 cm^{-1}) generally was observed. In agreement with our findings, no significant difference has been reported² for the band areas of epimers. A claim³ that axial hydroxyls have smaller areas was based, apparently, on data for a single epimeric pair (18 and 19). This result was not confirmed upon re-examination in the present study.

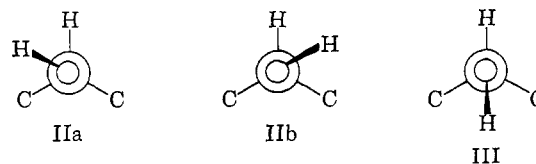
From a practical point of view, band shapes may be characterized as symmetrical (Figure 1) or unsymmetrical (Figures 2 and 3).⁴ Unsymmetrical bands are widely held to be composite bands, resulting from

Figure 3. Expanded O-H stretching band of *cis*-7,9-H-7-indolizidinol (9).

contributions of two (or more) symmetrical components. The composite shape of an unsymmetrical band will vary according to the intrinsic shapes, relative percentages, and degree of separation of its components. Figure 2 is representative of a band with maximal component separation ($>15 \text{ cm}^{-1}$). Such a band may show a pronounced shoulder even at normal survey scan and is generally observed as an unresolved doublet when recorded on an expanded frequency scale. Figure 3 represents a lesser degree of separation ($\sim 10 \text{ cm}^{-1}$) of the band components. These bands merely show an unsymmetrical bulge, generally visible on the low-frequency side of the expanded band. Graphical separations of unsymmetrical bands may be carried out. However, we have found it simpler and more convenient to characterize the band symmetry by the α/β ratio, which may be measured at several points, but which is reported here at the half-band width. In some cases, however, the asymmetry of a band may be better revealed by measurement below the half-band width. In questionable cases or to double check an assignment, if one simply folds a trace of the expanded band along a dividing line drawn through ν_{max} , the presence or absence of a minor component may be revealed.

Interpretation of the Results

The results of Table I provide strong, circumstantial evidence for the conformational theory.^{5,6} This theory recognizes the existence of rotational conformations of the hydroxyl group, designated (in secondary alcohols) as rotamer types II and III,^{7a} which differ slightly in the position of their absorption maxima, II being greater than III by about 10 cm^{-1} .⁵ Thus, the



observed free O-H band represents a composite of the bands of the individual rotamers, each contributing according to its relative population. Presumably,

(2) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959), and preceding papers in this series.

(3) S. Weinmann, J. Weinmann, and L. Henry, *Bull. Soc. Chim. Biol.*, 41, 777 (1959).

(4) For a theoretical review of the shapes and intensities of infrared absorption bands, see K. S. Seshadri and R. N. Jones, *Spectrochim. Acta*, 19, 1013 (1963).

(5) M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, 32, 950 (1959).

(6) R. Piccolini and S. Winstein, *Tetrahedron Letters*, No. 13, 4 (1959).

(7) (a) Rotamer type I would be represented by methanol. (b) A similar result might be obtained if rotamer III were better solvated than II, since it is known that even the "free" OH group is solvated in relatively nonpolar media: A. Allerhand and P. von R. Schleyer, *J. Am. Chem. Soc.*, 85, 371 (1963). However, we see no obvious stereochemical rationale for this suggestion.

the difference in the vibrational force constants of the rotamers is intrinsically related to their structures.^{7b}

If one applies this theory to a cyclohexanol system, one concludes that both rotamer types should be present when the hydroxyl group is equatorial. In an axial hydroxyl system, however, the population of rotamer III should be severely restricted owing to steric interactions of the axial 3,5-hydrogens with the hydroxyl hydrogen. For either system, in the absence of vicinal substitution, the two II rotamers would be essentially (if not exactly) equivalent, insofar as their immediate steric environment is concerned. Thus, one observes a symmetrical band (Figure 1) for a conformationally homogeneous axial hydroxyl group and an unsymmetrical band for its conformationally heterogeneous equatorial epimer (Figure 2).⁸

We have already mentioned Cole's correlation, whereby the band maximum of an axial alcohol is generally higher than that of its equatorial epimer. Because of the small differences we have observed in the band maxima of epimeric alcohols, and because of the uncertainties inherent in a graphical resolution of the equatorial alcohol bands, it is uncertain whether, for members of an epimer pair, ν_{\max}^{OH} of II_{axial} is more generally equal to or more generally greater than ν_{\max}^{OH} of II_{equatorial}. Examples of both situations appear to exist. In any event, the general validity of Cole's correlation would appear to be due, in large measure, to a shift of the apparent band maxima of equatorial alcohols by the contribution of their low-frequency component (III).

An alternate theory, which suggests that unsymmetrical hydroxyl band shapes result from weak intramolecular hydrogen bonding of the type $\text{CH}\cdots\text{OH}$, has been offered for acyclic systems.⁹ This theory is clearly not applicable to cyclic systems (as has been noted⁹) since the axial isomer should then have the lower absorption frequency.¹⁰

Scope and Limitations of the Method

The spectral criteria established from the data in Table I represent a useful method for the stereochemical assignment of the hydroxyl group.¹¹ Depending upon

(8) Strictly speaking, of course, the epimer of an equatorial alcohol need not necessarily be an axial alcohol. Such an exception will occur in a conformationally mobile system, where introduction of an axial OH group forces the system into either the alternate chair or a nonchair conformation. Generally speaking, however, such exceptions are undoubtedly rare.

(9) E. L. Saier, L. R. Cousins, and M. R. Basila, *J. Chem. Phys.*, **41**, 40 (1964).

(10) The failure of this theory to hold in cyclic systems raises a serious doubt as to its validity in acyclic systems. Moreover, the observed spectral shifts are difficult to attribute to the very weak $\text{CH}\cdots\text{OH}$ interaction, since the much stronger $\text{OH}\cdots\text{OH}$ intramolecular interaction results in no apparent spectral shift of the "unbonded" hydroxyl group. See, for example, L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

(11) Other useful spectroscopic methods (infrared and especially nmr) have been cited in ref 1. See also (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1965, p 142 ff; (b) C. P. Rader, *J. Am. Chem. Soc.*, **88**, 1713 (1966). A referee has suggested that a comparison of the nmr and infrared methods be given in order to define the circumstances under which infrared may better serve as the method of choice for stereochemical assignment. We offer the following comments. In many cases, either method may serve equally well, and the choice would be made on the basis of the available instrumentation or preference of the investigator. The advantage in having available (at least) two independent physical methods would probably be best realized in studies of systems in which the chosen method has not provided unequivocal results, or for confirmation of a result, especially where only one epimer is available for study. The infrared method has the advantage in that it may be used on very small

the instrumentation available, examination of either the fundamental band or the first overtone⁶ would appear to yield comparable results. Structures of new compounds may be assigned from a comparison of the data of both epimers, together with an examination of stereomodels, to reveal any unusual steric interactions that might affect otherwise normal rotamer populations. The greater the spectral distinctions between the epimers, of course, the more reliable will be the resulting assignments. Generally speaking, these distinctions have been more pronounced in the azabicyclic, compared to the carbocyclic systems we have examined.¹²

It is important to note that the criteria may not necessarily apply to carbinols that are either vicinally substituted or adjacent to a bridgehead position, since from the conformational theory the immediate steric environments of the two II rotamers will no longer be identical. Unfortunately, this restriction represents the major limitation to a more general utility of the method. As indicated from the data of Table I, however, 2-methyl-, 2-ethyl-, and 2-isopropyl- (but not 2-*t*-butyl-) cyclohexanol systems apparently can be assigned by this method, if both epimers are available for spectral comparison. Empirical correlations may be useful in other vicinally substituted systems.¹³ In theory, the criteria should apply also to carbinols that are symmetrically substituted at the two vicinal positions; however, none of these have been examined. The method is not applicable to intramolecularly bonded systems. Fortunately, unequivocal stereochemical assignments generally can be made here on the basis of such bonding.

When only a single (vicinally unsubstituted) epimer is available, its stereochemistry may be assigned directly on the basis of the band-shape criterion. Generally speaking, an α/β ratio of 1 ± 0.1 represents a rather firm indication of an axial hydroxyl group. Symmetrical band shapes for equatorial alcohols are rare. The only example we have found¹⁴ (except, perhaps, for epiandrosterone¹⁵) is 2- α -tropanol (7). Here, the type-III rotamer population is probably restricted owing to steric interactions of the hydroxyl group with the 7 α -hydrogen. Although the two II rotamers are not completely identical owing to the presence of

quantities, samples which would ordinarily require use of a time-averaging computer if studied by nmr. In general, infrared would be the method of choice for systems that exist in equilibrium between free and intramolecularly bonded OH conformations (e.g., 3). Of course, if a compound is insoluble in carbon tetrachloride, carbon disulfide, or tetrachloroethylene, this infrared method cannot be used. In general, nmr would be the method of choice for vicinally substituted cyclohexanols or for mobile cyclohexanol systems, which contain appreciable quantities of two ring-conformation forms.

(12) In the 3-hydroxy steroids (16-19), for example, the epimeric alcohol bands are not as distinctly different as would be desired. Similar results have been obtained by Professor G. D. Meakins, private communication.

(13) Differences in half-band widths and absorption band frequencies have been correlated with the configurations of *endo*- and *exo*-bicyclo-[2.2.1]heptanol systems: P. Hirsjarvi and K. Salo, *Suomen Kemistilehti*, **32**, 280 (1959).

(14) Another example has been reported in a divicinally substituted alcohol: H. Hirshmann, F. B. Hirshmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966). Although here both epimer bands are symmetrical at their half-band width ($\alpha/\beta = 1.0$), both contain a low-frequency component, which is observable in the published spectra and results in an unsymmetrical band, if measured below the half-band width.

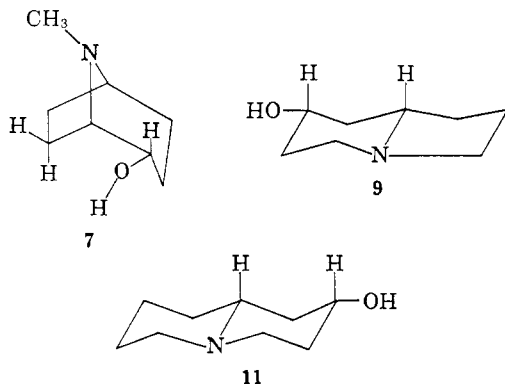
(15) Upon reexamination, epiandrosterone (18) was found to give a more symmetrical band than we originally reported, apparently due to misalignment of the spectrophotometer optics during the earlier recording. Folding a trace of the expanded band along ν_{\max} , however, reveals the presence of a minor component on the low-frequency side.

the bridgehead at one of the vicinal positions, their absorption maxima must be essentially equal, as judged from the symmetry of their composite absorption band.¹⁶

If only a single epimer is examined, however, it is possible that an erroneous stereochemical assignment might be made by the above method, if in the event a "relatively symmetrical" band must be classified. This inherent danger is illustrated by the disagreement to be found in the literature on the classification of band shapes of some simple alcohols. Thus, the methanol band has been classified as symmetrical^{5,6,9,17} and unsymmetrical;¹⁸ ethanol, symmetrical⁹ and unsymmetrical;^{5,6,17,18} *t*-butyl alcohol, symmetrical^{5,6,9,19} and unsymmetrical;¹⁹ and cyclohexanol, symmetrical¹⁸ and unsymmetrical.²⁰

In this study, these bands were all found to be "relatively symmetrical," but each appears to contain a small amount of a secondary component—that of methanol and *t*-butyl alcohol on the high-frequency side ($\alpha/\beta = 1.15$ and 1.1 , respectively), that of ethanol and cyclohexanol on the low-frequency side ($\alpha/\beta = 0.89$ and 0.86 , respectively). From the conformational theory, ethanol and cyclohexanol should be asymmetrical. For cyclohexanol, conformational analysis suggests about a 25% contribution from a type-III rotamer.²¹ For methanol and *t*-butyl alcohol, however, symmetrical bands should be expected. We cannot explain the apparent discrepancy (if real) of the methanol and butanol cases with the conformational theory.²²

Discrepancies in band-shape assignments may be due to any of several factors, such as subjective oversight, differences in instrument resolving power, the presence of trace impurities (including water), or minor instrumental aberrations. It is important that the spec-



(16) Folding the band, as above,¹⁶ indicates the presence of a minor component on the high-frequency side.

(17) F. Dalton, G. D. Meakins, J. H. Robinson, and W. Zaharia, *J. Chem. Soc.*, 1566 (1962).

(18) T. D. Flynn, R. L. Werner, and B. M. Graham, *Australian J. Chem.*, **12**, 575 (1959).

(19) P. Arnaud and Y. Armand, *Compt. Rend.*, **255**, 1718 (1962).

(20) J. Chevalley, *ibid.*, **256**, 950 (1963).

(21) Values for $-\Delta G^\circ_{\text{OH}}$ of 0.6 and 0.7 have been reported from conformational studies in carbon tetrachloride (see E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, **87**, 5031 (1965), and references cited therein). A value of 0.65 (25°) would give 75% equatorial hydroxyl, which results in a conformational composition of 25% rotamer type II_{axial}, 50% rotamer type II_{equatorial}, and 25% rotamer type III, as assigned on a purely statistical basis. A smaller value of $-\Delta G^\circ_{\text{OH}}$, of course, would result in a smaller contribution of the type-III rotamer.

(22) In the absence of any detectable absorption in the 3700-cm⁻¹ region, we discount the possibility of a contribution of the ν_{sym} of water at 3611 cm⁻¹ to the band asymmetry; see L. B. Borst, A. M. Buswell, and W. H. Rodebush, *J. Chem. Phys.*, **6**, 61 (1938).

trophotometer beams be in exact alignment and that matched cells (preferably fixed-path infrared-grade quartz) be used. A slight misalignment of optics, which may be insignificant when spectra are recorded on the conventional scan, becomes important, especially in regions of atmospheric absorption (water vapor and carbon dioxide), when spectra are recorded on an expanded scale presentation. Apparently a condition of this type was responsible for our earlier erroneous report¹ of a neomenthol doublet.²³

Analysis of Specific Systems

For an alcohol which exists in a conformational equilibrium, one should, in theory, be able to perform a conformational analysis by separation of the absorption band into its individual components. In practice, however, such an analysis would appear to be highly subjective.²⁴ In systems which are, in effect, conformationally fixed insofar as the hydroxylated ring is concerned, such as the 3-tropinols, 7-indolizidinols (e.g., **9**), and 2-quinolizidinols (e.g., **11**), analyses of band shapes have proven helpful for stereochemical assignments.²⁵ From this standpoint, therefore, let us examine the infrared data and conformational analysis of the 1-azabicyclo[3.3.1]nonan-3-ols (**1** and **2**) and the 3-granatanols (**3** and **4**).

The configurations of the epimeric 1-azabicyclo[3.3.1]nonan-3-ols may be assigned by their method of synthesis. Thus, reduction of the parent ketone (which undoubtedly exists in the double-chair form) with sodium in alcohol gives the more stable equatorial alcohol (**1a** \rightleftharpoons **1b**), which probably exists predominantly as **1a**, by analogy to findings in related systems^{26,27} and to 3 β -granatanol (see below). The percentage of conformation **1c** is undoubtedly small, in comparison to **1b**, in view of the relative bowsprit-flagpole interactions²⁸ present in these two forms. By this analysis, therefore, the piperidinol ring is considered to be, in effect, conformationally fixed.

Reductions of the parent ketone by either catalytic or metal hydride methods give the axial epimer (**2**), because of steric restrictions that limit both the mode of adsorption of the carbonyl group on the catalyst surface and the direction of steric approach by the hydride reagent.^{29,30} Once formed, **2** can exist in a

(23) Although the original instrument is no longer available to us (because of replacement of the grating unit), this result could not be duplicated upon reexamination on grating instruments of comparable resolving power, either in our laboratory or at the Perkin-Elmer Corp. In addition, certain minor features of asymmetry that we had earlier observed in many of the spectra were eliminated when the instruments were realigned and matched quartz cells were used.

(24) For example, the cyclohexanol band has been graphically separated²⁰ into two components, with relative areas (high/low frequency) of 57/43%. While not specifically assigned, the low-frequency component is presumably due to the type-III rotamer. By conformational analysis, however, this component should constitute only about 25%.²¹ Actually, the cyclohexanol band appears to us to be much more symmetrical than would be suggested either by the graphical separation²⁰ or the conformational analysis.

(25) (a) H. S. Aaron and C. P. Rader, *J. Org. Chem.*, **29**, 3426 (1964); (b) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *ibid.*, **29**, 2248 (1964); (c) C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *ibid.*, **30**, 1536 (1965).

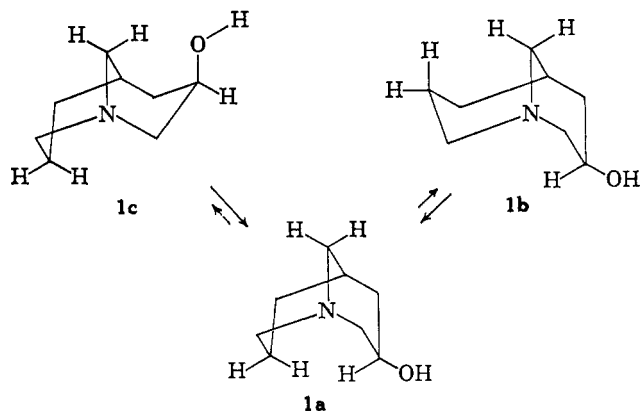
(26) R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.*, 356 (1965).

(27) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

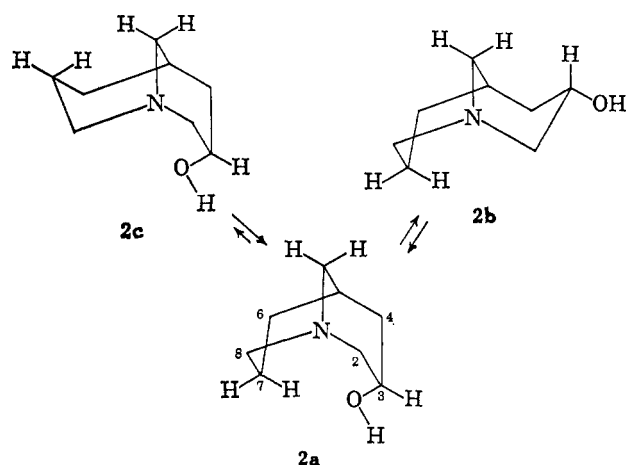
(28) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 205.

(29) M. J. Martell, Jr., and T. O. Soine, *J. Pharm. Sci.*, **52**, 331 (1963).

(30) C. L. Zirkle, F. R. Gerns, A. M. Payloff, and A. Burger, *J. Org. Chem.*, **26**, 395 (1961).



conformational equilibrium between **2a** and **2b**. A third form, **2c**, is undoubtedly small and can be discounted, relative to **2b**, in consideration of the 7-H and 2,4-CH₂ (in **2b**) vs. the 3-OH and 6,8-CH₂ (in **2c**) diaxial interactions.³¹



In agreement with these assignments, we find the band of the equatorial hydroxyl epimer (**1**) to be very unsymmetrical. It has a shoulder at 3604 cm⁻¹, more pronounced even than that shown in Figure 2. The band of its epimer (**2**) was found to be completely symmetrical. On this basis, the axial epimer would appear to exist mainly (if not entirely) as **2a**, since, from the conformational theory, **2b** would be expected to possess an unsymmetrical band similar to that of an equatorial alcohol.

It is pertinent to note that neither **1** nor **2** shows any definitive infrared absorptions in the 2990- or 1490-cm⁻¹ regions, which have been assigned as characteristic of severe nonbonded hydrogen interactions, especially for double-chair conformations of bicyclo[3.3.1]nonyl systems.^{27,32} This result might be disturbing if not for the fact that neither of the granatanols show these absorptions, although β -granatanol has been firmly deduced to exist as about 89% in the double-chair form (see below).

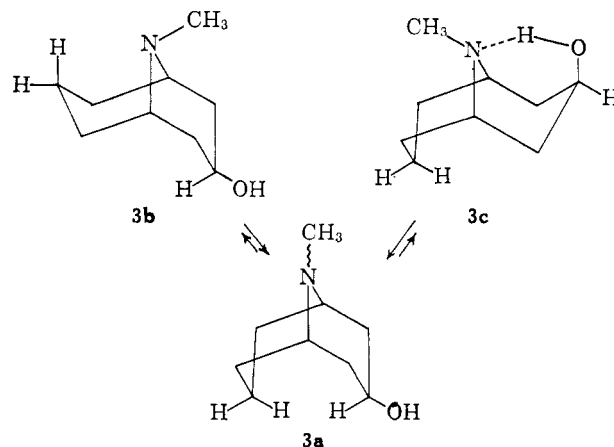
The nmr spectra of **1** and **2** were not helpful to us for conformational assignment. The carbinol proton signals were recorded as complex multiplets, which were not typical of axial and equatorial carbinol proton signals as observed for undistorted, conformationally fixed, piperidinol systems.^{25b}

(31) Reference 28, p 237.

(32) E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, **31**, 1669 (1966); E. J. Corey and E. Block, *ibid.*, **31**, 1663 (1966).

It should be pointed out that the assignment of **2a** is contrary to the view^{33,34} that hydroxylated double-chair forms related to **2a** should be less favored than a chair-boat alternative. There has been little or no actual evidence to support this view, however, prior to a recent nmr study³⁵ of α -granatanol. If conclusions based on the latter study are valid, then by analogy the conformational assignment of **2a** would not be unequivocal (as discussed below).

The configurations of the epimeric 3-granatanols have been established by unequivocal methods,³⁶ and recently a conformational analysis of this system has been reported.³⁵ With respect to the β isomer (**3**), our conclusions are in essential agreement, though they are based, in part, upon slightly different considerations. Thus, from our infrared study of the intramolecular hydrogen bonding recently confirmed³⁵ for β -granatanol, we find that the compound exists in carbon tetrachloride solution in an equilibrium between 89% free (**3a** + **3b**) and 11% intramolecularly bonded (**3c**) species, respectively.³⁷ The position of this equilibrium, which is believed to be reliable to $\pm 5\%$, is assigned from the integrated intensity of the free O-H stretching band (Figure 2) relative to that of its epimeric (**4**) alcohol (100% free OH).³⁸ Although the population of **3b** cannot be measured from the infrared data, it is probably small. In any event, it certainly must be less than 11%, since it lacks the driving force of intramolecular bond formation present



(33) W. D. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Letters*, 2589 (1965).

(34) L. A. Paquette and J. W. Heilmaster, *J. Am. Chem. Soc.*, **88**, 763 (1966).

(35) C.-Y. Chen and R. J. W. Le Fèvre, *J. Chem. Soc. Sect. B*, 539 (1966).

(36) K. Alder and H. A. Dortmann, *Chem. Ber.*, **86**, 1544 (1953).

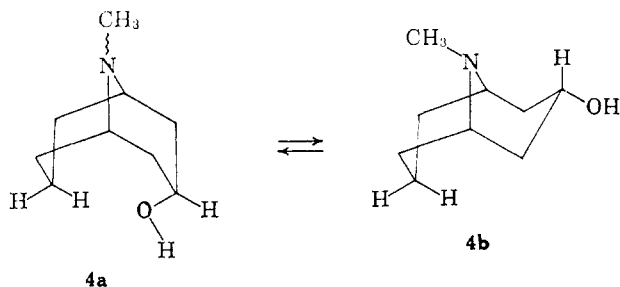
(37) Although a "twin-twist" or flexible double boat form²⁷ is possible in these systems, the very strong intramolecular hydrogen bond observed in **3** ($\Delta\nu$ 240 cm⁻¹) appears more compatible with the close approach attainable in the classical boat form, as depicted (**3c**), since a twist form should result in weaker bonding. Thus, α -1,3,5-trimethyl-2,6-diphenylpiperidin-4-ol was earlier assigned a classical boat conformation on the basis of intramolecular hydrogen bonding [M. Balasubramanian and N. Padma, *Tetrahedron Letters*, 49 (1963); C.-Y. Chen and R. J. W. Le Fèvre, *J. Chem. Soc.*, 3467 (1965)]. However, this assignment has been questioned, both on the basis of the weak bond observed [M. Tichý, *Advan. Org. Chem.*, **5**, 157 (1965)] and on stereochemical grounds (ref 11a, p 478). Apparently, the weak intramolecular hydrogen bond observed in the latter ($\Delta\nu$ 39 cm⁻¹) is due to a twist conformation. As such, however, it is uncertain whether the bond should be assigned to a weak OH...N or an OH...phenyl interaction.

(38) M. Tichý, J. Šipoš, and J. Sicher, *Collection Czech. Chem. Commun.*, **27**, 2907 (1962). In assigning these percentages, it is assumed that free rotation of the hydroxyl group in **3c** is prevented by the very strong intramolecular hydrogen bond ($\Delta\nu$ 240 cm⁻¹). Even in weaker bonded systems, free rotation of the OH group did not occur.^{25b,c}

in **3c**. Figure 2 presents the expanded free OH band of β -granatanol; it is unsymmetrical, in agreement with the stereochemical assignment.

The above results agree with recent conclusions based on other solution studies^{26,27} and parallel the finding that bicyclo[3.3.1]nonane systems containing α -hydrogen atoms in opposition at C₃ (or N) and C₇ exist in a twin-chair form in the crystal.³⁹

When a 3α -hydrogen is replaced by the bulkier hydroxyl group, however, it has been concluded from nmr data that the chair-boat (**4b**) is the preferred form.³⁵ The infrared band-shape data, however, may be in conflict with this conclusion. Thus, we find that the free O-H band of α -granatanol is only slightly less symmetrical than that of a typical axial alcohol (Figure 1). This result suggests, by the same arguments given for the assignment of **2a**, above, that the double-chair **4a** is the preferred form in this system.



Unfortunately, the infrared data do not absolutely prove the preferred conformation of **4** (or **2**), since they lack comparison to a known model **4b** system. Thus, it is possible that, in the boat form, the rotamers II and III could have the same absorption maximum, thus producing a symmetrical band.⁴⁰ However, pending future studies of related systems, it is our present view that **4a** (suitably distorted, of course, to accommodate the severe nonbonded interactions) should not be ruled out as the conformational preference of α -granatanol on the basis of the nmr conclusions, which in themselves are not unequivocal.⁴¹

Experimental Section

The spectra were recorded on a Perkin-Elmer Model 521 double-beam, grating, linear-frequency spectrophotometer, employing a spectral slit width of 3.8 cm^{-1} in the 3600-cm^{-1} region. In a few cases, a Perkin-Elmer Model 221 prism-grating instrument was used (spectral slit width of about 4 cm^{-1}). Absorbance correction factors for the spectral slit widths used were not applied.⁴² The compounds were run in carbon tetrachloride (Eastman Spectro Grade dried over phosphorus pentoxide) solution, generally at 2 to $3 \times 10^{-3}\text{ M}$, with a solvent blank, using 1- or 2-cm matched, quartz, infrared-grade cells (Pyrocell Co., Westwood, N. J.) in

plastic cell holders fabricated in these laboratories. In a few cases, however (see Table I), some dimer bands were obtained, even at low concentrations. For each compound, the spectrum was recorded first using a scan speed of $85\text{ cm}^{-1}/\text{min}$ and a normal scale presentation (down to 3000 cm^{-1}) to check on the absence of intermolecular hydrogen bonding. The free O-H band was then recorded on the expanded frequency scale ($10\times$) using a scan time of $11\text{ cm}^{-1}/\text{min}$. The ϵ_{max} data were taken from the normal scan; half-band widths, band-symmetry values, and band-area data (for graphical plotting) were obtained from the expanded bands. Frequency readings of the absorption maxima were taken directly from the frequency counter of the instrument. In every case, members of an epimeric pair were examined at the same time. There was no hydrochloride precipitation (clouding) problem with the amino alcohols, and all solutions appeared to be stable during the time required to obtain these data.⁴³

The apparent molecular absorption coefficient (ϵ) or molar absorptivity⁴⁴ was calculated from the familiar expression⁴⁵

$$\epsilon = \frac{1}{cl} \log \left(\frac{T_0}{T} \right)$$

where c is the concentration (M), l is the cell thickness (cm), and T_0 and T are the intensities of the incident and transmitted light of frequency ν . The apparent integrated band area (B) (integrated intensity²) was calculated from⁴⁵

$$B = 2.303 f \epsilon d \nu$$

where ϵ was plotted against ν on linear graph paper, and the area ($\epsilon d\nu$) was obtained by simple addition of the graph squares. The half-band width ($\Delta\nu_{1/2}$) was measured at $1/2\epsilon_{\text{max}}$.

The high purity of every sample reported in Table I was confirmed by glpc (Wilkins-Aerograph A-90-P, thermal conductivity detector): the amino alcohols and cyclohexanols on Carbowax 20M, the steroids on SE-30. The 3-tropanols (**5** and **6**), 7-indolizidinols (**9** and **10**), and 2- and 3-quinolizidinols (**11-14**) were obtained as previously reported.²⁵ The 2-tropanols¹⁶ (**7** and **8**) were obtained from the A. D. Little Co.⁴⁷ The 2 β -tropanol (**8**) was found to be completely intramolecularly bonded and to show no free O-H band, as might be implied from data earlier reported.⁴⁸ Scopine (**15**), mp $70-72^\circ$ (lit.⁴⁹ mp 76°), was prepared by Dr. L. Reiff of these laboratories. The cholestanols (**16** and **17**) were obtained from Steraloids, Queens, N. Y.: 3- α -ol, mp $185-186^\circ$ (lit.^{50a} mp 182°);⁵¹ 3 β -ol, mp $141-142^\circ$ (lit.^{50a} mp 142°). Androstosterone (**19**), mp $184-184.5^\circ$ (lit.^{50b} mp 183°), and epandrosterone (**18**), mp $173-174^\circ$ (lit.^{50b} mp 174°), were obtained from Mann Research Laboratories, New York, N. Y. *l*-Menthhol (**32**), mp $42-43^\circ$ (lit.⁵² mp 43°), was an Eastman White Label compound; the *dl*-neomenthol (**33**), mp $51.5-52^\circ$ (lit.⁵² mp 53°), was kindly furnished by the Organic Chemical Division of the Glidden Co., Jacksonville, Fla. The 4-*t*-butylcyclohexanols were obtained as a *cis-trans* mixture (Eastman White Label) and separated by chromatography on activated alumina (Woelm, grade 3) using pentane eluent.⁵³ The separation was followed by glpc. The *cis* isomer (**31**) was first eluted, mp $79.5-80.5^\circ$ (lit.⁵³ mp $81-82^\circ$), followed by the *trans* (**30**), mp $79-80^\circ$ (lit.⁵³ mp $81-82^\circ$). The 3-methylcyclohexanols were obtained from Mr. Ray Irino of these laboratories: the *trans* isomer was pure (glpc); the *cis* isomer contained 2% of the *trans*. All of the other

(39) W. A. C. Brown, J. Martin, and W. Parker, *J. Chem. Soc.*, 1844 (1965); M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964).

(40) Folding a trace of the α -granatanol band along ν_{max} does reveal the presence of a minor component on the low-frequency side, presumably due to a small contribution from another conformation, e.g., **4b**. The possibility of an equilibrium between comparable amounts of **4a** and **4b** (or **2a** and **2b**) is very remote, however, since such a situation would require the added coincidence that **4a** have the same absorption maximum as both rotamers II and III of **4b**.

(41) The conclusions drawn from the nmr analysis are based upon analogy to the 3-tropanol isomers as model compounds. However, it is not certain that the latter constitute suitable models for this purpose, due to the greater molecular distortions present in the double-chair form in bicyclo[3.3.1]nonyl systems. Difficulties inherent to the interpretation of nmr data for such systems have been mentioned^{33,34} (see also E. N. Marvell and S. Provant, *J. Org. Chem.*, **29**, 3084 (1964)).

(42) D. A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952).

(43) Cf. M. Tichý, *Advan. Org. Chem.*, **5**, 120 (1965).

(44) *Anal. Chem.*, **33**, 2558 (1964).

(45) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 17.

(46) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4642 (1960).

(47) Synthesized under a U. S. Army Research and Development Contract.

(48) W. A. M. Davies, J. B. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3504 (1960).

(49) J. Meinwald and O. L. Chapman, *J. Am. Chem. Soc.*, **79**, 665 (1957).

(50) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959: (a) p 28; (b) p 505.

(51) Although there is a slight discrepancy in the melting point of our sample, the identity of the compound was established by infrared spectral comparison with that published for authentic material: W. Neudert and H. Röpkke, "Atlas of Steroid Spectra," Springer-Verlag, New York, N. Y., 1965, compound no. 816.

(52) "Chemistry of Carbon Compounds," Vol. II B, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1953, p 515.

(53) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

alkylcyclohexanol samples were kindly furnished by Professor E. L. Eliel.

The 1-azabicyclo[3.3.1]nonan-3-ols (**1** and **2**) were prepared from the corresponding ketone. The latter, mp 126–131° (from hexane; lit.²⁹ mp 123–125°), was synthesized⁵⁴ as described²⁹ and gave a single peak on glpc analysis (Carbowax 20M).

Equatorial Hydroxyl Epimer (1). 1-Azabicyclo[3.3.1]nonan-3-one (1.5 g) in 7 ml of ethanol was reduced with 2 g of sodium in 5 ml of benzene as described⁵⁵ and then extracted with chloroform, which was evaporated to give 0.9 g of crude product, mp 90–93°. Three recrystallizations from cyclohexane gave **1**, mp 115–117°, which formed a picrate, mp 222–223° (benzene-methanol).

Anal. Calcd for C₁₄H₁₈N₄O₈: C, 45.41; H, 4.90; O, 34.56. Found: C, 45.75; H, 5.12; O, 34.23.

Axial Hydroxyl Epimer (2). 1-Azabicyclo[3.3.1]nonan-3-one (1.5 g) in dilute aqueous hydrochloric acid was hydrogenated over 0.6 g of 5% ruthenium-on-carbon (Englehard Industries, Newark, N.J.) for 6 hr at 60 psig and room temperature, then filtered, made basic with sodium hydroxide, and extracted with chloroform. The chloroform was distilled off and the residue (hygroscopic) was recrystallized from cyclohexane to give 0.4 g of **2**, mp 158–161° (which contained about 10–15% of **1**). Pure **2**, for infrared study, was separated and collected by preparative glpc. This product formed a picrate, mp 223–224° (benzene-methanol).

Anal. Calcd for C₁₄H₁₈N₄O₈: C, 45.41; H, 4.90; O, 34.56. Found: C, 45.32; H, 4.95; O, 34.48.

The epimeric picrates gave different infrared spectra, but depressed only 1° as a mixture melting point sample.

Previously, a product of mp 148–151° had been obtained by sodium borohydride reduction of the ketone.²⁹ From its melting point, it would appear to have been mainly **2**, as assigned.²⁹ Analogously, we have found that lithium aluminum hydride reduction gives about (±5%) an 80:20 mixture of **2** and **1**.

Epimers **1** and **2** were separated (but not completely) by glpc, with the following retention times (min): **1**, 8.5; **2**, 8.0; 1-azabicyclo[3.3.1]nonan-3-one, 5.1 (10 ft × 0.25 in column of 13% Carbowax 20M on 60–80 Gas Chrom P at 230°, 110 cc/min He flow rate). Older columns, which had lost their resolving power, did not separate the two isomers. Accordingly, a mixture of these two isomers was commonly used as a standard to check on newly prepared columns, and older ones whose resolution efficiency may have been in doubt.

3-β-Granatanol (3) was synthesized⁵⁴ from pseudopelletierine⁵⁶ by reduction with sodium in ethanol.⁵⁶ The product melted at 99–100° (hexane) (lit.^{55,56} mp 99–100°).

3α-Granatanol (4) was synthesized⁵⁴ by reduction of pseudopelletierine over platinum dioxide in ethanol at 1140 psig, then separated from unreduced ketone by the method of Werner,⁵⁷ and

distilled. The distillate crystallized on standing and melted at 94–96°. (This product contained about 3% unreduced ketone, as shown by glpc analysis.)

Anal. Calcd for C₁₅H₁₇NO: C, 69.63; H, 11.04; N, 9.02; neut equiv, 155.2. Found: C, 69.39; H, 11.2; N, 9.32; neut equiv, 155.

α-Granatanol gave a picrate, mp 285° dec (ethanol).

Anal. Calcd for C₁₅H₂₀N₄O₈: C, 46.87; H, 5.25; N, 14.58. Found: C, 47.15; H, 5.61; N, 14.71.

Reduction of pseudopelletierine with lithium aluminum hydride^{50,55,58} gave α-granatanol, mp 93.5–94.5° (petroleum ether, bp 30–60°) (lit. 85–87,⁵⁸ 85–88,⁵⁹ 69–70,⁶⁰ 69,^{30,61} 65,⁵⁷ 62–64°,³⁵ oil or crystals, no melting point reported^{56,62,63}) but which still contained some unreduced pseudopelletierine, as shown by glpc and infrared data.⁶⁴

The 3α-granatanol obtained from the hydride reduction gave a picrate, mp 284–285° (lit. 275–276,⁵⁶ 275,³⁰ 263–264,⁶¹ 260–290°⁶²).

The two granatanol epimers could not be separated by glpc on Carbowax 20M, a column which we have found ordinarily to be very effective for the separation of epimeric amino alcohols. However, the isomers were partially separated on Dow-Corning QF-1 (a fluoro silicone), obtained from Applied Science Laboratories, State College, Pa., with relative retention times (min) at 140°, 63 cc/min, as follows: 3-α-ol, 2.7; 3-β-ol, 3.3; pseudopelletierine, 4.9 (from air peak on 5% QF-1 on 60–80 Gas-Chrom P, 5 ft × 0.25 in column).

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(57) L. F. Werner, *J. Am. Chem. Soc.*, **40**, 669 (1918).

(58) K. Stach and G. Dold, *Arzneimittel-Forsch.*, **12**, 1022 (1962).

(59) W. M. Bryant, III, A. L. Burlingame, H. O. House, C. G. Pitt, and B. A. Tefertiller, *J. Org. Chem.*, **31**, 3120 (1966).

(60) R. Willstätter and H. Veraguth, *Ber.*, **38**, 1984 (1905).

(61) W. H. Hartung and S. M. Gaddekar, *J. Am. Pharm. Assoc.*, **42**, 715 (1953).

(62) J. Meinwald and S. L. Emerman, *J. Am. Chem. Soc.*, **78**, 5087 (1956).

(63) B. Matkovics, *Chem. Abstr.*, **54**, 17443e (1960).

(64) The discrepancies among the reported melting points would appear to be due to the hygroscopic nature of the compound and/or the relative purities of the products. Recently, the possibility of different crystalline forms has also been suggested.⁵⁹ Our product (**4**) gives an nmr spectrum in deuteriochloroform which essentially corresponds to that recently published⁵⁵ from lower melting material, except with respect to the broad band at τ 8.8 (which appears in our spectrum as a doublet of lower intensity) and the doublet at τ 9.1–9.2 (absent from our spectrum). Our sample gave no bands above τ 9.0.

(54) This synthesis was performed by Mr. C. Feit and co-workers, Regis Chemical Co., Chicago, Ill.⁴⁷

(55) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

(56) A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, *Org. Syn.*, **37**, 73 (1957).