unbuffered solutions showing that the rate is first order in both borohydride and acetone. We wish to report some preliminary data in aqueous solutions which were buffered. These data show that the rate of reduction of acetone by borohydride is zero order in hydrogen ion. Two aspects of the lack of hydrogen ion dependence for the acetone reaction are noteworthy. First, it might be considered unexpected since three out of four of the borohydride reactions previously reported are first order in hydrogen ion. The reaction with water,[2] the reaction with ferricyanide,[3] and the reaction with iodate[4] are first order in hydrogen ion while the reaction with permanganate[5] is zero order. Second, from a practical standpoint, if a borohydride reduction is carried out in a basic solution, less borohydride will be lost by hydrolysis. For example, at 25° in one hour at pH 9 over 90% of the borohydride will be lost by hydrolysis whereas at pH 13 (0.1 $M$ $OH^-$) less than 0.1% will be lost.

At 25°, we found the second order specific rate constant (sec.$^{-1}$) for the borohydride–acetone reaction to be $2.7 \times 10^2$ at pH 13.0, $2.8 \times 10^2$ at pH 11.6, and $3.0 \times 10^2$ at pH 10.2. These values compare to $1.8 \times 10^2$ found in 0.5 $M$ $OH^-$ by Jensen,[6] $2.3 \times 10^2$ found in the same base concentration by Stockmayer,[2] and $3.2 \times 10^2$ (estimated from Brown's 0° value and Stockmayer's activation energy value) found in an unbuffered solution by H. C. Brown.

(2) W. H. Stockmayer, R. R. Miller, and R. J. Zeto, *J. Phys. Chem.*, **65**, 1076 (1961).
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(5) T. Freund and N. Nuenke, *J. Am. Chem. Soc.*, **83**, 3378 (1961).
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## OPTICAL ROTATORY DISPERSION STUDIES. LXIX.[1] THE ABSOLUTE CONFIGURATION OF THE 2-METHYLCYCLOHEXANOLS AND SOME OBSERVATIONS ON A TWIST FORM IN THE CONFORMATIONAL EQUILIBRIUM OF 2-METHYLCYCLOHEXANONE

*Sir:*

Both *cis*- and *trans*-2-methylcyclohexanols have been resolved by Kenyon and collaborators[2] but no assignments of absolute configuration have as yet been made to the optically active antipodes. The simplest solution to this problem appeared to us to be through optical rotatory dispersion measurements[3] and a successful method is described herewith.

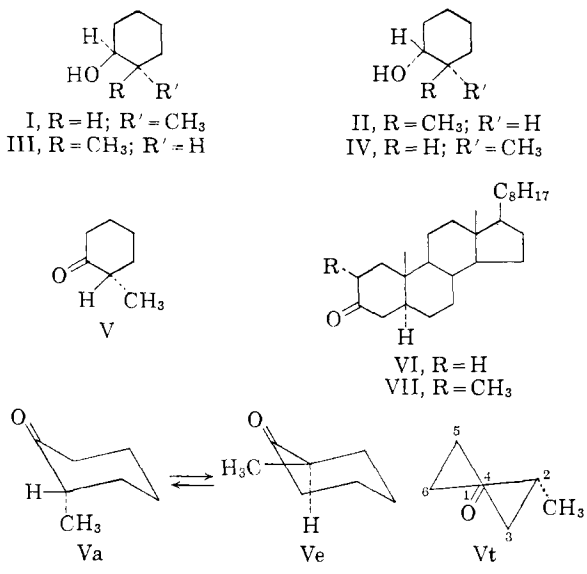
Kenyon, *et al.*,[2] already have shown that (+)-*trans*-2-methylcyclohexanol (I)[4] and (−)-*cis*-2-methylcyclohexanol (IV) both lead to (+)-2-methylcyclohexanone, thus proving that these two diastereoisomers possess the same absolute configuration at the methyl-bearing asymmetric center. Using partially resolved material, we have confirmed that (+)-*trans*-2-methylcyclohexanol (I) affords (+)-2-methylcyclohexanone (positive Cotton effect), while (+)-*cis*-2-methylcyclohexanol (III) gives (−)-2-methylcyclohexanone (negative Cotton effect). By feeding racemic 2-methylcyclohexanone to rabbits, it has been possible to isolate from the urine pure (+)-*trans*-2-methylcyclohexanol (I) in the form of its methyl tri-O-acetyl-β-D-glucosiduronate (m.p. 157–158°, $[\alpha]^{23}_D$ −9.8° in chloroform), which was cleaved by acid to (+)-I, characterized as the 3,5-dinitrobenzoate, m.p. 126–127°, $[\alpha]^{25}_D$ +56.6° (chloroform).

Rapid oxidation of the biologically-resolved alcohol I with chromium trioxide in acetone solution—conditions which do not cause racemization of the adjacent asymmetric center[5]—provided optically pure (+)-2-methylcyclohexanone with a positive Cotton effect (peak: $[\alpha]^{MeOH}_{305}$ +515°; trough: $[\alpha]^{MeOH}_{265}$ −565°) of molecular amplitude ($a$) + 1210°, which remained unchanged for at least five days when kept in methanol solution.

Application of the octant rule[6] should now lead to a decision regarding the absolute configuration of this ketone, since the rule predicts a negligible Cotton effect for Ve and a strongly positive one for Va, the reverse applying to the enantiomers of V. It follows, therefore, that *the sign of the Cotton effect will be governed by the axial conformer* present in the equilibrium and in view of the observed positive Cotton effect, we can assign stereoformula V to (+)-2-methylcyclohexanone, which in turn leads to I–IV as the correct absolute configurational representations for (+)-*trans*-, (−)-*trans*-, (+)-*cis*- and (−)-*cis*-2-methylcyclohexanol, respectively.

While these qualitative conclusions result in an unambiguous absolute configurational assignment, quantitative considerations now can shed some light on the conformational equilibrium existing in 2-methylcyclohexanone, which hitherto has only been studied in more highly substituted systems.[7,8] By subtracting the molecular amplitude of the Cotton effect of (+)-2,2-5-trimethylcyclohexanone[9] from that of (+)-*trans*-2,5-dimethylcyclohexanone[10] one obtains[6] a value of $a$ +5560°, which would represent the predicted molecular amplitude of the conformer Va. For the conformer Ve, we can assume $a \sim 0$, as judged from a comparison of the molecular amplitudes of (+)-3-methylcyclohexanone *vs.* (+)-*trans*-2,5-dimethylcyclohexanone or of cholestan-3-one (VI) *vs.* 2α-methylcholestan-3-one,[11] the introduction of the

(1) Paper LXVIII, K. Mislow, M. A. W. Glass, Robert E. O'Brien, Philip Rutkin, David H. Steinberg, J. Weiss and Carl Djerassi, *J. Am. Chem. Soc.*, **84**, in press (1962).
(2) G. A. L. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.*, 2052 (1926).
(3) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1960.
(4) Absolute configurations according to the steroid notation.
(5) (a) C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 3334 (1961); (b) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnkoff and D. Willner, *ibid.*, **83**, 3986 (1961); (c) G. Ohloff, J. Osiecki and C. Djerassi, *Ber.*, **95**, in press (1962).
(6) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).
(7) W. Klyne, *Experientia*, **12**, 119 (1956).
(8) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).
(9) C. Djerassi, J. Osiecki and E. J. Eisenbraun, *ibid.*, **83**, 4433 (1961).
(10) A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **39**, 441 (1956).
(11) Newly determined values.




equatorial methyl group adjacent to the carbonyl group producing in each pair a completely negligible rotatory contribution (less than 50° in terms of $a$). These values for Ve and Va together with the observed molecular amplitude $a$ + 1210° lead to a calculated equilibrium of 22% Va *vs.* 78% Ve, corresponding to an energy difference of 0.76 kcal./mole. These values are in excellent agreement with those (20% *vs.* 80%; 0.8 kcal./mole) calculated by Klyne[7] from equilibrium data on the carvomenthones, but differ significantly from the figures[12] (7% axial *vs.* 93% equatorial; 1.57 kcal./mole) of Allinger and Blatter[8] obtained by equilibration of the 2-methyl-4-*t*-butylcyclohexanones.

Our rotatory dispersion results on the "parent" 2-methylcyclohexanone cannot be reconciled with Allinger's conclusions[8] if an equilibrium between the two perfect chair forms Va and Ve is assumed. However, if either Va or Ve should exhibit a Cotton effect of greater amplitude than calculated (Va + 5560°; Ve, 0°) on the basis of exclusive chair conformations, then our observed value of +1210° would lead to results moving in the direction of Allinger's data.[8] In fact, the existence of either Va or Ve in the form of a small amount of twist[13] form (Vt), which will exhibit[5a,14] a much stronger positive Cotton effect than the corresponding chair form (Ve) because of the positive rotatory contribution of the ring carbons (C-3 and C-5), will tend to reduce or even resolve this apparent conflict. Obviously, the axial conformer Va is the much more likely candidate for partial existence in the twist form Vt, especially since the energy difference between Va and Vt is probably only of the order of 1 kcal./mole.[8,15]

At this stage, it is premature to speculate on the quantitative aspects of the equilibrium between Va, Ve and Vt, but we believe that the present rotatory dispersion data, when combined with Allinger's results[8] in the 2-methyl-4-*t*-butyl series, indicate the very probable existence of some of the twist form in 2-methylcyclohexanone, just as was the case with *cis*-2-*t*-butyl-5-methylcyclohexanone.[5a]

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(12) Both suffer from the presence of an additional alkyl substituent, which creates conformational complications. In this respect, Klyne's examples (ref. 7) seem to us to suffer from a greater disadvantage, since *cis*-carvomenthone (3-isopropyl group) should certainly consist of a mixture of conformers; however, Allinger's (ref. 8) 4-*t*-butyl derivative is also not ideal, since this substituent may cause deformations of the chair form (for discussion see E. Eliel, *J. Chem. Education*, **37**, 126 (1960); W. Hückel and K. Thiele, *Ber.*, **94**, 2027 (1961), and references cited).

(13) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Drieger and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(14) C. Djerassi and W. Klyne, *J. Chem. Soc.*, in press.

(15) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

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## THE SYNTHESIS OF DIGITOXIGENIN[1]

*Sir:*

The steroidal cardenolide glycosides and the derived aglycones, all of which possess a 17$\beta$-butenolide in addition to a 14$\beta$-hydroxyl substituent (as in VIb),[2,3] are a very important class of naturally occurring substances in view of their powerful action on the heart. No member of this series has been obtained by synthesis so far, despite the pioneering work of Ruzicka, Plattner *et al.*[4] and of Elderfield *et al.*,[5] which resulted in the development of methods for constructing the 17$\beta$-butenolide grouping in 14$\alpha$-steroids as well as a procedure for introducing the 14$\beta$-hydroxy group into 20-carbonyl steroids. The culmination of this research was the synthesis of "allo-uzarigenin," a biologically inactive compound differing from uzarigenin (VIb, 5$\alpha$-H instead of 5$\beta$-H) only by the configuration at C-17.[6]

We now describe the synthesis of digitoxigenin (VIb), a typical and widely distributed cardenolide

(1) This is part IV in the series "Syntheses in the Cardiac Aglycone Field." For part III, see F. Sondheimer, S. Burstein and R. Mechoulam, *J. Am. Chem. Soc.*, **82**, 3209 (1960).

(2) For reviews, see R. B. Turner, *Chem. Revs.*, **43**, 1 (1948); H. Heusser; *Fortschr. Chem. org. Naturstoffe*, **7**, 87 (1950); C. W. Shoppee and E. Shoppee in E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., Amsterdam, 1953, Vol. IIB, Chapter 19; L. F. Fieser and M. Fieser, "Steroids," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1959, chapter 20.

(3) An exception appears to be menabegenin, the 17-epimer of digitoxigenin (VIb) (M. Frèrejacque, *Compt. rend.*, **248**, 2382, 3027 (1959)). This compound, however, may well be an enzymatically formed secondary product (for such enzymatic inversions at C-17, see T. Reichstein *et al.*, *Helv. Chim. Acta*, **28**, 476 (1945); **42**, 1502 (1959); and references to earlier work quoted there.

(4) L. Ruzicka, T. Reichstein and A. Fürst, *Helv. Chim. Acta*, **24**, 76 (1941); L. Ruzicka, P. A. Plattner, *et al.*, *ibid.*, **24**, 716 (1941); **25**, 65, 79, 425 (1942); **26**, 2274 (1943); **27**, 988 (1944); **28**, 173, 1044, 1360 (1945); **29**, 248, 473, 936, 942 (1946); **30**, 385, 395, 1342 (1947); **32**, 1326, 1334 (1949).

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