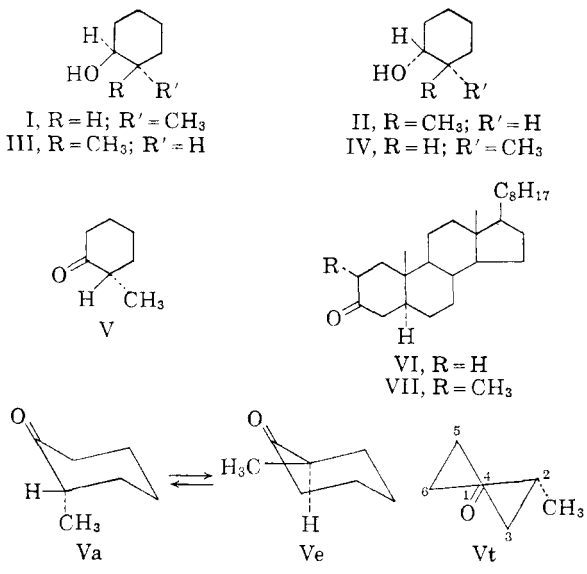

equatorial methyl group adjacent to the carbonyl group producing in each pair a completely negligible rotatory contribution (less than 50° in terms of a). These values for Ve and Va together with the observed molecular amplitude a + 1210° lead to a calculated equilibrium of 22% Va *vs.* 78% Ve, corresponding 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]

Acknowledgment.—We are indebted to Mrs. Ruth Records for the optical rotatory dispersion measurements and to the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service for a grant (No. CRTY-5061).

(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 17β-butenolide in addition to a 14β-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 17β-butenolide grouping in 14α-steroids as well as a procedure for introducing the 14β-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, 5α-H instead of 5β-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).

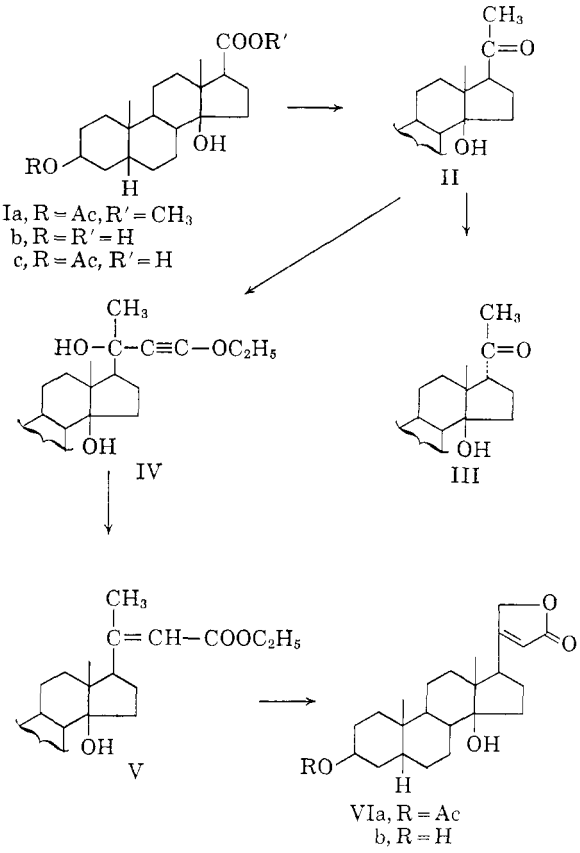
(2) For reviews, see R. B. Turner, *Chem. Revs.*, **43**, 1 (1948); H. Heusser; *Fortschr. Chem. org. Naturstoffe*, **7**, 87 (1950); C. W. Shoppee and E. Shoppee in E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., Amsterdam, 1953, Vol. IIB, Chapter 19; L. F. Fieser and M. Fieser, "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).

(5) R. C. Elderfield *et al.*, *J. Org. Chem.*, **6**, 260, 270, 289 (1941); **7**, 362 (1942).

(6) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 1073 (1947).



aglycone, which still possesses much of the cardiac activity of the glycosides from which it is derived (*e.g.*, digitoxin, a constituent of digitalis).[2] In this work the main difficulties in building up the natural 14β-hydroxy-17β-butenolide system have been overcome, namely, the ready isomerization of the side chain in 20-keto-C/D-*cis* steroids from the 17β- to the more stable 17α-configuration, the ease of dehydration of the 14β-hydroxyl group with acids and the facility with which this group undergoes reactions with functions in the 17β-side chain.[2,7]

Methyl 3β-acetoxy-14β-hydroxy-5β-etianate (Ia), available by a nine-step sequence from 5β-androstan-3β-ol-17-one acetate,[8] was saponified with potassium carbonate in boiling aqueous methanol to the hydroxy-acid Ib [m.p. 221–223°; $[\alpha]_D$ −9° (EtOH)] and then acetylated to the acetoxy-acid Ic [m.p. 226–228°; $[\alpha]_D$ + 36° ($CHCl_3$)]. Treatment of Ic with an excess of methyllithium in tetrahydrofuran afforded 45% of 5β-pregnane-3β,14β-diol-20-one 3-acetate (II) [m.p. 150–151°; $[\alpha]_D$ + 25° ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1727 and 1697 cm.$^{-1}$].[9]

The fact that II still possesses a 17β-oriented side chain was demonstrated by its ready inversion through treatment with boiling 3% methanolic potassium hydroxide to give (after re-acetylation) the 17-iso ketone III [m.p. 177–178°; $[\alpha]_D$ −44° ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1727 and 1712 cm.$^{-1}$]. The lowering in optical rotation on passing from II to III is in keeping with previously made observations regarding the change in rotation when inverting the side chain in 14β-hydroxypregnan-20-ones from 17β to 17α.[10]

Condensation of II with lithium ethoxyacetylide in tetrahydrofuran gave the ethoxyacetylenic carbinol IV ($\nu_{max}^{CHCl_3}$ 2272 cm.$^{-1}$) which was treated with aqueous methanol containing 2% of sulfuric acid for 1 hr. at room temperature. Re-acetylation of the product, followed by purification through repeated chromatography on silica, produced in 45% yield (based on II) the unsaturated ester V [λ_{max}^{EtOH} 232.5 mμ (ϵ 12,000); $\nu_{max}^{CHCl_3}$ 1724 and 1642 cm.$^{-1}$].

Oxidation of V with selenium dioxide under carefully defined conditions (boiling in benzene for 10 hr.) yielded 30% of digitoxigenin acetate (VIa) [m.p. 224–225°, $[\alpha]_D$ + 21° ($CHCl_3$)]. Finally, saponification with 5% hydrochloric acid in methanol (1:1) for 20 hr. at room temperature, or by absorption in ether solution on a column of alkaline alumina for 16 hr., in each case yielded over 80% of digitoxigenin (VIb) [m.p. 246–249°, $[\alpha]_D$ + 19° (EtOH)]. Both VIa and VIb were identified by direct comparison with authentic samples.

(7) Unpublished experiments by Drs. A. Meisels and S. Burstein, to be reported in the full paper.

(8) K. Meyer, *Helv. Chim. Acta*, **29**, 1580 (1946); L. Ruzicka, P. A. Plattner, H. Heusser and K. Meier, *ibid.*, 1342 (1947).

(9) This reaction was based on the corresponding one in the 5α-series carried out previously in these Laboratories by Dr. A. Meisels.

(10) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947); H. Hasegawa, Y. Sato and K. Tsuda, *Chem. Pharm. Bull.* (Japan), **9**, 409 (1961).

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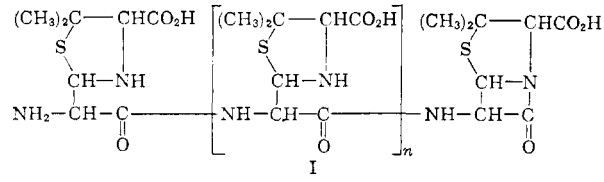
POLY-6-AMINOPENICILLANIC ACID

Sir:

The β-lactam of 6-aminopenicillanic acid (6-APA) is susceptible to cleavage by bases and penicillinase, giving an α-amino acid (penicic acid) as the product. Our study of facile catalytic β-lactam cleavage of 6-APA and penicillins in frozen systems showed that ring opening in 6-APA can occur in the absence of added catalyst.[1] Further study indicates that under various conditions polymerization to low molecular weight peptides accompanies ring opening in potassium 6-APA solutions.

The reaction apparently consists in nucleophilic attack by the primary amino group on the β-lactam of a neighboring molecule, forming polyamides of various chain lengths having the probable structure I.



I

The reaction has been observed in K 6-APA solutions in water (pH 6–7) or phosphate buffer,

(1) N. H. Grant, D. E. Clark and H. E. Alburn, *J. Am. Chem. Soc.*, **83**, 4476 (1961).