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# REACTIVITY OF GROUPS ATTACHED TO REDUCED CYCLIC RING SYSTEMS—II

## SOME ASPECTS OF THE REACTIVITY OF STEROIDAL-DIMETHYLAMINES AND TRIALKYLAMMONIUM SALTS: LINEAR FREE ENERGY RELATIONSHIPS AND PARTIAL EI CHARACTER IN E2 TRANSITION STATES FOR AXIAL QUATERNARY SALTS

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**Abstract**—Approximate quaternization rates for a series of steroidal dimethylamines in methyl iodide are reported and compared with rates for removal of N-methyl from the resultant trimethylammonium salts by nucleophilic displacement and with previously measured basic dissociation constants. Variable El character in transition states for alkaline E2 Hofmann eliminations is deduced from the effect of steric compression at positive nitrogen on the rates of degradation of several axial trimethylammonium salts, and on the olefin: tertiary steroidal base ratio in the products from alkaline degradation of *ax*-3α-cholestanyl-triethylammonium iodide.

Detailed kinetic work on the Menschutkin reaction of various 3-dimethylamino- and dimethylaminomethyl steroids has been described in previous publications[1] from this laboratory; in this work the solvent was a benzene-nitrobenzene mixture, and second order rate constants were derived from conductiometric measurements. To provide comparative information for a wider range of steroidal tertiary bases more rapidly than full kinetic investigations would allow, we have made approximate measurements of rates of quaternization of a series of steroidal dimethylamines in excess of neat methyl iodide, the proportion of each base quaternized in various times at room and sometimes at reflux temperatures being measured directly.

While we had initially expected to quote results simply in terms of approximate percentage reaction in a given time, we found that fairly satisfactory pseudo-first order rate constants could be calculated for the quaternization of each base examined, and approximate comparisons in reactivities are simplified by presentation of the data in this form (Table; $k_q$ column). We have also examined the rates of degradation at 83° of various trimethylammonium iodides in a large excess of 2N-potassium hydroxide in 94% ethanol (6% water). Again we found that quite satisfactory overall pseudo-first order degradation rate constants could be calculated from direct measurement of proportions of quaternary salt decomposed at varying times, and these constants are divided (Table) into those for Hofmann elimination ($k_{hc}$) and those for nucleophilic attack on N-methyl ($k_b$) in direct proportion to the molar steroidal olefin: steroidal base product ratios for the various reactions. Two of the quaternary salts (6β and 7α) are also degraded in the hot neutral solvent, but so much more slowly than in the alkali hydroxide solution that the comparative rounded data in the

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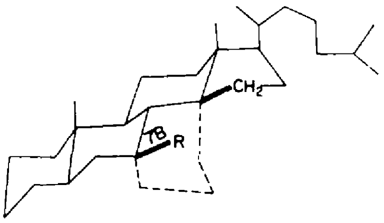
[1] B. B. Gent and J. McKenna, *J. Chem. Soc.* 573 (1956); P. B. Smith and J. McKenna, *Tetrahedron* (1964) **20**, 1933

Table can be taken without correction to provide a satisfactory semiquantitative indication of the rates* of bimolecular elimination (E2: $k_{hc}$) and bimolecular nucleophilic substitution at N-methyl (Sn2; $k_b$) for the quaternary salts studied.

If the logarithms of the observed pseudo-first order quaternization rates are plotted against the $pk_b$ values for the tertiary steroidal bases as previously determined by Bird and Cookson,[4] a satisfactory linear free energy plot is obtained (Diagram). Such relationships have only rarely been observed in alicyclic systems when the reactivity changes are due mainly to varying steric compression (as they are here) as it is unusual for such varying compression to affect the reactivities or equilibria under study in the uniformly comparable manner required for a single linear log-log plot over a sufficiently wide range. Bird and Cookson found, for example, that when $pK_B$'s for steroidal bases were plotted against logarithms of rates of chromic acid oxidation of the structurally corresponding secondary alcohols,[5] a series of parallel lines was obtained; while Brown and Ichikawa[6] could not demonstrate simple L.F.E. relationships between rates of reduction of cyclanones with sodium borohydride and displacement reactions of cycloalkyl halides and tosylates, although a reasonably linear relationship was shown between logarithms of the reduction rates and equilibrium constants for the dissociation of cyclic cyanohydrins.



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By extrapolation of our L.F.E. plot (Diagram) the pseudo-first order rate of quaternization of the equatorial 7β-dimethylaminocholestane in neat methyl iodide at 21° would seem to be ca. $10^{-8}$ sec$^{-1}$, in agreement with the qualitatively observed difficulty (previous paper)[7] in preparing the methiodide (even in higher boiling solvents) and the corresponding amine oxide, and in concord too with Bird and Cookson's especially low $pK_b$ value[4] for the tertiary base. It is clearly difficult at

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* These reaction rates between ions are very sensitive to solvent variation, and the water content of the solvent should properly have been stated in the preliminary communication.[2] Thus our approximate rate constants for the degradation reactions, when recalculated as bimolecular constants, are not directly comparable with the rates in water or in pure ethanol previously quoted[3] by Hughes and Wilby for menthyl and neomenthyl salts. Reaction rates of the type with which we are concerned are also very sensitive to salt effects: the large excess of alkali used in our degradations makes the observed results directly comparable with one another. Since the preliminary communication, further work on the trimethylammonium salts has resulted in some slight modifications (mostly by indicating the need for rounding off values) as well as extension of the originally quoted data.

[2] R. Ledger, J. McKenna and P. B. Smith, *Tetrahedron Letters* 1433 (1963).

[3] E. D. Hughes and J. Wilby, *J. Chem. Soc.* 4094 (1960).

[4] C. W. Bird and R. C. Cookson, *J. Chem. Soc.* 2343 (1960).

[5] cf. J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **38**, 1529 (1955).

[6] H. C. Brown and K. Ichikawa, *Tetrahedron* **1**, 221 (1957).

[7] R. Ledger, A. J. Smith and J. McKenna, *Tetrahedron* **20**, 2413

position 7β to increase the coordination number at nitrogen directly attached to the ring from three to four, all of the groups being reasonably bulky (at least in the transition state). The 15-methylene group appears (cf. Ref. 4) to be the structural feature responsible for this difficulty bearing as it does equivalent of a 1:3 diaxial relationship* to the nitrogenous group (cf. I). While this methylene group is particularly effective in hindering addition of a fourth fairly bulky co-ordinating group at the 7β-nitrogen atom, it has less effect in reactions involving changes between lower co-ordination numbers at a 7β- linked atom (as in the alkaline hydrolysis of epimeric cholestan-7-yl benzoates[8] where the equatorial ester is more rapidly hydrolysed)† or in 3→4 co-ordination changes where hydrogen can be accommodated in juxtaposition to the C-15 hydrogen atoms (as in e.g. protonation of the epimeric primary cholestan-7-ylamines, where the equatorial base is stronger[4]). A similar interesting variation in order of axial *vs* equatorial reactivity with the particular bulk and co-ordination

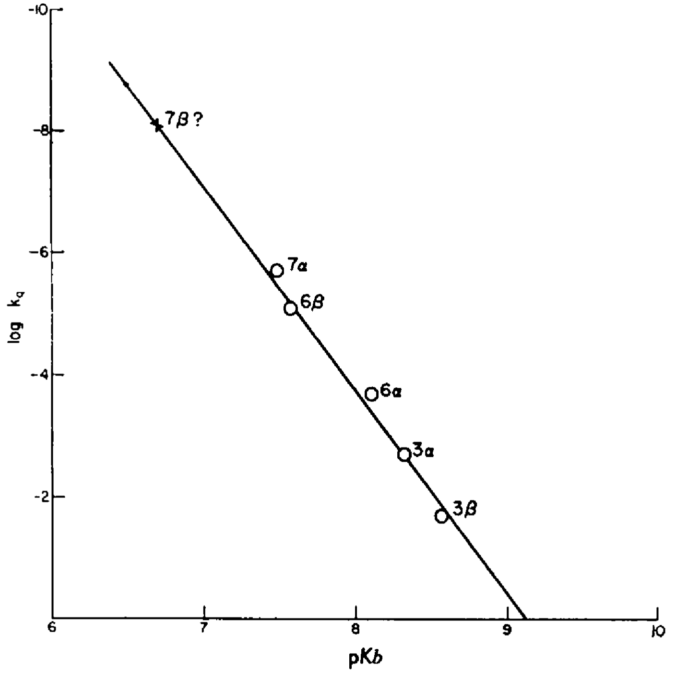

FIG. 1. Linear-free energy relationship between basic dissociation constants and quaternization rates with methyl iodide for dimethylamino-5α-cholestanes.

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* We thank Dr. J. C. P. Schwarz of the University of Edinburgh for pointing out this equivalent relationship.

† The overall coordination number change at the alkoxy oxygen atom in the alkaline hydrolysis is 2 → 1 (strongly solvated); for the sequential transition states in the two-stage reaction the changes are 2 → 2 (solvated) and 2 (solvated) → 1 (strongly solvated). For a detailed discussion see Ref. 1*b*.

[8] D. H. R. Barton and J. W. Rosenfelder, *J. Chem. Soc.* 1048 (1951); R. J. W. Cremlyn and C. W. Shoppee, *Ibid.* 3515 (1954).

number changes associated with other reactions at the atoms directly attached to C7 in the cholestane ring may be expected; reactivities of carboxylic acid derivatives seem worthy of particular study, and work in this field is in hand. Furthermore, positions 1, 11 and 12[9] in the 5α-cholestane system are structurally analogous to position 7 and reactions at these positions may well show the same interesting pattern of differential axial *vs* equatorial reactivities. Quite apart from such special examples, however, *it cannot in any case be expected that with axial-equatorial isomeric pairs and analogous diastereoisomers, each corresponding successive increase in bonded bulk and/or solvation will in general and of necessity be energetically more demanding at the epimeric position where groups are on average more sterically compressed.* Thus it is evidently less difficult to protonate or methylate at a 6β-$NMe_2$ group than at the analogous *ax* -7α -$NMe_2$ group, notwithstanding the fact that groups at the 6β-position are more compressed (by the $C_{10}$-methyl group) than at the 7α-, as exemplified by the far more rapid degradation of 6β- than of 7α-trimethylammonium salts. Detailed examination of such cases would clearly require consideration of the preferred rotational isomers (about the $C_6$β-N and $C_7$α-N bonds) for reactants and products (for equilibria) and for reactants and transition states (for rates); such consideration, however, would seem to be premature at the present time.

The values for $k_b$ in the Table provide direct evidence that reaction rates for the substitution $\overline{O}H \dashrightarrow Me\overset{\curvearrowright}{—}\overset{+}{N}R_3$ increase with increasing steric compression at nitrogen. As the carbon atoms of the methyl groups are two bond lengths from the alicyclic ring system the differential rates might be expected[1b] to be in the order observed, but so far as we know only indirect evidence on this point in a structurally similar system (t- butylcyclohexyl) has been previously available.[10]

Both neutral (E1) and alkaline (E2; $k_{hc}$) elimination rates for the axial 3-, 6-, and 7-trimethylammonium salts show clearly the effect of steric acceleration by compressive axial interactions, the rate order 6β > 7α > 3α being that expected on the basis of consideration of ring-rigidities and bulk of groups in axial opposition to the quaternary groups. That this is the order for both E1 and E2 reactions suggests that it is also the order for the degree of E1-character in the E2 transition states (cf Ref 3) and this expectation is in accord with the exclusive Saytzeff orientation in the E2 reaction of the 6β- salt.[7,11] However, the latter criterion is by itself not always satisfactory, as other factors affect the issue (preceding paper)[7]. We were interested, nevertheless, in devising a procedure for demonstrating effects due to partial E1 character in alkaline eliminations with *ax* -3-trialkylammonium salts, because in E2 transition states the quaternary groups in these are compressed to approximately the same extent as are the analogous groups in neomenthyl salts, where the postulated partial E1 character is believed[3] to control the orientation of the elimination. Since both the ring -β-carbon atoms are secondary in the steroidal salts we examined the alkaline degradation of cholestan-3α-yltriethylammonium iodide.

Preparation of the 3α, and also, for simple comparison, the 3β-triethylammonium salts, and the epimeric 3-diethylaminocholestanes from the corresponding aminocholestanes is described in the Experimental Section. Both tertiary bases had been

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[9] M. Aluaddin and M. Martin-Smith, *J. Org. Chem.* **28**, 886 (1963).

[10] D. Y. Curtin, R. D. Stolow and W. Maya, *J. Amer. Chem. Soc.* **81**, 3330 (1959).

[11] B. B. Gent and J. McKenna, *J. Chem. Soc.* 137 (1959).

prepared previously by Sauers,[12] using a Leuckart reductive amination of cholestan-3-one, and, so far as comparison is possible, the physical properties of our samples agree with those quoted, thus confirming Sauers' assigned configurations.

Degradation of both salts was done at a different period from the approximate rate work on the trimethylammonium salts, but as it was effected in a large excess refluxing 2N KOH in 94% alcohol (b.p. 81°), approximate comparisons are fortunately possible, and it is clear that not only (as expected) the rate of elimination of ethylene from each isomer is nearly the same, but also that the rates of formation of steroidal olefin (cholest-2-ene + cholest-3-ene) from the axial trimethyl- and triethylammonium salts are also quite close; E1 character in the relevant transition states is probably therefore nearly the same for the homologous 3-axial salts. The point of essential importance derived from this work is that the effect of such partial E1 character is quite evident from the observed ratio of attack on the $\beta$-methyl *vs* the $\beta$-methylene groups in the triethylammonium salt. Normally, in acyclic olefins this is of the rough order of 15–50:1 for reactions with different substrates under varying conditions.[13] In our case the molar ratio of steroidal diethylamine to steroidal olefin in the alkaline degradation at 81° of the 3$\alpha$-triethylammonium salt was 3–4:1 and we make the reasonable assumption that essentially all the steroidal base arises by Hofmann elimination of ethylene. When the degradation was performed by pyrolysis of the quaternary hydroxide at 130–170° the ratio was of the same order. Since three ethyl groups are in competition with statistically one (two halves: cf requirement for antiperiplanar elimination) ring methylene group the ratio to be compared with that

TABLE. APPROXIMATE FIRST ORDER RATE CONSTANTS (SEC$^{-1}$) FOR REACTION OF DIMETHYLAMINOCHOLESTANES IN EXCESS OF METHYL IODIDE AT 21° ($k_q$) AND FOR DEGRADATION OF TRIMETHYLAMMONIUM SALTS IN EXCESS OF 2N POTASSIUM HYDROXIDE IN 94% ETHANOL AT 83° TO STEROIDAL OLEFINS ($k_{hc}$) AND TERTIARY BASES ($k_b$)

| Isomer | $k_q$ | $k_{hc}$ | $k_b$ |
|---|---|---|---|
| 3$\beta$ | *$2 \times 10^{-2}$*[a] | *$1{\cdot}5 \times 10^{-7}$*[a] | $6 \times 10^{7}$ |
| 3$\alpha$ | $2 \times 10^{-3}$ | $6{\cdot}5 \times 10^{6}$[a] | $1{\cdot}5 \times 10^{-6}$ |
| 6$\alpha$ | $2 \times 10^{-4}$ | *$4 \times 10^{-7}$* | $6 \times 10^{6}$ |
| 6$\beta$ | *$8 \times 10^{-6}$*[b] | *$\geq 10^{2}$*[c] | |
| 7$\alpha$ | *$2 \times 10^{6}$*[b] | $2{\cdot}5 \times 10^{-4}$[c] | $2 \times 10^{5}$ |

[a] Italicized values are for various experimental reasons less accurate than the others.

[b] For the 6$\beta$- and 7$\alpha$- tertiary bases in neat methyl iodide at 42°, $k_b = 5{\cdot}5 \times 10^{-6}$ and $2 \times 10^{5}$ sec$^{-1}$ respectively.

[c] For the first order decompositions of the 6$\beta$- and 7$\alpha$-trimethylammonium salts in refluxing neutral ethanol, $k_{hc} = 4 \times 10^{4}$ and $1 \times 10^{-5}$ sec$^{-1}$ respectively; the latter salt has $k_{hc} - 7{\cdot}5 \times 10^{6}$ sec$^{1}$ in refluxing neutral 94% ethanol.

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[12] R. R. Sauers, *J. Amer. Chem. Soc.* **80**, 4721 (1958).

[13] cf. D. V. Banthorpe, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.* 4054 (1960); especially Tables 3, 9 and 10.

quoted above is only slightly greater than unity.* The considerable alteration is ascribed to loosening of the C3α-N bond, with associated development of partial E1 character, in the transition state for elimination (E2) of triethylamine (and of trimethylamine in the analogous reaction of approximately equal rate of the axial trimethylammonium salt) a factor which is not offset by hindrance by the $C_{10}$-methyl group to base approach to the axial ring β-hydrogen atoms. That E2 processes are under observation in these experiments is evident from the approximate pseudo first-order kinetics in excess of hot aqueous alcoholic alkali, and the failure of the axial trialkylammonium iodides to decompose in refluxing neutral ethanol.

## EXPERIMENTAL

Optical rotations were determined as described in the preceding paper.[7]

### 3α- *and* 3β-*Diethylaminocholestanes and ethiodides*

3α-Aminochloestane (0·22 g) in ethanol (5 ml) was refluxed with ethyl iodide (1 ml) in the presence of excess of finely divided solid $K_2CO_3$ for 48 hr, the solvents were evaporated and the residue was extracted with chloroform, giving a mixture of *cholestan-3α-yl-triethylammonium iodide* (40 mg) and 3α-*diethylaminocholestane*, which were separated by dissolution of the base in ether. After recrystallization from actone, the quaternary salt had m.p. 260-262°, $[\alpha]_D$ +56° (Found: C, 66·2; H, 10·8. $C_{33}H_{62}NI$ requires: C, 66·1; H, 10·4%). The tertiary base was an oil (as previously[12] reported) b.p. 160°/0·01 mm, $[\alpha]_D$ +27° (Found: C, 83·8; H, 12·6; N, 2·8. $C_{31}H_{57}N$ requires: C, 83·9; H, 12·9; N, 3·2%). The *hydrochloride*, after recrystallization from acetone, had m.p. 275–277°, $[\alpha]_D$ +27° (Found: C, 77·4; H, 12·5; Cl, 7·4. $C_{31}H_{58}NCl$ requires: C, 77·5; H, 12·2; Cl, 7·4%).

3β-Aminocholestane was similarly converted into 3β-diethylaminocholestane, m.p. 97–98°, $[\alpha]_D$ +18° (lit.[12] m.p. 101·5–103·5; $[\alpha]_D$ +18°). (Found: C, 84·3; H, 12·9; N, 3·4. Calc. for $C_{31}H_{57}N$: C, 83·9; H, 12·9; N, 3·2%) and *cholestan-3β-yltriethylammonium iodide*, m.p. 260–262° after recrystallization from acetone, $[\alpha]_D$ +17° (Found: C, 66·3; H, 10·7. $C_{33}H_{62}NI$ requires: C, 66·1; H, 10·4%). 3β-*Diethylaminocholestane hydrochloride* had m.p. 260–262°, $[\alpha]_D$ +18° (Found: Cl, 7·5. $C_{31}H_{38}NCl$ requires: Cl, 7·4%).

### *Semiquantitative kinetic investigations*

(a) *Quaternizations.* Approximate values for $k_q$ quoted in the Table were obtained by analysis of observed proportion of tertiary base converted into methiodide (some of which underwent further decomposition into steroidal olefin, in the reactions run at the higher temp), following quaternization at a constant temp (21°) in a large excess of neat methyl iodide, or, for reactions at 42°, in a gently refluxing solution in excess of methyl iodide containing suspended finely divided $K_2CO_3$. Experimental results obtained fitted the equation $k = 2{\cdot}3/t(\log_{10} a/a - x)$, where of an initial $a$ mg of tertiary base, $x$ mg had reacted in time $t$. It was possible in all experiments to account for ca. 99–101% of the initial tertiary base in the workup. It may be noted that the initial amount of methyl iodide used in an experiment, or its variation in volume during the experiment, is of no relevance to the rate-constant measurement provided a large excess is used. On average three experiments for each base were performed. The following details illustrate the procedure:

(i) 6α-Dimethylaminocholestane (217·6 mg) was at once dissolved in a large excess (in this experiment 22 ml) of methyl iodide and the solution allowed to stand at 21° for 14 min and then promptly evaporated at 0° *in vacuo*. The residue was separated with light petroleum into unreacted tertiary base (186·0 mg) and quaternary salt (43·0 mg) corresponding to a calculated initial 218·0 mg of tertiary base.

(ii) A solution of 6β-dimethylaminocholestane (357·2 mg) in a large excess of methyl iodide (in this experiment, 36 ml) was refluxed gently after addition of solid powdered $K_2CO_3$ for 300 min, the

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* Examination of the other alkaline elimination rates in the Table leads to the striking conclusion that the 7α- and especially the 6β-cholestanyltriethylammonium salts should even in kinetically bimolecular eliminations yield hardly any ethylene.

mixture was then promptly evaporated at 0° *in vacuo*, and the residue extracted with cold chloroform. The extract was evaporated at room temp *in vacuo*, and the residue from the chloroform separated with light petroleum into soluble and insoluble fractions. The former was treated with excess HCl aq and the mixture evaporated to dryness each time after several additions of benzene, and then separated into the ether-insoluble 6β-dimethylaminocholestane hydrochloride (148·0 mg) from which the tertiary base (138·0 mg) was obtained on appropriate treatment, and cholest-5-ene (177·5 mg). The petroleum-insoluble fraction was the quaternary salt (28 mg). The products isolated in total correspond to a calculated 357·9 mg of initial tertiary base.

(b) *Degradation of trimethylammonium iodides.* The following illustrates the procedure: A solution of 3α-cholestanyltrimethylammonium iodide (63·8 mg) in 94% 2N ethanolic KOH (2 ml) was heated in a sealed tube at 83° for 40 hr, and the cooled contents treated with water (8 ml) and light petroleum (8 ml). After shaking and separation of the phases, the aqueous phase was extracted three further times with light petroleum. The total petroleum extract was separated after HCl aq treatment as under (a) into steroidal olefin (21·9 ml) and base hydrochloride (6·0 mg); undecomposed methiodide (20·3 mg) was then extracted with chloroform from its suspension in the aqueous alcohol. A total of 60·7 mg of the initial methiodide is accounted for by the compounds isolated from the reaction mixture; the percentage accountancy in this experiment is rather less than average. Usually three degradations per quaternary salt were performed to provide an adequate range for analysis of the results on the basis of the first-order rate equation.

The methiodides and ethiodides were also examined for degradation in refluxing ethanol and 94% ethanol; only in the case of the 7α- and 6β-methiodides was any conversion into hydrocarbon noted, and again first order decomposition rate constants were evaluated (Table).

### *Alkaline decompositions of triethylammonium salts*

(a) Both 3α- and 3β- isomers were subjected to degradation in gently refluxing 2N KOH in 94% ethanol (internal temp 81°), quantities and workup procedure being similar to above. Thus not only were product ratios determined, but approximate pseudo-first order rate constants very roughly comparable with those in the Table could be evaluated, although these are obviously less accurate than those quoted for the methiodides. The 3β-ethiodide gave a steroidal base: steroidal olefin molar product ratio of > 100:1, the hydrocarbon being formed in too small quantities for accurate weighing. The ratio for the 3α-isomer in two experiments was 3–4:1. Approximate rate constants are of the order of $1–1{\cdot}5 \times 10^{-5}$ sec$^{-1}$ for $k_b$ for each salt, and $3–4 \times 10^{-6}$ sec$^{-1}$ for $k_{bc}$ for the 3α-salt (elimination of triethylamine).

(b) The 3α-triethylammonium iodide in methanol was shaken overnight with excess of freshly precipitated silver oxide, the mixture was filtered, the filtrate evaporated in a desiccator, and the residue pyrolysed at 130–170° (bath temp)/0·04 mm. The ether-soluble products were separated into base and hydrocarbon mixture by treatment with HCl aq. The molar ratio of these products in two experiments was 3–4:1. The hydrocarbon mixture (cholest-2-ene + cholest-3-ene) obtained both in experiments and those reported under (a) corresponded physically to that previously[14] obtained from the 3α-trimethylammonium salt; the recovered base hydrochloride was identical in IR spectrum with 3α-diethylaminocholestane hydrochloride.

*Acknowledgement*—We thank the Department of Scientific and Industrial Research for Maintenance Grants (to R. L. and P. B. S.) and the University of Sheffield for research facilities (to J. M. McK.).

[14] R. D. Haworth, J. McKenna and R. G. Powell, *J. Chem. Soc.* 1110 (1953).