116. *Structural and Stereochemical Investigations of Cyclic Bases. Part I.* 3-(*Tertiary Amino*)-*steroids.*

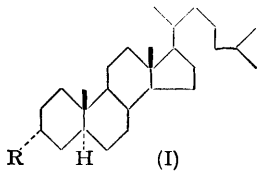
By B. B. Gent and J. McKenna.

A kinetic investigation of the Menschutkin reaction of methyl iodide with a series of 3-(tertiary amino)-steroids in nitrobenzene–benzene has shown that the equatorial bases examined have lower energies of activation and lower " frequency factors " than their axial epimers. Hofmann, Emde, and amine oxide degradations of some of the steroidal bases are also described.

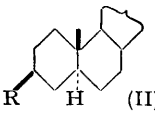
Equatorial hydroxyl (or carboxyl) groups are more readily esterified than the epimeric, axial groups, and a similar differentiation has been observed for other reactions, including ester hydrolysis (for discussions and leading earlier references see Barton [1] and Klyne [2]). These conclusions are based for the most part on qualitative observations or quantitative data of the simplest type, as few relevant kinetic investigations have been made. If we consider a group R–X–Y in which R is a *cyclo*hexane or reduced six-membered heterocyclic residue and –XY an equatorial or axial substituent, then addition or bimolecular substitution reactions *at* X (the atom directly attached to the nucleus) would, in general, be expected to proceed more readily for X (equatorial) than for X (epimeric and axial).

[1] Barton, *J.*, 1953, 1027.
[2] Klyne (Ed.), " Progress in Stereochemistry," Butterworths, London, 1954.

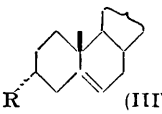
In each of these reaction types an additional atom or group becomes partially bonded to X in the transition state, and the prediction regarding differential reactivity is readily and directly based on the normal * fundamental greater accessibility, and lower steric compression of (in our example) equatorial rather than axial X. Alkaline hydrolysis of epimeric steroidal acetates and benzoates is probably classifiable, in relation to the group R–X–Y, as bimolecular substitution at Y, but, in general, predictions regarding differential reactivity are less readily made for this and other types of substitution reaction involving X–Y. Among other such reactions is displacement of a substituent at a *cyclo*hexane carbon atom (for a relevant discussion see Fieser [4]).



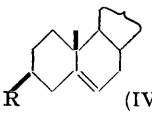
(I)



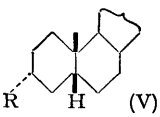
(II)



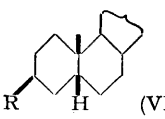
(III)



(IV)



(V)



(VI)

To provide some detailed information on an addition reaction of the type referred to above, we have made a kinetic study of the Menschutkin reaction, with methyl iodide, of the epimeric 3-dimethylamino-cholestanes (I and II; R = NMe_2), -cholest-5-enes (III and (IV; R = NMe_2), and -coprostanes (V and VI; R = NMe_2). A conductometric procedure was used, concentrations of quaternary iodide being determined by reference to empirical conductance–concentration curves, and only *ca.* 5 mg. of amine were required for each run. In a preliminary check of the apparatus a value $k = 5{\cdot}57 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ was observed for the second-order rate constant of the reaction of dimethylaniline and methyl iodide in methanol at 24·9°; using a different procedure Evans [5] recorded $k = 5{\cdot}62 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 25°. Preliminary results with the alicyclic bases in methanol suggested that an aprotic solvent was required at the low concentrations employed, and we therefore used nitrobenzene to which 10% w/w of benzene was added to permit runs at 0°. All six steroidal quaternary iodides gave the same calibration curve (conductance–concentration) at 24·9°; at other temperatures, therefore, the conductances for a random selection from the six salts were taken as applicable to all the others.

Good second-order rate constants were obtained for all the bases at 0·0°, 12·0°, and 24·9°; results for a typical run are shown in Table 1, together with the rate constants and values for E and log A derived by graphical analysis of the results using the Arrhenius equation $k = A \exp(-E/RT)$. The Arrhenius plots are excellent in some cases and satisfactory in all. Additional analysis on the basis of the absolute-rate expression is unnecessary for the purposes of our discussion.

Equatorial amines (II; IV; V; R = NMe_2) have lower energies of activation (heats of activation follow the same order) than have the axial bases (I; III; VI; R = NMe_2) and the results thus illustrate the soundness of one aspect of conformational theory. The Arrhenius "frequency factors" (which provide an indication of relative entropies of activation) for the equatorial bases are also lower than for their epimers; the difference is probably mainly due to the greater degree of solvation possible with intermediate complexes derived from the less hindered amines.[6]

* For a discussion of special cases where an equatorial group is more hindered than an epimeric axial group, see Klyne.[3]

[3] Klyne (Ed.), *op. cit.*, p. 53.
[4] Fieser, *Experientia*, 1950, **6**, 312.
[5] Evans, *J.*, 1944, 422.
[6] Cf. Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 25.

The kinetic runs were normally followed to about half completion, and no difficulties due to the reversibility of the reaction were encountered: results in all cases fitted the simple second-order rate expression. Equilibration experiments, however, showed that the Menschutkin interchange reaction, $R{\cdot}NMe_3\}I + R'{\cdot}NMe_2 \rightleftharpoons R{\cdot}NMe_2 + R'{\cdot}NMe_3\}I$, may be important at higher temperatures. An approximately equimolecular mixture of

TABLE 1. *Typical kinetic run, rate constants, and Arrhenius parameters for steroidal amines in the Menschutkin reaction.*

3β-Dimethylaminocoprostane at 0°; $[MeI]_0 = 180{\cdot}1$ mM; $[Base]_0 = 6{\cdot}87$ mM.

Time (min.)	50	70	90	110	130	150
Conductance (μmho)	90	116	139	159	178	194
[Quaternary iodide] (mM)	1·26	1·70	2·08	2·44	2·79	3·10
10^3k (l. mole^{-1} sec.$^{-1}$)	0·376	0·378	0·373	0·372	0·374	0·374

Average $k = 0{\cdot}375 \times 10^{-3}$; corr. for time, $0{\cdot}378 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$.

Base no.	I	II	III	IV	V	VI
$10^3k_{24{\cdot}9}$ (l. mole^{-1} sec.$^{-1}$)	1·14	81·5	6·41	54·6	89·2	2·51
$10^3k_{12{\cdot}0}$,,	0·42	44·0	2·51	28·0	43·9	0·96
$10^3k_{0{\cdot}0}$,,	0·16	24·1	0·98	13·2	23·8	0·38
E (kcal. mole^{-1})	12·7	7·9	12·2	9·3	8·7	12·4
log A	6·4	4·7	6·8	5·6	5·3	6·4

3β-dimethylaminocoprostane methiodide (VI; $R = NMe_3\}I$) and 3α-dimethylaminocoprostane (V; $R = NMe_2$) was heated in benzene–nitrobenzene at 200°; in our preliminary experiments the reaction mixture has not been fully analysed, but it was evident that the chief basic component was 3β-dimethylaminocoprostane (VI; $R = NMe_2$), the larger trimethylammonium group favouring the equatorial (3α) site. This type of equilibration may be of general interest in comparisons of steric compressions at different positions in reduced cyclic systems.

Previous work has shown that certain axial steroidal 3-trimethylammonium groups are readily eliminated by Hofmann fission, but that saturated equatorial quaternary hydroxides preferentially lose methanol on pyrolysis.[7] We have found that the same is true for the epimeric 3α(equatorial)- and the 3β(axial)-coprostanyltrimethylammonium hydroxide (V and VI; $R = NMe_3\}OH$); preliminary evidence regarding pyrolysis of the former was included in the earlier paper, but the structure of the related tertiary amine was not elucidated until later.[8] It is not at present known to what extent differences in the relative rates of the methanol-elimination reactions affect the composition of the reaction mixture in these pyrolyses.

We have examined some Emde reductions of steroidal 3-quaternary ammonium chlorides and iodides; the most interesting result concerns the epimeric cholest-5-enyl 3-quaternary salts. The tendency towards Hofmann elimination in the 3α-cholest-5-enyltrimethylammonium ion (III; $R = NMe_3^+$) is so strong (axial nitrogen; formation of conjugated diene system) that treatment of the chloride in water with sodium amalgam or of the iodide with sodium in liquid ammonia yields cholesta-3 : 5-diene; the normal Emde product, cholest-5-ene, has not been isolated from these reactions, but may be obtained in low yield by sodium amalgam reduction of 3β-cholest-5-enyltrimethylammonium chloride (IV; $R = NMe_3\}Cl$). Use of ethanol in alkali-metal–liquid ammonia reductions has been recommended by Birch [9] for countering reactions due to the strongly basic amide anion, and we found that 3α-cholest-5-enyltrimethylammonium iodide with sodium in ethanol–liquid ammonia gave cholest-5-ene. On Emde reduction (sodium amalgam) of four saturated quaternary chlorides (I, II, V, VI; $R = NMe_3\}Cl$), significant unsaturation could not be detected in the hydrocarbon fractions even from the two axial salts.

Pyrolysis of tertiary amine oxides affords, *inter alia*, the related tertiary amines and

[7] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[8] (*a*) Šorm, Lábler, and Černý, *Chem. Listy*, 1953, **47**, 418; 1954, **48**, 1058; (*b*) Haworth, Lunts, and McKenna, *J.*, 1955, 986.
[9] Birch, *Quart. Rev.*, 1950, **4**, 69.

olefins, and it has been suggested that the nitrogen-elimination reaction assumes a *cis*-steric course.[10] Thus, oxides derived from axial and equatorial amines would be expected to give comparable yields of olefin on pyrolysis, and we have demonstrated this for the four amines listed in Table 2; yields of crude olefin and tertiary amine obtained on Hofmann degradation are included for comparison (Hofmann yields for the epimeric 3-dimethylaminocholestanes are calculated from the data of Haworth, McKenna, and Powell [7]).

TABLE 2. *Yields of hydrocarbon and recovered tertiary base on Hofmann degradation or amine oxide pyrolysis of steroid bases.*

	Crude hydrocarbon (%)		Crude recovered base (%)	
Base no.	Hofmann	Amine oxide	Hofmann	Amine oxide
(I) R (axial) = NMe_2	79	87	17	6
(VI) R (axial) = NMe_2	66	58	17	16
(II) R (equatorial) = NMe_2	4	63	92	33
(V) R (equatorial) = NMe_2	18	58	63	17

In the preparation of the amine oxides it was observed qualitatively that equatorial bases reacted faster than the axial epimers. The pyrolysis mixtures were much cleaner and more readily purified than those from Hofmann degradations.

EXPERIMENTAL

Kinetic Investigation.—(a) *Preparation and purification of materials.* 3α-, m. p. 90—91° (methiodide, m. p. 285—286°), and 3β-Dimethylaminocholestane, m. p. 102—104° (methiodide, m. p. 285—286°), 3α-, m. p. 70—71·5° (methiodide, m. p. 289—290°), and 3β-dimethylaminocholest-5-ene, m. p. 149—150° (methiodide, m. p. 303—305°), 3α-, m. p. 72—74° (methiodide, m. p. 264—265°), and 3β-dimethylaminocoprostane, m. p. 62° [*methiodide*, m. p. 291—293° (Found : C, 64·2; H, 9·9; N, 2·2; I, 22·9. $C_{30}H_{56}NI$ requires C, 64·6; H, 10·1; N, 2·5; I, 22·8%)], and trimethylphenylammonium iodide, m. p. 216—217°, were prepared by described methods (for the steroid preparations see Haworth *et al.*[7] and Šorm *et al.*[8a]), recrystallised (bases from acetone; quaternary iodides from methanol) to constant m. p., and dried *in vacuo*. The m. p.s of the quaternary iodides vary considerably according to conditions of heating : those quoted are for immersion *ca.* 20° below the m. p. in an electrically heated block the temperature of which was then raised by approx. 10° per min.

Methanol was treated with magnesium and iodine [11] and distilled. Nitrobenzene was washed with water, dried ($CaCl_2$), and distilled. Benzene (" AnalaR ") was fractionally distilled, the first 10% being rejected. Methyl iodide was twice distilled from potassium carbonate, and stored in a dark bottle over mercury. Dimethylaniline (" AnalaR ") was distilled from potassium hydroxide. Fractions of steady b. p. in agreement with values in the literature were accepted from these distillations, in which a Widmer column was used where necessary.

A mixture of 1 part by weight of benzene and 9 parts of nitrobenzene had d 1 154 at 25°, and 1·173 at 0°; by intrapolation d at 12° was 1·164.

(b) *Apparatus and method.* The conductivity cell was a two-limbed Pyrex vessel of 6 c.c. volume, shaped like a Zerewitinoff tube, with bright platinum electrodes (20 × 5 × 0·5 mm.) firmly located about 4 mm. apart in one limb by glass spacers. In use the cell was closed with a rubber bung through which passed a glass rod terminating in a Polythene plug which fitted the outlet from the second limb. The glass rod also supported a Polythene washer against the lower face of the rubber bung. In each kinetic run the amine solution was placed in the electrode limb, and the methyl iodide solution (total vol. of both solutions about 3 c.c.) in the other which was then closed with the Polythene plug. The cell was kept for 15—30 min. in a bath the temperature of which (measured with a standardised thermometer) was held constant within 0·01°. The Polythene plug was then withdrawn without disturbing the rubber bung or its Polythene washer, the cell contents were mixed, and readings were started; resistances (usually 2500—100,000 ohms) were measured on a conventional Wheatstone-bridge circuit with earphone detector and compensating condenser, using A.C. at 5 v and 1250 c.p.s. supplied from an oscillator kept about 6 ft. from the rest of the apparatus. Conductances (10—400 μmho) were

[10] Cope, Pike, and Spencer, *J. Amer. Chem. Soc.*, 1953, **75**, 3212 and earlier papers; Cram and McCarty, *ibid.*, 1954, **76**, 5740 and earlier papers; Rogers, *J.*, 1955, 769.
[11] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.

also checked approximately during a run with a Mullard conductivity bridge. Molar concentrations were corrected for temperature, and it was found that concentrations of amine or methyl iodide of the same order as those required for the kinetic work had no appreciable effect on the conductances of quaternary iodide solutions.

Variations in rate constants were less than 1·5% from the arithmetical means quoted, which are for ranges of 15—40% reaction; it was usually necessary to reject the first few readings.

Equilibration Experiments.—3β-Coprostanyltrimethylammonium iodide (95 mg.) and 3α-dimethylaminocoprostane (61 mg.) in benzene–nitrobenzene (as used in kinetic work; 10 c.c.) were heated in a sealed Pyrex tube at 200° for 1 hr., the solvent was evaporated, and the basic fraction (50 mg.) was crystallised twice from acetone, yielding 3β-dimethylaminocoprostane as prisms, m. p. 59—60°, undepressed on admixture with an authentic specimen of m. p. 62°. For further characterisation the base was converted into the *picrate*, m. p. 202—203° (from methanol) undepressed on admixture with an authentic specimen prepared as described below.

When 3α-coprostanyltrimethylammonium iodide (35 mg.) and 3β-dimethylaminocoprostane (27 mg.) were heated in benzene–nitrobenzene (5 c.c.) at 200° for 1 hr., recovered 3β-dimethylaminocoprostane, m. p. 60—61°, was the main component of the basic fraction.

Emde Reduction of 3α-Dimethylaminocholest-5-ene Metho-salts.—(a) *With sodium amalgam.* The amine (111 mg.) was converted into the quaternary iodide and thence into the quaternary chloride in the usual way. The chloride in water (30 c.c.) was treated at 100° with 5% sodium amalgam (5 g.) during 6 hr., and the mixture was separated into neutral (72 mg.) and basic (15 mg.) components. The latter was distilled *in vacuo* and the distillate crystallised from acetone, yielding crude 3α-dimethylaminocholest-5-ene, m. p. 66—67°, undepressed on admixture with an authentic specimen of m. p. 70—71°. The neutral component after chromatography on alumina and recrystallisation from methanol–ether gave cholesta-3 : 5-diene, m. p. and mixed m. p. 75—76°, together with fractions of lower m. p. (*ca.* 55°) which exhibited a strong band at 2350 Å (in EtOH; log ε 4·10). No cholest-5-ene could be isolated.

(b) *With sodium in liquid ammonia.* A suspension of methiodide (500 mg.) from 3α-dimethylaminocholest-5-ene in liquid ammonia (300 c.c.) was treated during 30 min. with sodium until a slight excess was present, and the solvent was then allowed to evaporate. After one recrystallisation from methanol–ether the neutral product (200 mg.) had m. p. 75—76° undepressed on admixture with cholesta-3 : 5-diene.

(c) *With sodium in ethanol–liquid ammonia.* Methiodide (239 mg.), suspended in liquid ammonia (50 c.c.) and ethanol (5 c.c.), was treated portionwise with a slight excess of sodium, and the mixture was separated into basic and neutral fractions. The basic fraction (40 mg.), on crystallisation from acetone, yielded 3α-dimethylaminocholest-5-ene, m. p. and mixed m. p. 69—70°. Two recrystallisations of the neutral fraction (65 mg.) from methanol–ether gave cholest-5-ene, m. p. and mixed m. p. 89—90°.

Emde Reduction of 3β-Dimethylaminocholest-5-ene Methochloride.—Base (97 mg.) was converted into the methochloride and reduced with sodium amalgam by the method outlined above. The ether-soluble products were 3β-dimethylaminocholest-5-ene (6 mg.), m. p. (from acetone–chloroform) 149—150°, undepressed on admixture with an authentic specimen, and a neutral fraction (3·3 mg.) which after distillation *in vacuo*, chromatography on alumina, and recrystallisation from methanol–ether gave cholest-5-ene, m. p. 84—85°, undepressed on admixture with an authentic specimen of m. p. 88—89°; a yellow oil, which failed to exhibit the characteristic absorption band of cholesta-3 : 5-diene at 2350 Å, was obtained from the final eluates of the chromatogram.

Emde Reduction of Saturated Quaternary Chlorides.—3α-Dimethylaminocholestane (65 mg.) on conversion into the methochloride and reduction with sodium amalgam gave recovered base (11 mg.) m. p. and mixed m. p. 88—89° after crystallisation from acetone, and an oily neutral fraction (12 mg.) which exhibited no appreciable unsaturation in a test with ethereal monoperphthalic acid at 0°. A solution of the oil in light petroleum (b. p. 40—60°) was chromatographed on alumina, and the product crystallised from methanol–ether, giving leaflets, m. p. 75°, undepressed on admixture with cholestane, m. p. 78—79°. 3β-Dimethylaminocholestane methochloride gave similar yields of recovered amine, m. p. 101—102°, and a saturated neutral oil from which, however, only partly crystalline material could be obtained on attempted purification.

3α-Dimethylaminocoprostane methochloride gave a similar result, only recovered amine, m. p. 69—70°, being characterised. 3β-Dimethylaminocoprostane methochloride (from methiodide; 69 mg.) gave recovered amine (8 mg.), m. p. 58—59° undepressed on admixture with 3β-dimethylaminocoprostane of m. p. 60—62°, and a saturated neutral fraction (8 mg.)

which on chromatography on alumina and crystallisation from methanol–ether yielded colourless needles of coprostane, m. p. and mixed m. p. 70—71°.

Hofmann Degradation of 3α- *and* 3β-*Dimethylaminocoprostanes.*—3α-Dimethylaminocoprostane methiodide (49 mg.) was converted in the usual way into the quaternary hydroxide which was pyrolysed at 160—180° (bath)/0·01 mm., yielding recovered amine (23 mg.), m. p. (from acetone) 68—69° undepressed on admixture with an authentic specimen of m. p. 72—74°, and an oily hydrocarbon (6 mg.). Hydrogenation of the hydrocarbon in ether–acetic acid in presence of platinum, and crystallisation of the product from ether–methanol, gave coprostane, m. p. and mixed m. p. 67—68°.

Similar treatment of 3β-dimethylaminocoprostane methiodide (112 mg.) afforded recovered amine (14 mg.), m. p. (from acetone) 60—61°, together with a neutral oil (49 mg.) which on hydrogenation yielded coprostane, m. p. and mixed m. p. 70—71° after crystallisation from methanol–ether.

Preparation and Characterisation of Amine Oxides.—The saturated tertiary amine, in methanol or methanol–chloroform, was treated at 70° for 24 hr. (equatorial bases) or 48 hr. (axial bases) with 30% hydrogen peroxide (2 mol.); excess of hydrogen peroxide was then decomposed by addition of a little platinum black.[12] When (in a few hours) the mixture failed to bleach lead sulphide paper the catalyst was separated by filtration and the filtrate evaporated. The white residue of amine oxide was triturated with boiling ether, and for characterisation was converted into picrate which was recrystallised from ethanol–chloroform. For comparison the tertiary amine picrates were prepared and recrystallised from ethanol or ethanol–chloroform. Data are as follows: 3α-, irregular yellow prisms, m. p. 198—200° (Found: C, 65·2; H, 8·9; N, 8·2. $C_{35}H_{56}O_7N_4$ requires C, 65·2; H, 8·8; N, 8·7%), and 3β-*dimethylaminocholestane picrate*, yellow prismatic needles, m. p. 260° (decomp.) (Found: C, 65·1; H, 8·7; N, 8·5%); 3α-, prisms, m. p. 199—201° (Found: C, 65·0; H, 9·0; N, 8·4%), and 3β-*dimethylaminocoprostane picrate*, prismatic needles, m. p. 202—203° (decomp.) (Found: C, 65·1; H, 8·8; N, 8·4%); 3α-, prisms, m. p. 166—168° (decomp.) (Found: C, 63·4; H, 8·8. $C_{35}H_{56}O_8N_4$ requires C, 63·6; H, 8·5%), and 3β-*dimethylaminocholestane oxide picrate*, plates, m. p. 200° (decomp.) (Found: C, 63·7; H, 8·8%); 3α-, prisms, m. p. 158—159° (Found: C, 63·3; H, 8·4%), and 3β-*dimethylaminocoprostane oxide picrate*, prisms, m. p. 155—157° (Found: C, 63·5; H, 8·8%).

Pyrolysis of Amine Oxides.—3α-Dimethylaminocholestane oxide (I; R = NMe_2O) (24 mg.) was heated for 15 min. at 170° (bath)/0·03 mm. and the distillate separated into basic (1·3 mg.) and neutral (18 mg.) fractions; the former was not examined. Hydrogenation of the neutral fraction in ether–acetic acid in presence of platinum oxide and crystallisation of the product from methanol–ether gave cholestane, m. p. and mixed m. p. 76—77°.

3β-Dimethylaminocholestane oxide (II; R = NMe_2O) (22 mg.) on pyrolysis at 170° (bath)/0·01 mm. similarly gave basic (7 mg.) and neutral (12 mg.) products; the base on crystallisation from acetone had m. p. 101—102°, undepressed on admixture with 3β-dimethylaminocholestane of the same m. p. Hydrogenation of the neutral fraction yielded cholestane, m. p. and mixed m. p. 77—78° after crystallisation from methanol–ether.

3α-Dimethylaminocoprostane oxide (V; R = NMe_2O) (18 mg.), on pyrolysis, likewise yielded 3α-dimethylaminocoprostane (3 mg.), m. p. 69—70° after crystallisation from acetone, undepressed on admixture with an authentic specimen of m. p. 72—74°; hydrogenation of the neutral pyrolysis product (9 mg.) and crystallisation from methanol–ether yielded coprostane, m. p. and mixed m. p. 67—68°.

Pyrolysis of 3β-dimethylaminocoprostane oxide (VI; R = NMe_2O) (26 mg.) gave tertiary base (4 mg.), m. p. 60—62° after crystallisation from acetone, undepressed on admixture with 3β-dimethylaminocoprostane of m. p. 62°, and a neutral fraction (13 mg.) which afforded coprostane, m. p. and mixed m. p. 69—70°, after hydrogenation and crystallisation of the product from methanol–ether.

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

THE UNIVERSITY, SHEFFIELD. [*Received, July 11th*, 1955.]

[12] Feulgen, *Ber.*, 1921, **54**, 360.