

## THE METHOD OF MOLECULAR ROTATION DIFFERENCES APPLIED TO 3-KETO STEROIDS OF THE ALLO SERIES

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Since the first attempt by Callow and Young (1) on the correlation of optical rotatory power with constitution in the steroid field, a number of papers have appeared, which demonstrated clearly the usefulness of such a tool. Wallis and co-workers (2, 3, 4) and more recently Barton (5-8) have amply reviewed the theoretical grounds on which such work is based, and several investigators (2, 5, 9) have examined the errors inherent in such polarimetric measurements.

During the past few years, incidental to a study of the bromination of 3-keto steroids (10-13), we have measured the rotations of a large number of steroid ketones and related compounds. Since, except for isolated instances, no attempt has been made as yet to correlate the optical properties of these ketones with constitution, such a correlation has been made in this paper. The present work has the advantage that nearly all of the rotations were determined in one laboratory, on the same apparatus, by the same investigator, and under controlled conditions of temperature and concentration. Following the suggestion of Wallis, *et al.*, (2) all measurements were carried out in chloroform.

The data are presented in nine tables and specific literature reference is made only to those rotations which were not measured in our laboratory. In all other cases the rotations given in the tables refer to our measurements, even though some of those rotations have been reported previously.

Wallis and co-workers (2) have examined the contribution of the 3-keto group in four sterols related to cholestane. In Tables I and II are given some additional data on the influence of the 3-keto group in some androstane derivatives. The average value of  $\Delta[M]_D = +70$  is in excellent agreement with that obtained by Wallis (2), (+68).

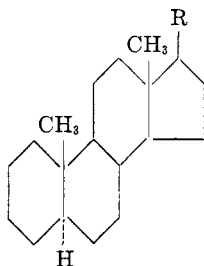
The increase in dextrorotation caused by the introduction of the 4,5 double bond in the saturated ketone II has been noted qualitatively by Callow and Young (1). By subtracting the molecular rotation<sup>1</sup> of the saturated ketone II from that of the unsaturated ketone III, the contribution made by the 4,5 double bond is obtained (Table III). The average increase in molecular rotation due to this factor was 220. If the molecular rotation of the completely saturated steroid I were subtracted from that of the unsaturated ketone III, the "dichromophore  $\Delta$  value" introduced by Barton (7) would be obtained. Such a calculation is of little use in our case, however, since the rotations of the corresponding hydrocarbons with a 4,5 double bond are unknown except for  $\Delta^4$ -cholestene and, therefore, the "dichromophore rule" could not be tested.

A practical application of the method of molecular rotation differences is

$$^1 \text{Molecular rotation } [M]_D = \frac{[\alpha]_D \times M.W.}{100}$$

illustrated in considering the effect of the 1,2 double bond<sup>2</sup> (Table IV). The average value of  $\Delta[M]_D$ , the contribution of the 1,2 double bond, of 6 examples was found to be +67. Two  $\Delta^1$ -3-keto *allosteroids* have been reported in the literature, whose  $\Delta[M]_D$  values are beyond the experimental error, although a change in solvents may have been involved.  $\Delta^1$ -Androstene-3,17-dione has been reported to have  $[\alpha]_D + 148.5^\circ$  ( $\Delta[M]_D = +125$ ). This high value was very probably due to contamination with the corresponding  $\Delta^4$ -derivative, since

TABLE I  
STERIODS UNSUBSTITUTED IN RING A



R	$[\alpha]_D$	REF.	$[M]_D$
$C_6H_{11}$ .....		(2)	92
$OCOC_6H_{11}^a(\beta)^b$ .....	+10		39
$COOCH_3(\beta)^b$ .....	+52	(17, 18)	165
$OCOCH_3(\beta)^b$ .....	+2		6
$OH(\beta)^b$ .....	+8		22
$H_2$ .....	-0.3		0
$=O$ .....	+89		244
$CH_3$   $OH(\beta)^c$ .....	-17		-49

<sup>a</sup>  $C_6H_{11}$  denotes the cyclohexyl radical.

<sup>b</sup> These compounds have all recently been shown (23) to possess the  $\beta$  configuration. It should be noted that in two of our earlier papers (11, 13), the old configuration ( $\alpha$ ) was still employed.

<sup>c</sup> This refers to the isomer derived from active 17-methyltestosterone.

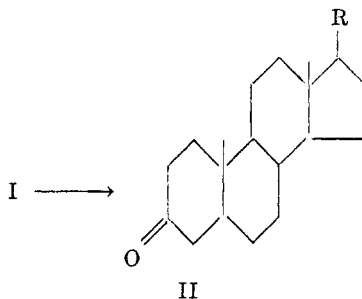
the compound was prepared (14) by collidine dehydrobromination of the 2-bromo derivative, a reaction which in two related instances has been shown (13) to result in the simultaneous formation of the  $\Delta^4$ -derivative. A repetition of this reaction, described in the experimental section, actually showed this to be the case, and for the pure  $\Delta^1$ -compound we have found the value for  $\Delta[M]_D$  to be +64, in good agreement with the other examples. The German investigators (14) also reported the rotation of  $\Delta^1$ -allopregnene-3,20-dione to be +126° ( $\Delta[M]_D = -6$ ). This negative value can be attributed to contamination with

<sup>2</sup> The two examples of this type discussed by Callow and Young (1), were actually *hetero*- $\Delta^1$ -ketones [cf. Butenandt and Ruhstroth-Bauer, *Ber.*, **77**, 397 (1944)].

the corresponding  $\Delta^{16}$ -derivative, which has been reported (15) to have a lower rotation than the parent ketone, and which could easily have been present as an impurity, particularly since the product was not chromatographed. Another possibility may have been that the rotation of the saturated ketone was measured in ethanol and that of the unsaturated derivative in chloroform.

A further illustration of the usefulness of this method is given in Table V, in which is considered the influence of a bromine atom in position 2. As can be seen, the  $\Delta[M]_D$  values of the seven examples differ widely and no apparent correlation seems possible. It is evident that in introducing a bromine atom into

TABLE II  
INFLUENCE OF 3-KETO GROUP

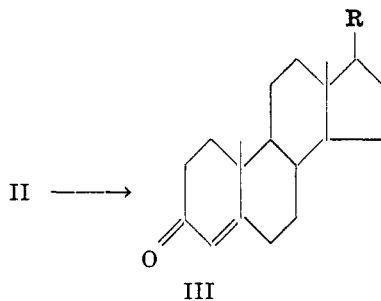


R	$[\alpha]_D^a$	$[M]_D^a$	$\Delta[M]_D^a$ II-I
$C_8H_{17}$ .....	41	158	66
$OCOC_8H_{11}$ .....	27	108	69
$COOCH_3$ .....	72	239	74
$OCOCH_3$ .....	26	86	80
OH.....	30	87	65
$H_2$ .....	27	74	74
$=O$ .....	105	302	58
$CH_3$			
$\square$ OH.....	7	21	70

<sup>a</sup> All values in Tables II to VI are positive and are not marked by (+) signs.

the 2-position of a 3-keto steroid II, two diastereoisomers are possible, although, as yet only one isomer has been isolated in all the instances described in the literature. Indirect evidence for the presence of two diastereoisomers in the introduction of a bromine in the 4-position of 3-keto steroids of the *normal* series has been presented frequently (*cf.* 16), since in that case only one diastereoisomer can be dehydrobrominated with ease. Such evidence is not available for 2-bromo-3-keto *allosteroids* V, since *trans* elimination of hydrogen bromide is possible with both diastereoisomers. The data presented in Table V point towards the presence of both isomers. Four of the examples showed  $\Delta[M]_D$  values of *ca.*  $+30^\circ$  and two compounds exhibited  $\Delta[M]_D$  values around  $+92^\circ$ . 2-Bromoandrostan-17 $\beta$ -ol-3-one 17-acetate had an intermediate value, which

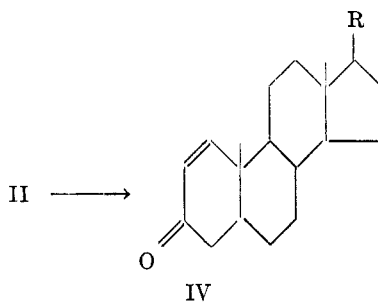
TABLE III  
INFLUENCE OF 4,5 DOUBLE BOND



R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ III-II
$C_8H_{17}$ .....	93	357	199
$OCOC_6H_{11}$ .....	83	330	222
$COOCH_3$ .....	145	479	240
$OCOCH_3$ .....	91	300	214
$OH$ .....	109	314	227
$H_2$ .....	101	275	201
$=O$ .....	187	535	233
$CH_3$			
$OH^a$ .....	80	242	221

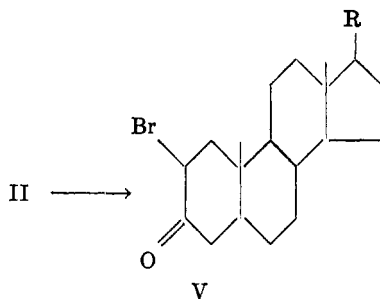
<sup>a</sup> 17-Methyltestosterone.

TABLE IV  
INFLUENCE OF 1,2 DOUBLE BOND



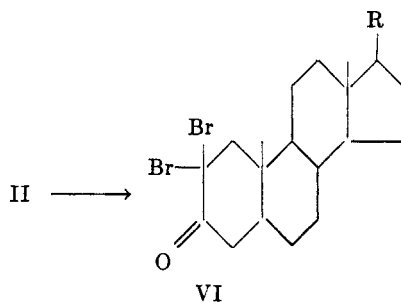
R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ IV-II
$C_8H_{17}$ .....	58	223	65
$OCOC_6H_{11}$ .....	45	178	70
$COOCH_3$ .....	93	307	68
$OCOCH_3$ .....	47	155	69
$OH$ .....	52	150	63
$=O$ .....	128	366	64

TABLE V  
INFLUENCE OF BROMINE IN 2-POSITION



R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ V-II
$C_8H_{17}$ .....	40	186	28
$OCOC_6H_{11}$ .....	43	206	98
$COOCH_3$ .....	79	325	86
$OCOCH_3$ .....	35	144	58
OH.....	33	122	35
$H_2$ .....	29	102	28
$=O$ .....	90	330	28

TABLE VI  
INFLUENCE OF BROMINES IN 2,2-POSITION



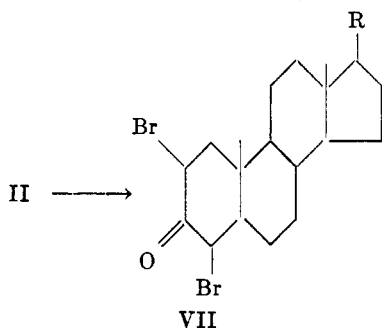
R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ VI-II
$C_8H_{17}$ .....	111 <sup>a</sup>	604	446
$OCOC_6H_{11}$ .....	110	614	506
$COOCH_3$ .....	136	666	427
$OCOCH_3$ .....	111 <sup>b</sup>	544	458

<sup>a</sup> The rotation of the analytical sample (12) was  $+104^\circ$ , but it has been possible to demonstrate (13) by a polarimetric method that the highest rotation of this compound should be  $+111^\circ$ .

<sup>b</sup> The analytical sample (13) had  $[\alpha]_D +106^\circ$  (cf. Footnote a).

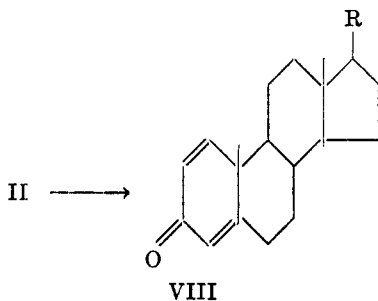
might indicate that the compound is an approximately 1:1 mixture of the two diastereoisomers. Tentatively, we assign the  $\alpha$ -notation to the more dextrorotatory compounds and the  $\beta$ -notation to the lower rotating ones.

TABLE VII  
INFLUENCE OF BROMINES IN 2,4-POSITION



R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ VII-II
$C_8H_{17}$ .....	+3	+16	-142
$OCOC_8H_{11}$ .....	-6	-33	-141
$COOCH_3$ .....	+24	+118	-121
$OCOCH_3$ .....	-11	-54	-140

TABLE VIII  
INFLUENCE OF 1,2 AND 4,5 DOUBLE BONDS



R	$[\alpha]_D$	REF.	$[M]_D$	$\Delta[M]_D$ VIII-II
$C_8H_{17}$ .....	31		+118	-40
$OCOC_8H_{11}$ .....	45		+178	+70
$COOCH_3$ .....	82		+269	+30
$OCOCH_3$ .....	28	(19)	+92	+6
OH.....	20		+57	-30
$=O$ .....	116	(19)	+329	+27

Additional evidence for the presence of two diastereoisomeric 2-bromo ketones V is presented in Tables VI and VII, which contain data relating to substitution of two bromine atoms in the 2,2 and 2,4 positions respectively. In both instances, the agreement of the  $\Delta[M]_D$  values is within the experimental error.

Such agreement is to be expected, since in 2,2-dibromo ketones VI only one isomer is possible and since it has been shown (13) that the 2,4-isomers VII, even when prepared directly, always are formed by rearrangement of the intermediate 2,2-dibromo compounds. Thus, although in the case of the 2,4-dibromo derivatives diastereoisomerism is possible, it is quite conceivable that always only one and the same isomer is formed predominantly in the four series examined.

The simultaneous introduction of a 1,2 and 4,5 double bond (Table VIII) seems to result in vicinal effects (20, 21), which preclude any correlation of polarimetric data.

Table IX contains a summary of the average  $\Delta[M]_D$  values and the deviations from the arithmetic mean. The agreement is in general within 10% except in the case of the  $\Delta^{1,2} + \Delta^{4,5}$  double bond.

TABLE IX  
SUMMARY

CONTRIBUTION OF:	AV. $\Delta[M]_D^a$	NO. OF EXAMPLES	RANGE OF DEVIATION FROM ARITHMETIC MEAN <sup>a</sup>	
3-Ketone.....	+70	8	-12	+10
$\Delta^{4,5}$ double bond.....	+220	8	-21	+20
$\Delta^{1,2}$ double bond.....	+67	6	-4	+3
2-Br.....	(+52)	7	(-24)	(+46)
$\alpha$ .....	+92	2	-6	+6
$\beta$ .....	+30	4	-2	+5
2,2,-Br.....	+459	4	-32	+47
2,4-Br.....	-136	4	-6	+15
$\Delta^{1,2} + \Delta^{4,5}$ double bond.....	(+11)	6	(-51)	(+59)

<sup>a</sup> The figures given in parentheses are not significant.

#### EXPERIMENTAL

All rotations were determined on 5-10 mg. of sample in 1.2 cc. of chloroform in a 1 cm. tube of 1 cc. capacity at 23-24°, using the sodium D line.

*Androstan-17 $\beta$ -ol-17 hexahydrobenzoate.* Androstan-17 $\beta$ -ol was refluxed for four hours with hexahydrobenzoyl chloride (22) and pyridine, the solution diluted with water, and the product was recrystallized from ethanol to constant rotation and melting point; m.p. 112.5-113°,  $[\alpha]_D^{25} +9.7^\circ$ .

*Anal.* Calc'd for  $C_{26}H_{42}O_2$ : C, 80.77; H, 10.95.

Found: C, 81.18; H, 11.11.

*2-Bromoandrostan-3-one.* Androstan-3-one was brominated in C.P. glacial acetic acid and the product which crystallized out was filtered and recrystallized from ethanol; m.p. 210.5-211.5° (dec.),  $[\alpha]_D^{25} +29.3^\circ$ .

*Anal.* Calc'd for  $C_{19}H_{29}BrO$ : C, 64.58; H, 8.27; Br, 22.62.

Found: C, 64.15; H, 8.35; Br, 22.65.

*Dehydrobromination of 2-bromoandrostan-3,17-dione.* A solution of 1.5 g. of 2-bromoandrostan-3,17-dione in 6 cc. of  $\gamma$ -collidine was refluxed for one hour and the reaction mixture was worked up by chromatography and spectrophotometric analysis of the chromatogram fractions as described earlier for similar cases (13); there was thus obtained 0.14 g. (12%) of crude  $\Delta^4$ -androstan-3,17-dione (max. at 242.5  $\mu$  log E = 4.09,  $[\alpha]_D^{25} +175.4^\circ$ ) and

0.42 g. (36%) of the  $\Delta^1$ -isomer ( $[\alpha]_D^{24} +129.6^\circ$ ). After recrystallization from hexane,  $\Delta^1$ -androstene-3,17-dione was obtained as rosettes of needles, m.p. 140–142°,  $[\alpha]_D^{24} +127.5^\circ$ , max. at 230 m $\mu$  log E = 4.01 (ethanol); Butenandt and co-workers (14) reported m.p. 138–139°,  $[\alpha]_D^{23} +148.5^\circ$  (solvent unspecified) for the  $\Delta^1$ -isomer which was obtained on direct crystallization rather than purified by chromatographing.

*Anal.* Calc'd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>: C, 79.68; H, 9.15.

Found: C, 80.11; H, 9.41.

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#### SUMMARY

The method of molecular rotation differences has been applied to a number of steroid ketones of the *allo* configuration and it has been shown that definite values can be assigned to the contribution of the following substituents on the molecular rotation of the compound: 3-ketone, 1,2 double bond, 4,5 double bond, 2,2-dibromide, 2,4-dibromide. Evidence is presented for diastereoisomerism in the 2-bromo-3-keto steroids of the *allo* series.

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