

experiment, the temperature fluctuation was less than 0.2°, and temperature settings could be duplicated to within 0.5°.

The flask was attached to a high-vacuum line which permitted introduction of reactant and periodic sampling of the reaction mixture. Sampling was accomplished by means of a hollow-plug, high-vacuum stopcock attached to the flask through a short length of capillary tubing. A hole in the plug in addition to the one provided for evacuation permitted withdrawal of a sample with volume equal to that of the hollow core of the plug and transfer of the sample through a gas-sampling valve to a gas chromatography column. The sample volume was ~8 ml. A 2-m column packed with 1,2,3-triscyanoethoxypropane (25% on Chromosorb) and operated at 110° with He flow of 40 cc/min was used for the analyses.

A 0.25–0.30-ml sample of 1,5-hexadiyne was introduced into the vacuum line and thoroughly degassed. The reaction flask was thoroughly evacuated, and after temperature equilibrium was established, the diyne was distilled rapidly into the flask, the inlet stopcock was closed, and timing was started. Samples were removed for analysis at 12–15-min intervals by means of the hollow-plug stopcock. The rate at which a high vacuum could be reestablished after removal of a sample limited the sampling frequency. Reactions at 210° were carried to 72% of completion, and those at 218 and 232° were carried to 88% of completion. Plots of log (1/fraction of 1,5-hexadiyne unchanged) were linear. A slight upward curvature was observed at points beyond 92% of completion. First-order rate constants were computed by a least-squares treatment of the data, and are presented in Table I.

## Optical Rotary Dispersion Studies. CIX.<sup>1</sup> An Octant Rule for the Azide Chromophore<sup>2</sup>

Carl Djerassi, Albert Moscowitz, Kurt Ponsold, and Günter Steiner

*Contribution from the Department of Chemistry, Stanford University, Stanford, California, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota, and Institute for Organic Chemistry, Friedrich Schiller University, Jena, Germany. Received September 16, 1966*

**Abstract:** An analysis of the relevant orbitals involved in the 280–290- $\mu$  transition of azides has led to the development of an octant rule, which may prove useful in conformational studies of optically active azides. The optical rotatory dispersion and circular dichroism properties of 34 steroidal azides have been measured and analysis of some of the data in terms of the newly developed octant rule has been attempted. Difficulties associated with the potentially free rotation of the chromophore in the steroidal azides are noted and discussed.

For the purpose of correlating optical activity with molecular structure some chromophores have been designated as "inherently symmetric."<sup>3</sup> The term is meant to signify that the local symmetry, *i.e.*, the symmetry of the isolated chromophore, is sufficiently high to preclude optically active chromophoric transitions. Only when the chromophore is placed in a dissymmetric molecular environment will its transitions manifest optical activity, and the signed magnitude of this activity will depend upon the detailed nature and geometry of the extrachromophoric environment. For this reason, an inherently symmetric chromophore can be useful as a molecular probe with which to explore molecular geometries.

The most extensive application of the above concept has been made in connection with the carbonyl group of saturated ketones,<sup>4</sup> for which an "octant rule" could

be formulated.<sup>5</sup> However, it has been emphasized<sup>6</sup> that any inherently symmetric chromophore whose transitions are readily accessible can be used in an analogous manner; one need only ascertain the nature of the orbitals involved in the pertinent transition so as to be able to specify the shape of the sign determining regions in space. This latter task, of course, may not be a trivial one.

In the present work, we shall be concerned with the inherently symmetric azide chromophore which in alkyl azides exhibits a weak transition ( $\epsilon \sim 30$ ) in the vicinity of 280–290  $\mu$ . Closson and Gray<sup>7</sup> and Lieber, *et al.*,<sup>8</sup> have discussed the pertinent orbitals. The former<sup>7</sup> attribute the transition roughly to the promotion of an electron from a nonbonding 2p<sub>y</sub> orbital, situated mainly on the nitrogen atom N<sub>1</sub> con-

from the more recent literature may be found in P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965.

(5) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961). For recent theoretical comments see G. Wagniere, *ibid.*, **88**, 3937 (1966); Y. H. Pao and D. P. Santry, *ibid.*, **88**, 4157 (1966).

(6) A. Moscowitz, *Dansk Kemi*, **43**, 113 (1962); A. Moscowitz, *Advan. Chem. Phys.*, **4**, 67 (1962).

(7) W. D. Closson and H. B. Gray, *J. Am. Chem. Soc.*, **85**, 290 (1963).

(8) E. Lieber, J. S. Curtice, and G. N. R. Rao, *Chem. Ind.* (London), 586 (1966).

(1) For paper CVIII, see E. Bach, A. Kjaer, R. Dahlbom, B. Sjöberg, E. Bunnenberg, C. Djerassi, and R. Records, *Acta Chem. Scand.*, in press.

(2) The work at Stanford University was supported by the National Institutes of Health (Grant No. CA 07195) and by the National Science Foundation (Grant No. GP 4304).

(3) W. Moffitt and A. Moscowitz, *J. Chem. Phys.*, **30**, 648 (1959); A. Moscowitz, *Tetrahedron*, **13**, 48 (1961); A. Moscowitz, K. Mislów, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962).

(4) (a) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960. (b) Additional references

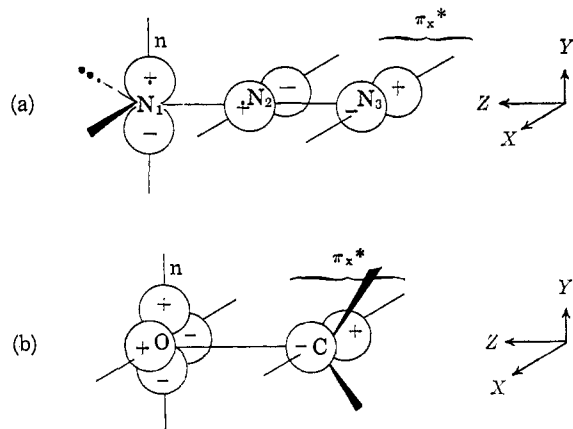


Figure 1. Orbitals involved in 290- $m\mu$  transition of azides (a) and ketones (b).

cerned with bonding to the alkyl group, to an antibonding  $\pi^*$  orbital, associated principally with  $2p_x$  atomic orbitals from the remaining two nitrogen atoms. These orbitals are depicted schematically in Figure 1. The strong analogy to the idealized description of the 290- $m\mu$   $n-\pi^*$  transition in saturated ketones<sup>9a</sup> becomes apparent from a comparison of Figures 1a and 1b. The principal difference lies in the fact that the  $n$  orbital and one of the  $2p_x$  atomic orbitals are on different centers ( $N_1$  and  $N_2$ ) in azides; in carbonyls both of the atomic orbitals are situated on the oxygen atom. The primary effect of this separation of orbital centers is to reduce the magnitude of the relevant magnetic dipole transition moment from its value in ketones, roughly by about a factor of one-fifth. However, the basic symmetry of the situation posed by the electronic promotions leading to the 290- $m\mu$  transitions is the same in both cases. Hence, one is immediately led to an octant rule for the 280–290- $m\mu$  azide transition quite analogous to the one previously given for saturated ketones.<sup>5</sup>

### The Azide Octant Rule

As in the case of the saturated ketones, only two of the surfaces specifying the "octants" are well defined on symmetry grounds.<sup>9b</sup> These are the  $XZ$  and  $YZ$  planes in Figure 1. In the absence of more precise information regarding the azide orbitals, the third surface must remain ill defined. We shall approximate it by a third plane perpendicular to the other two planes, and passing through the central nitrogen atom. However, we emphasize the crudity of such an approximation [*cf.* ref 5, footnote 4].

For a specification of the sign to be associated with a particular octant, it is most convenient to view the chromophore along the  $N-N-N$  axis from  $N_3$  toward  $N_1$ , with the bond specifying the lone pair of electrons on  $N_1$  lying in a vertical plane (see Figure 2).<sup>10</sup> From this vantage, the signs of the azide octants are the same as those of the carbonyl octants (Figure 2). This follows from the fact that the analogous viewpoint for  $C=O$  would be along the  $C-O$  bond from  $C$  toward

(9) (a) H. L. McMurry, *J. Chem. Phys.*, **9**, 231 (1941); (b) J. A. Schellman, *ibid.*, **44**, 55 (1966).

(10) When using Dreiding models, this can be done very conveniently by connecting an acetylene to a carbonyl group and considering the oxygen atom as the representative of the lone pair of electrons on  $N_1$  and the carbonyl carbon atom at  $N_1$ .

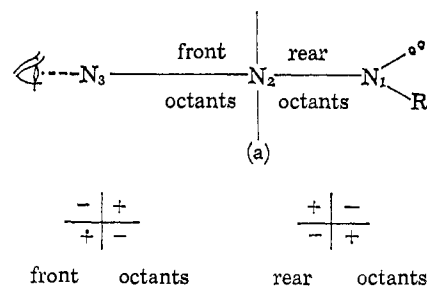


Figure 2. Octant diagram of azide chromophore.

O, with the carbonyl group rotated through  $90^\circ$  about the  $C-O$  axis from its normal orientation for application of the octant rule.<sup>5</sup> This corresponds to a double change in signs which is, of course, equivalent to no sign changes at all.

We have already noted that the 290- $m\mu$  magnetic dipole transition moment in azides will be reduced from its value in ketones. Further, the higher effective nuclear charge for a nitrogen atom will tend to make orbitals less extended in space in azides than are the analogous orbitals in carbonyls. It follows that the magnitude of the contribution to the 290- $m\mu$  Cotton effect of a given asymmetrically disposed perturber should be considerably less in azides than in saturated ketones. This is borne out in the examples considered below (Table I). It also accounts, in part, for the failure of Levene and Rothen<sup>11</sup> to observe a 290- $m\mu$  Cotton effect in a number of optically active azides, although conformational mobility of the azide groups can play a significant role here too.

### Analysis of Experimental Data

The octant rule<sup>5</sup> for ketones emanated from a large body of optical rotatory dispersion measurements performed by us among steroidal ketones.<sup>4a</sup> It was felt, therefore, that as far as possible, it would be desirable to examine analogous steroidal azides. One of the simplest ways of synthesizing such azides is by nucleophilic displacement of azide anion on epoxides,<sup>12</sup> but this procedure leads invariably to axial azides containing an adjacent axial hydroxyl function. In order to secure equatorial azides or azides lacking adjacent hydroxyl functions, the displacement of steroidal mesylates with sodium azide in dimethyl sulfoxide<sup>13</sup> was utilized as described in the Experimental Section. In addition, a few steroidal azides described in the literature<sup>14,15</sup> were also included in our studies.

As noted above, the rotational strength of the azide chromophore is considerably weaker than that of the carbonyl group and, in a number of instances, the Cotton effect in the 280- $m\mu$  region was discernible only with difficulty by optical rotatory dispersion (ORD) means because of the relatively strong background rotation<sup>16</sup>

(11) P. A. Levene and A. Rothen, *J. Chem. Phys.*, **5**, 985 (1937).

(12) K. Ponsold, *Chem. Ber.*, **95**, 1727 (1962); **96**, 1855 (1963).

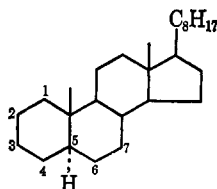
(13) W. R. Hertler and E. J. Corey, *J. Org. Chem.*, **23**, 1221 (1958).

(14) Compounds 11 and 18 were kindly provided by Professor R. Goutarel (Gif-sur Yvette, France).

(15) Professor A. Hassner of the University of Colorado furnished us with 3 $\alpha$ -iodo-2 $\beta$ -azidocholestane (9) as well as 3 $\alpha$ -iodo-2 $\beta$ -( $N$ -acetyl-amino)cholestane.

(16) For a pertinent discussion of the operation of such background effects in ORD work and their absence in CD measurements see C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **84**, 4552 (1962).

Table I. ORD and CD Properties (Dioxane Solution) of Azidocholestanes



Compd no.	Position of azide	Other subst	Cotton effect sign	CD, maximum	ORD	
					Peak	Trough
1	1 $\alpha$	2 $\beta$ -OH	+	$[\theta]_{295} + 267$	$[\Phi]_{312} + 139$	$[\Phi]_{270} + 65$
2	1 $\alpha$	3 $\beta$ -OH 2 $\beta$ -OH 3 $\beta$ -OAc	+	$[\theta]_{295} + 392$	$[\Phi]_{310} + 312$	$[\Phi]_{287} + 275$
3	2 $\alpha$		-	$[\theta]_{270} - 225$	$[\Phi]_{280}^{infl} + 1054$	$[\Phi]_{315}^{infl} + 525$
4	2 $\beta$		+	$[\theta]_{284} + 187 (25^\circ)$ $[\theta]_{310} - 92 (-192^\circ)$ $[\theta]_{245} + 128 (-192^\circ)$	$[\Phi]_{300} + 502$	$[\Phi]_{275} + 355$
5	2 $\beta$	3 $\alpha$ -OH	+	$[\theta]_{315} - 98$ $[\theta]_{280} + 122$		
6	2 $\beta$	3 $\alpha$ -OAc	+	$[\theta]_{285} + 390$	$[\theta]_{298} + 297$	$[\Phi]_{270} + 246$
7	2 $\beta$	1 $\alpha$ -OH 3 $\beta$ -OH	+	$[\theta]_{284} + 390$		
8 <sup>a</sup>	2 $\beta$	1 $\alpha$ -OH 3 $\beta$ -OAc	+	$[\theta]_{285} + 1156 (25^\circ)$ $[\theta]_{284} + 1986 (-192^\circ)$	$[\Phi]_{304} + 704$	$[\Phi]_{248} - 752$
9	2 $\beta$	3 $\alpha$ -I	+	$[\theta]_{281} + 7485$	$[\Phi]_{275} + 8015$	
10 <sup>a</sup>	3 $\alpha$		+	$[\theta]_{290} + 200 (25^\circ)$ $[\theta]_{292} + 360 (-192^\circ)$	$[\Phi]_{302} + 500$	$[\Phi]_{280} + 289$
11	3 $\alpha$	$\Delta^5$	+	$[\theta]_{290} + 721$	$[\Phi]_{302} + 952$	$[\Phi]_{275} + 710$
12	3 $\alpha$	2 $\beta$ -OH	+	$[\theta]_{289} + 147$		
13	3 $\alpha$	2 $\beta$ -OAc	+	$[\theta]_{289} + 416$	$[\Phi]_{300} + 420$	$[\Phi]_{280} + 400$
14	3 $\alpha$	4 $\alpha, 5\alpha$ -oxide	+	$[\theta]_{285} + 509$		
15	3 $\alpha$	2 $\alpha$ -CH <sub>3</sub>	-	$[\theta]_{290} - 517$	$[\Phi]_{250}^{infl} + 7014$	$[\Phi]_{300}^{infl} + 2024$
16	3 $\alpha$	4 $\alpha$ -CH <sub>3</sub>	+	$[\theta]_{284} + 497$	$[\Phi]_{305}^{infl} - 874$	$[\Phi]_{250}^{infl} - 2591$
17	3 $\beta$		-	$[\theta]_{282} - 233$	$[\Phi]_{260}^{infl} + 850$	$[\Phi]_{310}^{infl} + 500$
18	3 $\beta$	$\Delta^5$	-	$[\theta]_{283} - 460$	$[\Phi]_{300} - 470$	$[\Phi]_{275} - 400$
19 <sup>b</sup>	3 $\beta$	2 $\alpha$ -Br	-	$[\theta]_{291} - 886$	$[\Phi]_{268} + 580$	$[\Phi]_{307} - 467$
20	3 $\beta$	4 $\alpha, 5\alpha$ -Oxide	+	$[\theta]_{290} + 321$		
21	3 $\beta$	4 $\beta, 5\beta$ -Oxide	-	$[\theta]_{285} - 514$		
22	4 $\beta$	5 $\alpha$ -OH	+	$[\theta]_{286} + 392$		
23	4 $\beta$	3 $\beta$ -OH	+	$[\theta]_{322} + 72$ $[\theta]_{275} - 216$		
24	4 $\beta$	3 $\beta$ -OAc 5 $\alpha$ -OH	-	$[\theta]_{283} - 800$	$[\Phi]_{284} + 555$	$[\Phi]_{300} + 52$
25	5 $\alpha$	3 $\beta$ -OH 6 $\beta$ -OH	-	$[\theta]_{285} - 837$		
26	5 $\alpha$	3 $\beta$ -OAc 6 $\beta$ -OAc	-	$[\theta]_{287} - 2484$	$[\Phi]_{270} - 368$	$[\Phi]_{305} - 623$
27	6 $\beta$		-	$[\theta]_{305} - 108$	$[\Phi]_{275}^{infl} - 1000$	$[\Phi]_{310}^{infl} - 500$
28	6 $\beta$	3 $\beta$ -OAc 5 $\alpha$ -OH	+	$[\theta]_{287} + 280$	$[\Phi]_{320}^{infl} - 265$	$[\Phi]_{253} - 765$
29	6 $\beta$	3 $\beta$ -OAc 7 $\alpha$ -OH	-	$[\theta]_{295} - 201$		
30	6 $\beta$	3 $\beta$ -OAc 7 $\alpha$ -OAc	+	$[\theta]_{312} - 56$ $[\theta]_{278} + 389$	$[\Phi]_{290} + 138$	$[\Phi]_{280} + 12$
31 <sup>c</sup>	7 $\alpha$	3 $\beta$ -OAc	+	$[\theta]_{295} + 325$	$[\Phi]_{310} + 1168$	$[\Phi]_{272} + 995$
32	7 $\alpha$	3 $\beta$ -OAc 6 $\beta$ -OH	-	$[\theta]_{293} - 412$		
33	7 $\alpha$	3 $\beta$ -OAc 6 $\beta$ -OAc	+	$[\theta]_{317} - 36$ $[\theta]_{282} + 468$	$[\Phi]_{295} + 132$	
34 <sup>d</sup>	7 $\beta$	3 $\beta$ -OAc	-	$[\theta]_{308} - 19$ $[\theta]_{275} + 27$		$[\Phi]_{305} - 900$

<sup>a</sup> CD results in EPA solvent mixture. <sup>b</sup> Practically no wavelength shift was encountered in methanol. <sup>c</sup> Practically no wavelength shift was encountered in acetonitrile. <sup>d</sup> Essentially the same CD results were obtained in methanol and isooctane solution. Values in degrees.

upon which it is superimposed. A typical example is given in Figure 3, and for that reason circular dichroism (CD) measurements were performed for all of the 34 azides encompassed in our present work. The relevant data are summarized in Table I using the conventional ORD and CD notations in terms of molecular rotation  $[\Phi]$  and molecular ellipticity  $[\theta]$ .<sup>17</sup> In accordance with

expectation, the molecular ellipticity values are quite low with the exception of 3 $\alpha$ -iodo-2 $\beta$ -azidocholestane (9). This is not due to an unusually high rotational strength of the 290-m $\mu$  azide transition in this molecule, but rather is associated with the much stronger molecular

(17) C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957); C. Djerassi and E. Bunnenberg, *ibid.*, 299 (1963).

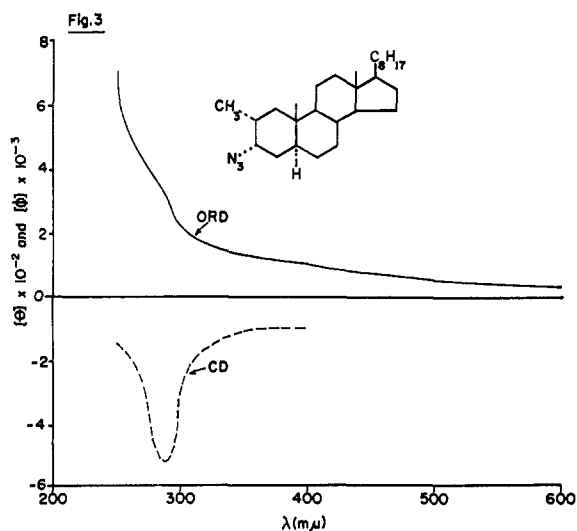


Figure 3. Optical rotatory dispersion and circular dichroism (dioxane solution) of 2 $\alpha$ -methyl-3 $\alpha$ -azidocholestane (15).

ellipticity of a transition involving the iodine atom. This is demonstrated by the wavelength of the Cotton effect, which occurs in the 250-m $\mu$  region typical of iodides,<sup>18</sup> and by the fact that 3 $\alpha$ -iodo-2 $\beta$ -(N-acetylamino)cholestane<sup>15</sup> exhibited a very similar Cotton effect.

The only stereochemical factor which needs to be taken into consideration in an octant rule analysis of cyclohexanones<sup>5</sup> is ring conformational alterations. In azides, the situation is much more complicated since the entire chromophore is subject to rotation. This is best illustrated by some concrete examples.

2 $\alpha$ -Azidocholestane (3) is a typical equatorial azide in which there exist no serious impediments to rotation of the chromophore. For our purposes, it is sufficient to consider six rotamers in which the azide substituent is rotated around the N<sub>1</sub>-carbon bond in 60° increments. These rotamers are most conveniently depicted in terms of Newman projections (A-F) by looking from the N<sub>1</sub> atom (corresponding to the carbonyl carbon atom in the Dreiding model<sup>10</sup>) toward C-2 of the steroid nucleus. Rotamer A then corresponds to that geometrical situation in which the lone electron pair on N<sub>1</sub> is exactly in a vertical plane bisecting the 1 $\alpha$  and 3 $\alpha$  hydrogens and terminating at the 5 $\alpha$ -hydrogen atom. By swinging the entire azide substituent counterclockwise in 60° increments one obtains the remaining rotamers (B-F). The Cotton effect sign predicted by the azide octant rule is indicated under each Newman projection, with rotamers A, D, and E being quite unambiguous since essentially all substituents are located in either a negative or positive rear octant (see Figure 2). In rotamer B, all substituents are in positive rear octants with the possible exception of carbon atoms 11 and 12, while in F there are substituents in both negative and positive rear octants, but the latter are much more distant (C-9 is the closest one in a positive octant) from the azide chromophore and a negative Cotton effect is, therefore, assumed. In rotamer C most of the substituents appear in positive front or rear octants. The observed (Table I) negative Cotton

(18) C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **85**, 324 (1963).

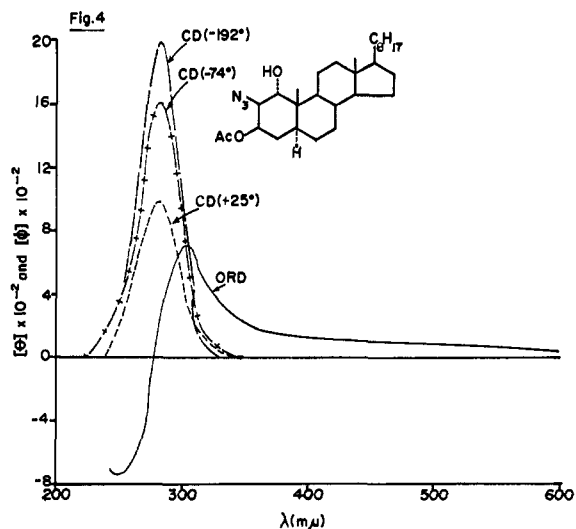
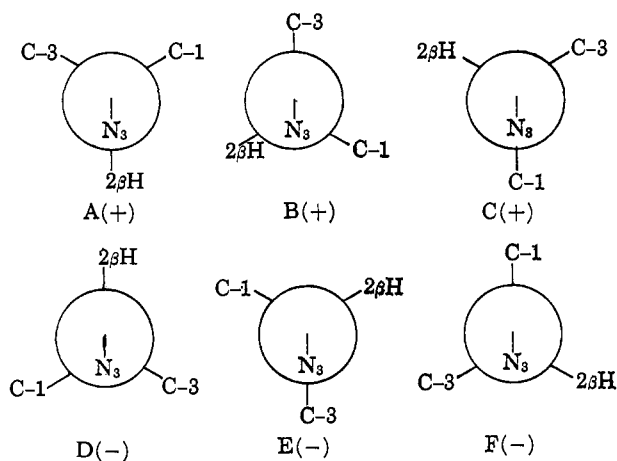


Figure 4. Optical rotatory dispersion (dioxane) and variable-temperature circular dichroism (EPA) of 2 $\beta$ -azidocholestane-1 $\alpha$ ,3 $\beta$ -diol 3-acetate (8).

effect might be taken to be indicative of the preponderance of one or more of rotamers D, E, and F, but this would be based on the completely unfounded premise that the rotatory contribution of each rotamer is quantitatively identical. The energy difference between the various rotamers contributing to the equilibrium mixture is apparently very small, because no difference (within experimental error) in molecular ellipticity was noted on lowering the temperature to -192°.<sup>19</sup>



Thus it is not possible to draw any stereochemically significant conclusion from an octant rule analysis of the ORD and CD behavior of 2 $\alpha$ -azidocholestane (3).

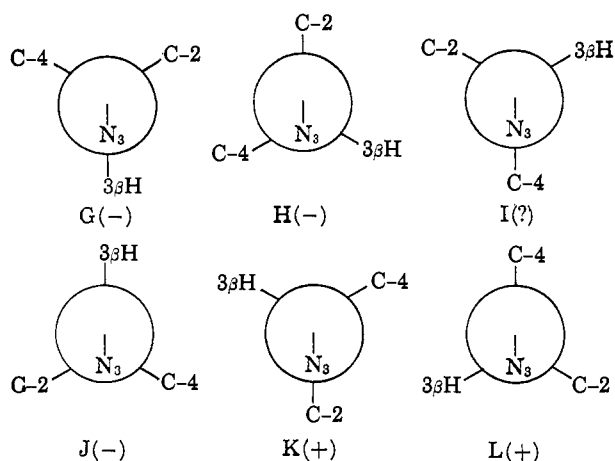
The 2 $\beta$ -azidocholestanes are noteworthy in that the double-humped CD curves (compound 4 at -192° and compound 5 at room temperature) clearly indicate the existence of a multiplicity of molecular species. Although some of these species undoubtedly represent rotameric variations of the azide group, the possibility that these species may be associated with different

(19) The use of low temperature circular dichroism measurements for conformational mobility and free rotational isomerism studies was first described by K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1870 (1963), and leading references to subsequent applications of this technique are cited by W. S. Briggs and C. Djerassi, *Tetrahedron*, **21**, 3455 (1965).

degrees of asymmetric solvation<sup>20,21</sup> cannot be excluded, especially so since hydroxyl groups are involved in some instances. Similar behavior may be noted among the axial  $6\beta$  (27–30) and  $7\alpha$  (31–33) azides. In view of this complication, and because of the added difficulties in deciding on conformational variations of the acetoxy group, it seems pointless at this time to speculate about the rotameric preferences among such azides. The removal of the various oxygen substituents and the introduction of methyl groups adjacent to the azide might offer more useful information, but such compounds are synthetically not readily available.

A particularly interesting situation is presented by the seven  $3\alpha$ -azidocholestanes (10–16), which in addition to the unsubstituted parent 10 encompass methyl (15, 16), hydroxyl (12), acetoxy (13), oxido (14),<sup>22</sup> and double bond (11) variants. All but the  $2\alpha$ -methyl-substituted azide 15 exhibit positive Cotton effects (Table I), and it is pertinent to inquire into the reasons for sign inversion upon introduction of a  $2\alpha$ -methyl substituent.

The six pertinent rotamers of  $3\alpha$ -azidocholestane (10) are represented by Newman projections G–L. Of these only I presents some difficulty in terms of Cotton-effect prediction because of competition between negative rear octant and positive front octant substituents; G would be expected to be weakly negative because of virtual compensation of all substituents except for the negative contribution of the C-6 and C-7 carbon atoms. On conformational grounds, rotamers I, J, and K appear to be the least favored since each of them contains at least one 1,3-diaxial hydrogen–azide interaction. The observed positive Cotton effect for 10, which becomes more strongly positive upon lowering the temperature, suggests that L is probably the most favored rotamer. However, this is one of two rotamers (the other one being K) in which there is produced an appreciable nonbonded interaction between the azide and the  $2\alpha$ -methyl (15) but not the  $4\alpha$ -methyl (16) group, which explains why inversion in sign occurs upon  $2\alpha$  methylation. In the latter case (Figure 3), rotamer H would appear to be the most favored one.



(20) A. Moscovitz, K. M. Wellman, and C. Djerassi, *Proc. Natl. Acad. Sci. U. S.*, **50**, 799 (1962).

(21) For further significance of such double-humped CD curves see K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscovitz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 73 (1965).

(22) For rotatory contribution of epoxides in cyclohexanones see C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965).

In summary, in the present series of compounds, the amount of definitive stereochemical information that can be obtained is severely limited because of the very many accessible rotameric conformations and other complications noted. Hopefully, more promising situations will exist for other azides, e.g., sugar azides, currently being synthesized by H. Paulsen and co-workers (private communication).

## Experimental Section<sup>28</sup>

**General Procedure for Azide Synthesis.** To an ice-cold pyridine solution of the appropriate hydroxycholestane was added excess methanesulfonyl chloride, and the mixture was left in the refrigerator until no more unreacted alcohol was detectable by thin layer chromatography. After pouring onto ice, the product was extracted with ether, washed successively with water, ice-cold dilute hydrochloric acid, water, sodium bicarbonate solution, and water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The crude mesylate was dried further over phosphorus pentoxide, dissolved in dimethyl sulfoxide solution,<sup>24</sup> and stirred with excess sodium azide at 80–90° until all of the mesylate had reacted. Dilution with water and extraction with ether followed by washing with water, drying, and evaporation left a gum which was chromatographed over neutral aluminum oxide (activity I) with petroleum ether (bp 30–50°). The order of elution was first olefin, then azide, and finally ketone and was monitored by thin layer chromatography of the individual eluates.

**$2\alpha$ -Azidocholestane (2).** From 4.0 g of cholestan-2 $\beta$ -ol<sup>26</sup> there was obtained 3.3 g of yellowish brown oil, which in addition to azide contained 35% of  $\Delta^2$ -cholestene, 25% of  $\Delta^1$ -cholestene, and 3% of cholestan-2-one. Chromatography provided 0.95 g of colorless azide, mp 51–52°,  $[\alpha]^{20D} +15^\circ$ , after recrystallization from acetone-methanol. *Anal.* Calcd for  $C_{27}H_{47}N_3$ : C, 78.38; H, 11.46; N, 10.16. Found: C, 77.92, H, 11.47; N, 10.19.

The  $2\alpha$  stereochemistry was substantiated by reduction (1 day, room temperature) of 0.25 g of azide in ether solution with 0.25 g of lithium aluminum hydride.<sup>26</sup> The ether solution was concentrated and treated with a few drops of acetic anhydride, and the precipitated crystals (0.22 g) were recrystallized from ethyl acetate to provide  $2\alpha$ -acetamincholestane, mp 215–216°,  $[\alpha]^{20D} -12^\circ$  (lit.<sup>27</sup> mp 215–216°,  $[\alpha]^{20D} -14^\circ$ ).

**$2\beta$ -Azidocholestane (4).** Cholestan-2 $\alpha$ -ol (2.3 g)<sup>25</sup> yielded 2.2 g of pale yellow syrup, which contained 17% of  $\Delta^2$ -cholestene and 3% cholestan-2-one; after chromatography there was isolated 1.35 g of colorless azide, mp 55–56°,  $[\alpha]^{20D} +26^\circ$ , after recrystallization from acetone-methanol. *Anal.* Calcd for  $C_{27}H_{47}N_3$ : C, 78.38; H, 11.46; N, 10.16. Found: C, 78.25; H, 11.53; N, 10.06.

The stereochemical assignment was confirmed by lithium aluminum hydride reduction of 0.5 g of azide followed by isolation of the amine and warming with acetone, which yielded 0.45 g of  $2\beta$ -isopropylideneaminocholestane, mp 115–116°,  $[\alpha]^{20D} +4^\circ$  (lit.<sup>27</sup> mp 115–117°,  $[\alpha]^{20D} +4^\circ$ ).

**$3\beta$ -Azidocholestane (17).** The usual treatment of 2.25 g of cholestan-3 $\alpha$ -ol afforded 20% of a mixture of  $\Delta^2$ - and  $\Delta^3$ -cholestene, 5% of cholestan-3-one, and 75% of azide (mp 65–66°,  $[\alpha]^{20D} +26^\circ$ , after recrystallization from acetone-methanol). *Anal.* Calcd for  $C_{27}H_{47}N_3$ : C, 78.38; H, 11.46; N, 10.16. Found: C, 78.54; H, 11.49; N, 10.37.

Reduction of 0.25 g of azide with lithium aluminum hydride followed by acetylation and recrystallization from acetone-ethyl acetate led to 0.2 g of  $3\beta$ -acetamincholestane, mp 243–246°,  $[\alpha]^{20D} +12^\circ$  (lit.<sup>28</sup> mp 245–246°,  $[\alpha]^{20D} +12^\circ$ ).

(23) Rotatory dispersion and circular dichroism measurements were performed by Mrs. R. Records on a Japan Spectroscopic Co. automatically recording spectropolarimeter with circular dichroism attachment. Specific rotations mentioned in the Experimental Section were determined in chloroform solution (*c* 1.0).

(24) The over-all yield of azide based on the starting alcohol was higher when no purification of the intermediate mesylate was attempted.

(25) W. G. Dauben, E. J. Blanz, J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(26) Cf. K. Ponsold, *Chem. Ber.*, **96**, 1411 (1963).

(27) C. W. Shoppee, R. J. W. Gremlynn, D. E. Evans, and G. H. R. Summers, *J. Chem. Soc.*, 4364 (1957).

(28) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *ibid.*, 1649 (1956).

**2 $\alpha$ -Methyl-3 $\alpha$ -azidocholestane (15).** 2 $\alpha$ -Methylcholestan-3 $\beta$ -ol<sup>29</sup> was transformed in 77% yield into the azide, which exhibited mp 110–111°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> +92°. *Anal.* Calcd for C<sub>28</sub>H<sub>49</sub>N<sub>3</sub>: C, 78.62; H, 11.55; N, 9.83. Found: C, 78.41; H, 11.73; N, 9.72.

**4 $\alpha$ -Methyl-3 $\alpha$ -azidocholestane (16).** In an analogous manner, 4 $\alpha$ -methylcholestan-3 $\beta$ -ol<sup>29</sup> yielded 63% of azide (mp 104–105°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –54°) accompanied by 15% of olefin and 5% of 4 $\alpha$ -methylcholestan-3-one. *Anal.* Calcd for C<sub>28</sub>H<sub>49</sub>N<sub>3</sub>: C, 78.62; H, 11.55; N, 9.83. Found: C, 78.35; H, 11.51; N, 9.83.

**6 $\beta$ -Azidocholestane (27).** Cholestan-6 $\alpha$ -ol<sup>30</sup> was transformed in 40% yield into the azide, which crystallized in needles (mp 69–70°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –30°) from acetone. *Anal.* Calcd for C<sub>27</sub>H<sub>47</sub>N<sub>3</sub>: C, 78.38; H, 11.46; N, 10.16. Found: C, 78.58; H, 11.47; N, 10.01.

**7 $\alpha$ -Azidocholestan-3 $\beta$ -ol Acetate (31).** An over-all yield of 66% of azide (mp 68–69°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> +35°, after recrystallization from acetone-methanol) was realized starting with cholestan-3 $\beta$ ,7 $\beta$ -diol 3-acetate.<sup>31</sup> *Anal.* Calcd for C<sub>29</sub>H<sub>49</sub>O<sub>2</sub>N<sub>3</sub>: C, 73.84; H, 10.47; N, 8.91. Found: C, 73.80; H, 10.61; N, 8.86.

(29) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).

(30) R. Tschesche, *Ber.*, **65**, 1842 (1932).

(31) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **65**, 1503 (1943).

Saponification of **31** with 5% methanolic potassium hydroxide solution (30-min reflux) and recrystallization from acetone-methanol provided 7 $\alpha$ -azidocholestan-3 $\beta$ -ol mp 125–126°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> +82°. *Anal.* Calcd for C<sub>27</sub>H<sub>47</sub>ON<sub>3</sub>: C, 75.47; H, 11.03; N, 9.78. Found: C, 75.65; H, 10.93; N, 9.79.

Reduction of 0.1 g of the hydroxy azide with lithium aluminum hydride followed by acetylation in ether solution and recrystallization from methanol furnished colorless needles (0.085 g) of 7 $\alpha$ -acetamincholestan-3 $\beta$ -ol, mp 268–270°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –3° (lit.<sup>27</sup> mp 270–272°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –9°).

**7 $\beta$ -Azidocholestan-3 $\beta$ -ol Acetate (34).** Starting with cholestan-3 $\beta$ ,7 $\alpha$ -diol 3-acetate<sup>31</sup> there was obtained 34% of  $\Delta^7$ -cholesten-3 $\beta$ -ol acetate and 50% of the azide **34**, which exhibited mp 110–111°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –50°, after recrystallization from acetone-methanol. *Anal.* Calcd for C<sub>29</sub>H<sub>49</sub>O<sub>2</sub>N<sub>3</sub>: C, 73.84; H, 10.47; N, 8.91. Found: C, 73.86; H, 10.66; N, 8.85.

Saponification in the above described manner led to 7 $\beta$ -azidocholestan-3 $\beta$ -ol, mp 158–159°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –40° (*Anal.* Calcd for C<sub>28</sub>H<sub>47</sub>ON<sub>3</sub>: C, 75.47; H, 11.03; N, 9.78. Found: C, 75.68; H, 11.00; N, 9.69), which was reduced with lithium aluminum hydride and acetylated to yield, after recrystallization from methanol, 7 $\beta$ -acetamincholestan-3 $\beta$ -ol, mp 253–255°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> +60° (lit.<sup>27</sup> mp 255–259° [ $\alpha$ ]<sub>D</sub><sup>20</sup> +63°).

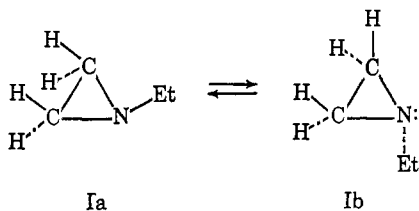
## Nuclear Magnetic Resonance Spectra and Nitrogen Inversion in 1-Acylaziridines<sup>1</sup>

F. A. L. Anet and J. M. Osyany

*Contribution No. 1888 from the Department of Chemistry, University of California, Los Angeles, California, and from the Department of Chemistry, University of Ottawa, Ottawa, Ontario. Received August 17, 1966*

**Abstract:** The nmr spectra of several 1-acylaziridines were determined over a range of temperatures. Rates of nitrogen inversion were obtained for 1-methanesulfonyl, 1-(N,N-dimethylcarbamyl)-, and 1-carbomethoxyaziridine. A barrier to rotation about the carbon-nitrogen bond in the side chain of 1-(N,N-dimethylcarbamyl)aziridine was also observed. The rates of nitrogen inversion in 1-acylaziridines were found to be much higher than those of 1-alkylaziridines.

The rates of nitrogen inversion in many derivatives of aziridine (ethylenimine) are of a suitable magnitude for study by nmr spectroscopy.<sup>2,3</sup> Thus, at room temperature the ring protons in 1-ethylaziridine (I) give<sup>2</sup> rise to an A<sub>2</sub>B<sub>2</sub> pattern, showing that the rate constant ( $k$ , in units of sec<sup>-1</sup>) for the nitrogen inversion process (Ia  $\rightleftharpoons$  Ib) is much less than the chemical shift,  $\nu_{AB}$  (in units of cps). At higher temperatures the spectrum broadens and then collapses (at 108°) to a single



(1) Supported by the National Research Council of Canada and the National Science Foundation (Grant No. GP 3780).

(2) (a) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5126 (1956); **80**, 5203 (1958); (b) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960).

(3) H. S. Gutowsky, *Ann. N. Y. Acad. Sci.*, **70**, 786 (1958); T. J. Burdos, C. Szantay, and C. K. Navada, *J. Am. Chem. Soc.*, **87**, 5796 (1965).

band. At the coalescence temperature,<sup>4</sup>  $k$  is approximately equal to  $\pi\nu_{AB}/\sqrt{2}$ .

Since the rate constants in many cases were obtained<sup>2,3</sup> only at the coalescence temperatures, a comparison of one compound with another is not simple. Table I shows some results calculated from literature data<sup>5</sup> and given in the form of the temperature at which  $k$  is  $\sim 60$  sec<sup>-1</sup>.

A change of the group on nitrogen from ethyl to cyclohexyl produces only a small effect, but a *t*-butyl group apparently increases the rate of nitrogen inversion tremendously. This has been ascribed to steric repulsions of the *t*-butyl group with the ring hydrogen atoms. Such repulsions should be largely relieved in the transition state for nitrogen inversion. However, the effect of the *t*-butyl group cannot be regarded as firmly established because the ring protons still form a single band at the lowest temperature reached. There are in fact two possible explanations for this behavior:

(4) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); 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 218.

(5) For compound V, a temperature coefficient for the rate constant similar to that found for compound IV was used in the calculation.