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THE CONFIGURATION OF 3-BROMO-3-METHYLCHOLESTANE AND THE CONFORMATIONAL EQUILIBRIUM IN 1-BROMO-1-METHYLCYCLOHEXANE[1,2]

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Abstract—The compound previously assigned the 3β-bromo-3α-methylcholestane structure is shown to be a 3α-bromo-3β-methylcholestane, and the thermodynamically favored conformation of 1-bromo-1-methylcyclohexane is inferred to be that with the bromine axial and the methyl equatorial, contrary to earlier conclusions.

IN 1956 Barton *et al.* published a description of a 3-bromo-3-methylcholestane to which they assigned the 3β-bromo-3α-methyl structure on the basis of the fact that the compound showed absorption in the infrared at 780 cm^{-1} (in carbon disulfide).[3] Earlier work by Barton *et al.*[4] had shown that for bromine atoms attached to secondary carbons on cyclohexane rings, equatorial configurations led to absorption in the range of 704–754 cm^{-1} while the corresponding axial epimers showed absorption at 591–692^{-1}. It was therefore concluded that the bromine atom in the 3-bromo-3-methylcholestane was in the equatorial position, and this was also considered to be the stable epimer. At that time there was a general feeling that since a bromine atom and a methyl group are very similar in their effective van der Waals radii, they would probably also have similar conformational energies, and no surprise was occasioned by the findings quoted. Subsequently it was ascertained that the conformational energy of a bromine is a good deal less than that of a methyl (0·4 as compared to 1·8 kcal/mole).[5] The assignment of the 3β-bromo-3α-methyl structure to the cholestane derivative and its consideration as the thermodynamically stable epimer at C-3 therefore presented an anomaly which appeared worth investigating.

It was conceivable that the relative conformational energies of the methyl and halogen might change when both groups were attached to a common carbon, rather than separately to secondary carbons in cyclohexane rings. This is, however, contrary to what one would expect from all that is presently known about conformational analysis. Two alternative possibilities remained, either the compound obtained by Barton was not the thermodynamically stable epimer or its configuration at C-3 was incorrectly assigned. The present work is concerned with showing which of these three possibilities corresponds to reality.

We were able to experimentally duplicate the work of Barton and synthesize

[1] Paper XXXIX, N. L. Allinger, J. G. D. Carpenter and M. A. DaRooge, *J. Org. Chem. in press.*

[2] This investigation was supported by Public Health Service Research Grant A-5836 from the National Institute of Arthritis and Metabolic Diseases.

[3] D. H. R. Barton, A. D. S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956).

[4] D. H. R. Barton, J. E. Page and C. W. Shoppee, *J. Chem. Soc.* 331 (1956).

[5] E. L. Eliel, N. L. Allinger, G. B. Morrison and S. J. Angyal, *Conformational Analysis* p. 436. Interscience Division, J. Wiley, New York (1965).

the compound referred to as 3β-bromo-3α-methylcholestane. We prepared this bromide by a number of variations in synthetic procedure using hydrogen bromide or phosphorous tribromide under various reaction conditions and always obtained only this epimer, and in good yield. It seems clear that the isomer obtained is the thermodynamically stable isomer, as stated by Barton, since rapid equilibration would be expected under the strongly acidic reaction conditions.[6]

The experiments described above led us to conclude that there was a strong possibility of the configuration of the compound having been assigned incorrectly. The so-called C-Br stretching frequencies in the infrared, upon which the configurational assignment was based, actually result from vibrations which are not well understood.[8] It was reported[3] that the strong IR band present at 783 cm^{-1} in the corresponding chloride was not present when the compound contained a deuterium at C_3, so that whatever the vibration really involves, it appears to be strongly coupled with one of the deformations of at least one of the hydrogens at C_3. It therefore seems quite hazardous to conclude that a *t*-bromide at C_3 will show this "stretching frequency" within the same range as does a secondary bromide at C_3, although this could be the case. (The corresponding alcohols do show their C—O stretching frequencies in the same range, whether secondary or tertiary, but here the frequencies appear to more reliably assigned,[9] and may be less influenced by coupling with other vibrations. Even with the alcohols there are well authenticated cases where the usual relationship between conformation and frequency is reversed[9].)

It was decided to carry out the configurational assignment on the basis of a less equivocal method than the earlier workers had used, and the dipole moment method was selected. If the bromine in the known isomer of 3-methyl-3-bromocholestane were axial, the C—Br dipole would point in a rather different direction than if it were equatorial, and it would be possible to determine the configuration by placing another dipole in the molecule and measuring the resultant moment. The molecule chosen for synthesis was 3-bromo-3-methylandrostane-17-one, since the 17-ketone system has previously been studied by dipole moments and its geometry relative to ring A is well known.[10] 3α-Hydroxy-3β-methylandrostane-17-one is a known compound,[12] and upon treatment with hydrogen bromide it gave a bromide which as will be shown below is 3α-bromo-3β-methylandrostan-17-one. That the configuration at C_3 is the same in this compound as in the cholestane derivative is indicated by the method of synthesis, and by the IR absorption, there being present in the "C-Br stretching region" a single strong band at 780 cm^{-1}. That this compound

[6] By way of comparison, the half life for the solvolysis of t-butylbromide in the less acidic formic acid can be estimated (Ref. 7) to be 27 sec at 25°.

[7] S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.* **70**, 846 (1948).

[8] Studies of this region of the IR spectra of simple alkyl chlorides have been made (J. J. Shipman, V. L. Folt, and S. Krimm, *Spectrochem. Acta* **18**, 1603 (1962)), and indicate that until similar studies have been made for the bromides, difficulty in the band assignments for the latter are to be anticipated.

[9] Ref. 5, P. 143.

[10] The moment has been recalculated from the data given by N. L. Allinger and M. A. DaRooge, *J. Amer. Chem. Soc.* **84**, 4561 (1962) making no allowance for atomic polarization as indicated by Ref. 11.

[11] N. L. Allinger, J. Allinger and M. A. DaRooge, *J. Amer. Chem. Soc.* **86**, 4061 (1964).

[12] J. Kathol, U.S. Pat. 2,713,061 (1955).

is the stable epimer is quite clear from the ease with which it loses hydrogen bromide, some effort being required to prevent this reaction and isolate the compound.

A Dreiding model of the androstanone system was prepared, placed in a coordinate system, and the coordinates of the pertinent dipole moments were measured for the 17-ketone, and for the 3α- and 3β-substituents. The group moment of the 17-ketone is known from earlier work[10] to be 3·05 D, while the group moment of the 3-halogen was measured on the cholestane derivative and found to be 2·21 D. Utilizing these data previously developed methods,[13] the resultant moment for the 3α-bromo-3β-methylandrostane-17-one was calculated to be 3·73 D, while that of the other epimer was calculated to be 1·99 D, and these values may be conservatively estimated to be accurate to ±0·20. The observed moment, 3·89 D, clearly shows that the compound is 3α-bromo-3β-methylandrostane-17-one.

EXPERIMENTAL

3α-Bromo-3β-methylcholestane. This compound was prepared from both 3α-methylcholestan-3β-ol and 3β-methylcholestan-3α-ol according to Barton,[8] and had the same m.p. and IR spectrum reported (but assigned to the other C-3 epimer).

17β-Hydroxy-5α-androstan-3-one. Testosterone was reduced with lithium and ammonia (following Wisenborn and Applegate[14]) to 17β-hydroxy-5α-androstan-3-one, m.p. 179–180° (lit.[14] m.p. 184–185°) Acetylation furnished the 17β acetate, m.p. 156–157° (lit.[15] m.p. 156–157°).

3α-Bromo-3β-methylandrostan-17-one. Addition of the Gringard to the acetate[15] furnished 3β-hydroxy-3α-methylandrostane-17β-acetate, m.p. 198–199° (lit.[15] m.p. 194–195°), and the epimeric 3α-hydroxy-3β-methylandrostane-17β-acetate, m.p. 204–205° (lit.[15] m.p. 205–207°). Saponification of the latter furnished the corresponding diol, m.p. 168–169°, (lit.[15] m.p. 168–170°). Oxidation of this diol according to Kathol[12] gave 3α-hydroxy-3β-methylandrostan-17-one,[16] m.p. 145–147° (lit.[12] m.p. 145–146°). The keto alcohol, 1·5 g, was treated with dry hydrogen bromide in ethyl ether (20%, 60 ml) at room temp for 2 days. The volatile material was then evaporated from the mixture, (which had separated into two layers) by blowing a stream of dry N_2 gas onto the solution. The solid residue was recrystallized from hexane or from acetone and yielded 1·1 g bromide, m.p. 139–140·5°. The IR spectrum showed a strong band at 780 cm^{-1}. (Found C, 65·44; H, 8·40; Br, 21·92. Calc. for $C_{20}H_{31}OBr$: C, 65·39; H, 8·44; Br, 21·80).

Dipole moments. The apparatus and method,[17] and the details of the computations[18] have all been described previously, no allowance for atomic polarization being made in line with the conclusions in Ref. 11. The following results were obtained in benzene solution at 25°.

3α-Bromo-3β-methylcholestane. M_2 131·13 cc

N_2	d_{12}	ϵ_{12}
0·00000000	0·873289	2·2750
0·00047896	0·873741	2·2778
0·00096804	0·874229	2·2812
0·00142014	0·874690	2·2846
0·00195665	0·875183	2·2884
α 6·921	ϵ_1 2·2747	d_1 0·87329
β 0·976	$P_2\infty$ 230·8	μ 2·21 ± 0·03 D

[13] N. L. Allinger, M. A. DaRooge, M. A. Miller and B. Waegell, *J. Org. Chem.* **28**, 780 (1963).
[14] F. L. Wisenborn and H. E. Applegate, *J. Amer. Chem. Soc.* **81**, 1960 (1959).
[15] B. Pelc, *Coll. Czec. Chem. Comm.* **25**, 1624 (1960).
[16] We have assigned the configuration at C-3 from the similarity of the C—O stretching frequency to that of the corresponding cholestane derivatives.
[17] N. L. Allinger, M. A. DaRooge, H. M. Blatter and L. A. Freiberg, *J. Org. Chem.* **26**, 2550 (1961).
[18] N. L. Allinger and J. Allinger, *J. Org. Chem.* **24**, 1613 (1959).

3α-Bromo-3β-methylandrostan-17-one. M_R 93·91 cc

N_2	d_{12}	ϵ_{12}
0·00000000	0·873356	2·2749
0·00037298	0·873792	2·2830
0·00074080	0·874168	2·2912
0·00109696	0·874627	2·2989
0·00154884	0·875212	2·3079

α 21·391	ϵ_1 2·2751	d_1 0·87334
β 1·192	$P_2\infty$ 403·1	μ 3·89 $\pm$ 0·03 D

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