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REACTIVITY OF SOME STEROIDAL TERTIARY AMINES AND THEIR DERIVATIVES

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IN the Table are listed approximate first order rate constants for the following pseudo-unimolecular reactions: (a), the quaternisation of some 3-dimethylaminocholestanes in a large excess of neat methyl iodide at 21° (k_q); (b) the conversion of the resultant trimethylammonium salts and also of two triethylammonium salts into steroidal olefin (k_{ho}) and steroidal tertiary base (k_b) in a large excess of 2N-alcoholic potassium hydroxide at 83°. The results are of interest for several reasons:

(1) Although steric compression at the axial $-\overset{+}{N}Me_3$ and $-\overset{+}{N}Et_3$ groups in the 3α- salts must be of the same order as that at the $-\overset{+}{N}Me_3$ group in neomenthyltrimethylammonium salts, which is believed (3) to account for the tendency towards Saytzeff orientation in their E 2 degradations, attack at the β-protons of the N-ethyl groups in the 3α-triethylammonium salt is still higher than the statistical expectation. The relevant reaction rates suggest that this would not be true for the difficultly accessible 6β- and 7α-triethylammonium analogues.

(2) Direct evidence is provided that reaction rates for the substitution $\overset{-}{O}H \rightarrow Me \overset{\curvearrowright}{-} \overset{+}{N}R_3$ tend to increase with increasing steric compression at nitrogen. Indirect evidence, the interpretation of which involves some assumptions, has previously (4) led to the same conclusion for the similar reaction of 4-t-butylcyclohexyltrimethylammonium chlorides with t-butoxide anion.

TABLE

Approximate First order Rate Constants for Reaction of Dimethylamino-cholestanes in Excess of Methyl Iodide at 21° (k_q) and for Degradation of Quaternary Ammonium Salts in Excess of 2N-Alcoholic Potassium Hydroxide at 83° to Steroidal Olefins (k_{hc}) and Tertiary Bases (k_b)

		For $RNMe_3I$		For $RNEt_3I$	
Isomer	k_q	k_{he}	k_b	k_{hc}	k_b
3β	*ca.* 2×10^{-2}	*ca.* 1.6×10^{-7}	6.0×10^{-7}	~ 0	1.2×10^{-5}
3α	1.9×10^{-3}	6.5×10^{-6}	1.5×10^{-6}	3.9×10^{-6}	1.3×10^{-5}
6α	1.8×10^{-4}	*ca.* 3×10^{-7}	6.1×10^{-6}	-	-
6β	*ca.* 8×10^{-6}	$>10^{-2}$	-	-	-
7α	*ca.* 2×10^{-6}	2.4×10^{-4}	2.1×10^{-5}	-	-

Notes:

(a) 7β-dimethylaminocholestane reacts too slowly with methyl iodide (2) for measurement of k_q.

(b) k_{hc} for 6β-cholestanyltrimethylammonium iodide is calculated from the expectation (1) that there is at least 95 % decomposition in 2N-alcoholic KOH in 5 min. If the product contained *ca.* 0.1 % base (experimentally hardly detectable with the quantities used) k_b would be *ca.* 10^{-5} (between the 6α- and the 7α- values).

(c) For the first-order decompositions of the 6β- and 7α- trimethylammonium salts in refluxing neutral ethanol k_{hc} = *ca.* 4×10^{-4} and 1×10^{-5} respectively.

(d) Reactions of the triethylammonium salts were studied at 81°. k_b for these salts relates to Hofman elimination of ethylene; for the other salts to removal of methanol by nucleophilic displacement at $\overset{+}{N}$ - Me.

(e) All rate constants in sec^{-1}.

Rates for the replacement reaction with the steroidal salts are remarkably high, that for the 7α-salt being higher than for the Hofmann elimination of trimethylamine (measured as k_{hc}) with the axial 3α-salt.

(3) The quaternisation rates (k_q) for the dimethylaminocholestanes increase in the same order as their previously measured (5) basic dissociation constants, and a reasonably good linear free energy relationship can be demonstrated by a log k_q *vs*. pK_b plot. Values for k_b are in the inverse order, but with other reactions, e.g. chromic acid oxidation of steroidal secondary alcohols (6) the order is different and some previously discussed (5) L.F.E. plots for steroids are grouped into families of parallel lines. It is probably relevant that in the conversion of the tertiary steroidal bases into hydrogen- or quaternary ammonium salts and in the re-conversion of the latter into the bases by nucleophilic attack, we have as a common factor the addition or removal of a fourth bonding group at a nitrogen atom already attached to three methyl groups. It is interesting that the observed steric effects are greater for such processes at position -7α than -6β, in spite of the fact that overall steric compression on groups in the latter position must be greater (axial methyl interaction) as is shown, for example, by the total decomposition rates (see Table) for the isomeric trimethylammonium salts: the critical stage (particularly sensitive to steric compression) for addition of bulk at a 6β- group is evidently earlier than that corresponding to the last stage in tetrahedral bonding with the 6β-tertiary base. On the other hand, reactions involving similar final-stage bonding with *eq*-7β-dimethylaminocholestane give particularly strong indications of the effects of steric compression: in addition to examples previously discussed (2) we now record that conversion of the tertiary base into the corresponding amine oxide is more difficult than the same reaction with the *ax*-7α-epimer. The responsible structural feature is in this case easily identified: the 15-methylene group introduces a strong compressional salient into one relatively narrow segment

of the space around the 7β-nitrogen atom, the effect of which is particularly obvious in reactions involving the last bonding stage for this atom (3 → 4 change in co-ordination) when at least the first three of the four bonded groups are reasonably bulky. Similar structural circumstances arise at the equatorial positions 1β, 11α, and 12β; in appropriate reactions of amines and their derivatives at these and the epimeric positions, and in certain other reactions at the same positions including alkaline hydrolysis of esters of the relevant steroidal carboxylic acids, a tendency towards reversal of the normally observed axial-equatorial rate order may be expected which will be greater than for reactions involving less bulky functional groups or lower-level co-ordination changes at the atoms directly attached to the ring system. Interesting relevant facts and comment for some reactions at C-12 have been provided by Aluaddin and Martin-Smith (7).

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