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REACTIVITY OF GROUPS ATTACHED TO REDUCED CYCLIC RING SYSTEMS—I

KINETICS OF THE MENSCHUTKIN REACTION OF 3-DIMETHYLAMINOMETHYL STEROIDS WITH METHYL IODIDE, AND CONSIDERATION OF THE REASONS FOR THE OBSERVED DIFFERENTIAL RATES IN SOME OTHER REACTIONS AT EPIMERIC AXIAL AND EQUATORIAL GROUPS[1]

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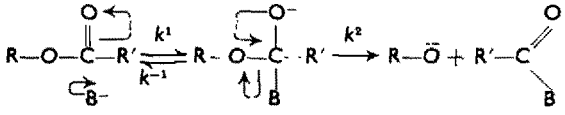
Abstract—In contrast to the previously examined[2] epimeric dimethylamino steroids, epimeric dimethylaminomethyl steroids (containing the group —CH_2NMe_2) react at approximately the same rates with methyl iodide in nitrobenzene–benzene. This observation is significant for the consideration of differential reactivity in other reactions with epimeric axial–equatorial pairs: the relative ease of hydrolysis of esters of epimeric axial and equatorial alcohols, for example, is probably due mainly to differential hindrance to solvation at the relevant alkoxy oxygen atoms during reaction.

REACTIONS at groups attached to reduced 6-ring systems for which there is an increase in the bulk at transition-state level are well known to proceed, in general, more rapidly with equatorial groups than with the corresponding epimeric axial groups; a similar rule holds for equilibria. The limits of these generalizations have not been adequately explored, however, and the precise reasons for the applicability of the reactivity rule in some classical examples, e.g. the alkaline hydrolysis of esters of alicyclic alcohols, are not very clear. The first point is obviously rather a wide one; a particular aspect is examined in this paper, and it will be considered further later. The quaternization rates of steroidal bases containing the group *eq.*- or *ax.*-—CH_2NMe_2, reported here, also permit some discussion of the ester-hydrolysis question and other reactions.

The previously reported[2] higher reactivity of equatorial relative to epimeric axial dimethylamino steroids in the Menschutkin reaction, $RNMe_2 + MeI \rightarrow \overset{+}{R}N\overset{-}{Me_3}I$ is readily intelligible, as there is an increase in bonding and solvation at the nitrogen atoms during the reaction. In so far as the corresponding differential reactivity of esters of equatorial and axial alcohols has been considered in detail,[3] it has usually been assumed that differential ease of attack on the carbonyl carbon atom (*two* bond lengths from the ring) is the deciding feature; a smaller differentiation in reactivity than is observed with esters of equatorial and axial carboxylic acids (where base attack takes place on atoms directly attached to the ring) therefore seems intelligible. We are not too happy about accepting the above explanation for the differential ease of hydrolysis of esters of equatorial and axial alcohols, however: *ab initio* it has

[1] Preliminary communication: R. Ledger, P. B. Smith and J. McKenna, *Chem. & Ind.* 863 (1963).
[2] B. B. Gent and J. McKenna, *J. Chem. Soc.* 573 (1956).
[3] cf. the discussion in E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 222–223. McGraw-Hill (1962).

seemed that the important determining feature must be a bulk increase during reaction at the alkoxy oxygen atoms *directly attached to the ring*. This view is based on the expectation that bulk increases at atoms two bond-lengths removed from the ring will usually be subject to rather similar steric environments irrespective of whether the relevant groups are as a whole axially or equatorially attached, *provided that the shapes of the groups are such that, as will often but not always (see below) be the case, the reactive parts are disposed well clear of the ring systems, or can become so during reaction without the introduction of appreciable steric interactions involving other parts of the groups.* Alkaline hydrolysis of esters normally involves an unstable intermediate:[4]



Both the formation of this intermediate and its decomposition would result in increase in solvation around the alkoxy-oxygen atom in each case, and this seems to be the critical feature for the observed differential reactivity. The formation step is probably the more important ($k^2 > k^{-1}$) in determining the overall rate for alicyclic esters, as the decomposition step, although it involves additional solvation of alkoxy oxygen, also involves removal of the covalently bonded acyl group. Thus, if $k^2 < k^{-1}$, esters of axial alcohols would probably be more rapidly hydrolysed.[5]

These views can be tested in several ways: by detailed rate and isotopic exchange work on the hydrolysis of esters of epimeric axial and equatorial alcohols, by studying the rates of hydrolysis of esters of epimeric equatorial and axial acetic acids, R-CH_2·COOR′, where base attack is two bond lengths removed from the ring and where the intervening group (methylene) in this case cannot be involved in the reaction, and (initially in our programme) by examination of rates of analogous reactions e.g. the quaternization of axial and equatorial epimers R·CH_2NMe_2.

The tertiary bases employed in the work were 3α- and 3β-dimethylaminomethyl-5α-cholestane (I and II respectively; R = CH_2NMe_2), 3α- and 3β-dimethylaminomethylcholest-5-ene (III and IV respectively; R = CH_2NMe_2) and 3β-dimethylaminomethyl-5β-cholestane (V; R = CH_2NMe_2). Synthesis of these bases involved the use of reaction sequences A or B (see Chart). Apart from the 3β-acids in the 5β-cholestane series, all the other acids involved as reaction intermediates in schemes (A) or (B) had been made before,[6,7] and the physical properties of our samples, prepared usually by the reported procedures, agreed closely with those quoted in the literature. In the separation of 3α- and 3β-cholest-5-enylacetic acids, we preferred chromatography of the mixed methyl esters to the described procedure[6] involving partial fractionation of the mixture of related malonic acids.

The kinetics of the quaternizations of the dimethylaminomethyl steroids were examined in nitrobenzene–benzene essentially by the method described[2] for the

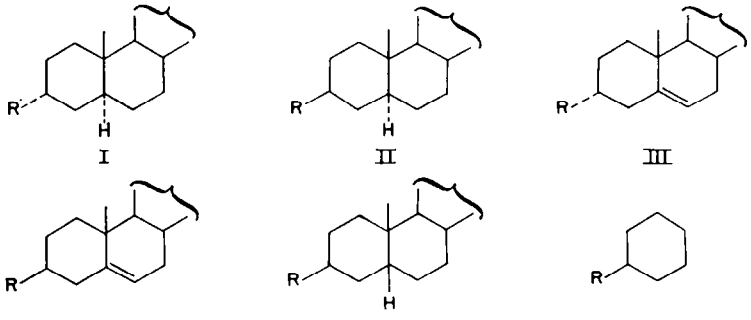
[4] cf. the discussion in J. Hine, *Physical Organic Chemistry* (2nd. Edition) Chap. 12. McGraw-Hill (1962).

[5] cf. the discussion in G. Whitham, *Alicyclic Chemistry* p. 69. Oldbourne Press, London (1963).

[6] C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.* 2230 (1954); and references quoted therein.

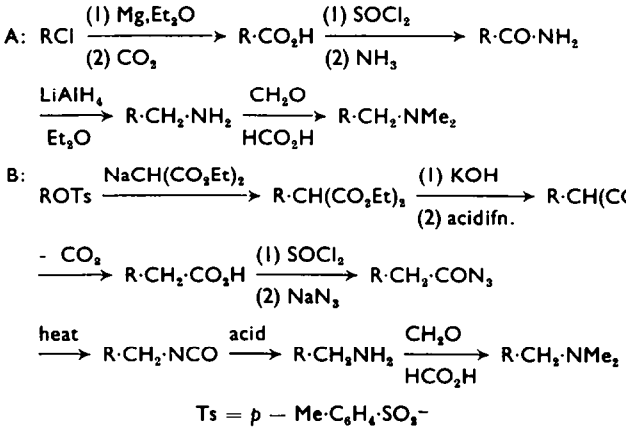
[7] G. Roberts, C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.* 2705 (1954); and references quoted therein.

dimethylamino steroids, and the results, together with comparative values for dimethylamino steroids, dimethylaminomethylcyclohexane, and dimethylaminocyclohexane are presented in Tables 1 and 2. It is seen that rates and Arrhenius parameters for members of epimeric pairs of dimethylaminomethyl steroids are closely similar, a result which supports the views on ester hydrolysis expressed above. An unexpected incidental feature is that while rates and Arrhenius parameters for the dimethylaminomethyl steroids are intermediate between corresponding values for axial and equatorial



I II III

IV V VI



dimethylamino bases, on the whole the resemblance to values for the axial bases is greater. It seems improbable that the same would be true for groups attached, for example, to C-6, where the axial position is highly hindered.

In view of the above results, it may at first sight appear anomalous that an axial carboxyl group is evidently more hindered than the epimeric equatorial group in equilibria (cf. pK_a values[8]) or reactions (e.g. esterification with diphenyldiazomethane[9]) involving bulk increase at one or both oxygens (which are of course two bond lengths from the ring). With such a group (trigonal carbon), however, one oxygen atom can swing clear of the ring system only at the expense of increased non-bonded interactions involving the other oxygen; these interactions are stronger for the axial carboxyl, which will therefore be more subject to steric compression irrespective of whether

[8] For recent work see C. Pascual and W. Simon, *Helv. Chim. Acta* **47**, 683 (1964).

[9] N. B. Chapman, J. Shorter and K. J. Toyne, *J. Chem. Soc.* 1077 (1964); cf. J. D. Roberts. W. Watanabe and R. E. McMahon, *J. Amer. Chem. Soc.* **73**, 760 (1951).

TABLE 1. SECOND-ORDER RATE CONSTANTS FOR REACTION OF 3-DIMETHYLAMINOMETHYL STEROIDS AND DIMETHYLAMINOMETHYLCYCLOHEXANE WITH METHYL IODIDE IN NITROBENZENE CONTAINING 10% W/W BENZENE

Base no. (R = CH_2NMe_2)	I	II	III	IV	V	VI
10^3k_0 (l. $mole^{-1}sec^{-1}$)	3·00	2·47	1·28	1·46	0·96	1·97
$10^3k_{34.9}$	14·9	12·5	6·27	7·24	4·50	11·0
$10^3k_{84.7}$	27·7	23·2	11·0	13·8	7·31	16·9

TABLE 2. ARRHENIUS PARAMETERS AND COMPARATIVE SECOND ORDER RATE CONSTANTS AT 0° (3α-DIMETHYLAMINO-5α-CHOLESTANE = 1) FOR REACTION OF TERTIARY BASES WITH METHYL IODIDE IN NITROBENZENE CONTAINING 10% W/W BENZENE

Base type	Base no.	Comparative rate constant	E (kcal.$mole^{-1}$)	log A
Eq- or *Ax*-CH_2NMe_2	I(R = CH_2NMe_2)	19	10·6	6·0
	II(R = CH_2NMe_2)	15	10·7	6·0
	III(R = CH_2NMe_2)	8	10·3	5·4
	IV(R = CH_2NMe_2)	9	10·7	5·7
	V(R = CH_2NMe_2)	6	9·9	4·9
	VI(R = CH_2NMe_2)	12	10·7	5·9
Ax-NMe_2	I(R = NMe_2)	1	12·7	6·4
	III(R = NMe_2)	6	12·2	6·8
	V(R = NMe_2)	2	12·4	6·4
Eq-NMe_2	II(R = NMe_2)	150	7·9	4·7
	IV(R = NMe_2)	82	9·3	5·6
	VI(R = NMe_2)[13]	110	9·3	5·6

the bulk increases take place at one or both oxygens. As regards differential ease of bulk increase at X (or X'), epimeric groups —CXX' thus are in something of a different category to groups —O—X(YZ) or —CH_2—X(YZ).

EXPERIMENTAL

Optical rotations were determined in $CHCl_3$ at room temp (ca. 20°) at concentrations of 0·5–2% using an ETL-NPL automatic polarimeter, type 143A, with a 0·2 dm cell. Spence's alumina (type H) and "AnalaR" solvents were used for chromatography. Light petroleum refers to the fraction of b.p. 40–60°.

Cholest-5-en-3α- and 3β-yl-acetic acids. The light petroleum insoluble fraction (3α + 3β; 9 g) of malonic acids prepared from cholesteryl tosylate (40 g) and sodiodiethyl malonate followed by alkaline hydrolysis was decarboxylated at 205°/0·1 mm during 2 hr, and the mixed acetic acids methylated with diazomethane in ether. Chromatography on neutral alumina gave, on elution with benzene, methyl cholest-5-en-3α-yl-acetate (1·3 g) m.p. 107–108° (lit,[6] 105–108°), a mixture (6 g) of 3α- and 3β-esters, m.p. 63–75°, which was re-cycled, and methyl cholest-5-en-3β-yl-acetate (0·5 g) m.p. 78–79° (lit,[6] m.p. 76–78°). Hydrolysis with KOH in methanol followed by acidification gave the 3α-acid, m.p. 207–209° (lit,[6] m.p. 205–210°) and the 3β-acid, m.p. 165–167° (lit,[6] m.p. 165–167°) respectively.

5β-cholestan-3β-yl-acetic acid. 5β-cholestan-3α-yl-tosylate[10] (4 g) was heated under reflux for 48 hr in toluene (75 ml) with sodiodiethyl malonate prepared from the ester (3 ml). The precipitated sodium toluene-*p*-sulphonate was removed by filtration, the solvent evaporated, the residue

[10] D. D. Evans and C. W. Shoppee, *J. Chem. Soc.* 540 (1953).

TABLE 3. PHYSICAL PROPERTIES AND ANALYSES FOR STEROIDAL BASES AND DERIVATIVES

No. and synthetic route	Systematic name	M.p. (Recryst. solvent in brackets)	$[\alpha]_D$	Analysis Found (upper line) Reqd. (lower line) C	H	N	Cl	I	Molecular formula
I($R = CH_2NH_2$) (B)	3α-Aminomethyl-5α-cholestane hydrochloride	312–314°		77·0	11·9	3·3	8·3		
		(AcMe–EtOH)		76·7	12·0	3·2	8·1		$C_{28}H_{52}NCl$
I($R = CH_2NMe_2$)	3α-Dimethylaminomethyl-5α-cholestane	57–59°(AcMe)	+20°	84·1	12·7				
				83·9	12·8				$C_{30}H_{55}N$
II($R = CH_2NMe_2$) (Hydgn. of 5-ene)	3β-Dimethylaminomethyl-5α-cholestane	129–131°	+19°	84·1	12·9	3·5			
		(AcMe)		83·9	12·8	3·3			$C_{30}H_{55}N$
	Methiodide	270–275°		65·2	9·6				
		(AcMe)		65·1	10·0				$C_{31}H_{58}NI$
III($R = CH_2NMe_2$) (B)	3α-Dimethylaminomethylcholest-5-ene	oil,	−23°	84·5	12·2	3·3			
		b.p. 170°/0·01 mm.		84·3	12·4	3·3			$C_{30}H_{53}N$
IV($R = CH_2NH_2$) (A; B)	3β-Aminomethylcholest-5-ene hydrochloride	297–300°		77·2	11·7				
		(EtOH–AcMe)		77·1	11·5				$C_{28}H_{50}NCl$
	N-Acetyl derivative	177–178°		81·4	11·1	3·6			
		(AcMe)		81·6	11·6	3·2			$C_{30}H_{51}NO$
IV($R = CH_2NMe_2$)	3β-Dimethylaminomethylcholest-5-ene	152–154°	−28°	84·6	12·7	3·3			
		(AcMe)		84·3	12·4	3·3			$C_{30}H_{53}N$
	Methiodide	290–293°						22·5	
		(AcMe)						22·3	$C_{31}H_{56}NI$
V($R = CH_2NMe_2$) (B)	3β-Dimethylaminomethyl-5β-cholestane	oil,	+29°	84·2	12·5	3·6			
		b.p. 170°/0·01 mm.		83·9	12·8	3·3			$C_{30}H_{55}N$

(4·1 g) refluxed with a large excess of 5% methanolic KOH for 16 hr, and the product separated into neutral (2·8 g) and acidic (1·3 g) fractions. The former, an oil which partially crystallized after chromatography, was probably mainly a mixture of 5β-cholestenes (Found: C, 86·8; H, 12·8. Calc. for $C_{27}H_{46}$: C, 87·5; H, 12·5%). The acid fraction after recrystallization from ether-light petroleum gave pure *5β-cholestan-3β-yl-malonic acid*, m.p. 192° (dec) $[\alpha]_D$ + 25° (Found: C, 75·7; H, 10·8. $C_{30}H_{50}O_4$ requires: C, 76·0; H, 10·5%). Decarboxylation at 200°/0·01 mm during 4 hr gave the crude acetic acid which was purified by chromatography of the crude methyl ester (prepared with diazomethane in ether) on alumina and hydrolysis of this with 5% methanolic KOH. *5β-Cholestan-3β-yl-acetic acid* separated from acetone in needles, m.p. 128–130°, $[\alpha]_D$ + 25° (Found: C, 81·1; H, 11·9. $C_{29}H_{50}O_2$ requires: C, 80·9; H, 11·7%); the methyl ester was an oil, b.p. 160°/0·05 mm. (Found: C, 80·9; H, 11·4. $C_{30}H_{52}O_2$ requires: C, 81·1; H, 11·7%).

Lithium aluminium hydride route (route A) to bases

Preparation of 3β-aminomethylcholest-5-ene and 3β-dimethylaminomethylcholest-5-ene. Cholest-5-ene-3β-carboxylic acid was prepared by carbonating cholesteryl magnesium chloride[11] and converted into the amide, m.p. 227–229° (lit.[7,11] m.p. 227–229°). This (2·1 g) was reduced during 48 hr with $LiAlH_4$ (4 g) in refluxing ether (500 ml), excess of hydride was decomposed with moist ether, and the resulting primary base was purified *via* the hydrochloride and characterized as the N-acetyl derivative. (Physical properties and analysis of the steroidal bases and their derivatives are listed in Table 3.) An identical product was obtained by Curtius degradation from cholest-5-en-3β-yl-acetic acid. Methylation of the primary base (1·4 g) by refluxing it with formaldehyde (40%; 1·4 ml), formic acid (98%; 1·4 ml) and water (2·8 ml) for 6 hr gave the corresponding unsaturated N,N-dimethyl base. Hydrogenation of this base (0·21 g) in glacial acetic acid (10 ml) in presence of a Pt catalyst (from Adams' catalyst; 33·5 mg) at atm press. was complete in 2 hr, yielding 3β-dimethylaminomethyl-5α-cholestane. Dimethylaminomethylcyclohexane was prepared by reduction of N,N-dimethylhexahydrobenzamide with $LiAlH_4$, and gave a picrate of m.p. 133° (lit.[12] m.p., 133°).

Example of Curtius degradation route (route B) to bases

Preparation of 3α-aminomethyl-5α-cholestane. 5α-Cholestan-3α-yl acetic acid (2·0 g, m.p. 210°; lit.[6] m.p. 210°) was refluxed in benzene (60 ml) with thionyl chloride (4·5 ml) for 3 hr and the resulting crude acid chloride in a mixture of acetone (75 ml) and dioxan (35 ml) was treated dropwise, with stirring, with a solution of sodium azide (0·65 g) in water (4·5 ml). After 30 min, water (150 ml) was added and the precipitated acid azide collected and dried. The azide was converted into isocyanate in refluxing benzene (100 ml) during 2 hr; glacial acetic acid (80 ml) and 10N HCl (20 ml) were then added and the mixture refluxed for a further 2 hr and then evaporated under red. press. to leave the crude primary amine hydrochloride. Methylation of the primary to the N,N-dimethyl tertiary base was carried out as above, using the formaldehyde–formic acid process.

Kinetic investigation. The method and apparatus were those previously employed,[2] except that conductances were measured on a Wayne–Kerr Universal Bridge Model B 221 with an operating frequency of 1592 c/s. Solvents and methyl iodide were purified as previously described. The mixed nitrobenzene–benzene solvent for the kinetic runs was 9:1 w/w, and had *d* 1·180 at 0°, *d* 1·157 at 24·9°, and *d* 1·148 at 34·7°. Initial amine concentrations were typically of the order of 5mM and the reactions usually followed to around half-life. The dimethylaminomethyl steroid methiodides examined all gave the same calibration curve for each temp, which was identical with that previously obtained for the methiodides of 3-dimethylamino steroids at the same temp.

We thank the Department of Scientific and Industrial Research for a Maintenance Grant (to P. B. S.).

[11] R. H. Baker and E. N. Squire, *J. Amer. Chem. Soc.* **70**, 1487, 4134 (1948).

[12] M. Mousseron, R. Jacquier and R. Zagdoun, *Bull. Soc. Chim. Fr.* 197 (1952).

[13] Results for this base (in which $-NMe_2$ is mainly equatorial) are taken from B. B. Gent, Thesis, University of Sheffield (1956).