27. *Stereochemical Investigations of Cyclic Bases. Part IV.* Hofmann Degradation of 6α- and 6β-Cholestanyltrimethylammonium Salts.*

By B. B. Gent and J. McKenna.

Cholestan-6-one has been obtained as a by-product of formaldehyde–formic acid methylation of 6β-aminocholestane but not of the 6α-epimer; and 6β-cholestanyltrimethylammonium salts are much less stable that the 6α-analogues. These effects probably arise from steric interaction of the 6β-(axial)-nitrogenous group with the angular 10-methyl group; the reaction of cholestan-6α-yl toluene-*p*-sulphonate with dimethylamine, however, is accompanied by Walden inversion. Nearly pure cholest-5-ene was obtained by Hofmann fission of 6β-cholestanyltrimethylammonium salts even under strongly alkaline conditions, while pyrolysis of 6α-cholestanyltrimethylammonium hydroxide resulted mainly in reversion to the tertiary steroid base, but yielded also a little cholest-5- and -6-ene.

Previous examination [1] of the Hofmann degradation of a number of steroidal trimethylammonium salts with the quaternary group attached to $C_{(3)}$ has shown that axial salts are readily degraded to olefins while the equatorial epimers preferentially revert to tertiary steroid bases. The degradation of epimeric 6-cholestanyltrimethylammonium salts described in this paper follows the same pattern, but the results include additional features of mechanistic and stereochemical interest.

6α-Aminocholestane (I; R = NH_2) was prepared by reduction of the oxime of either cholestan-6-one or 3β-chlorocholestan-6-one with sodium and ethanol or pentanol; a little of the 6β-amine (II; R = NH_2) was also obtained from one of these reactions, and this base was in our hands the sole product of reduction of cholestan-6-one oxime or 6-nitrocholest-5-ene with lithium aluminium hydride. Our use of a large excess of hydride in the ketoxime reduction appears to have suppressed the formation of a little 6α-amine which has been reported by other workers.[2,3] The configurations of the primary bases are evident from the methods of preparation and from other work previously reported,[2,3] and are supported by the degradations described in this paper.

Methylation of 6β-aminocholestane with formaldehyde and formic acid yielded the tertiary base (II; R = NMe_2) together with cholestan-6-one; an identical tertiary base

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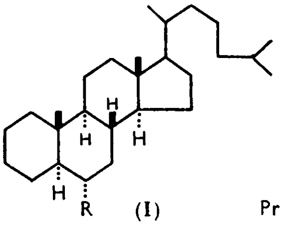
* Part III, *J.*, 1958, 2759.

[1] Haworth, McKenna, and Powell, *J.*, 1953, 1110; Gent and McKenna, *J.*, 1956, 573.

[2] Shoppee, Evans, and Summers, *J.*, 1957, 97.

[3] Bird and Cookson, *Chem. and Ind.*, 1955, 1479.

was obtained by methylation with methyl iodide and potassium carbonate, so that no appreciable racemisation occurred during the first reaction in spite of the possibility of equilibrium of intermediates $>CH{\cdot}N{:}CH_2 \rightleftharpoons >C{:}N{\cdot}CH_3$ suggested by ketone formation. This accords with previous experience.[4, 5] 6β-Cholestanyltrimethylammonium iodide (II; $R = NMe_3\}I$) was very unstable, and readily yielded cholest-5-ene (III) and trimethylammonium iodide on being heated either alone or in organic solvents. Care was therefore necessary to avoid extensive decomposition of the methiodide during methylation, particularly as the quaternisation was rather slow; further, it was necessary to use alkali (potassium carbonate) even in the direct conversion of the *tertiary* base into the methiodide in order to prevent formation of the base hydriodide [6] (together with cholest-5-ene and tetramethylammonium iodide). All samples of cholest-5-ene obtained by degradation of 6β-cholestanyltrimethylammonium iodide were of quite high purity, and, in particular, no evidence for admixture with cholest-6-ene was obtained. The same was true for the hydrocarbon obtained from the quaternary hydroxide (II; $R = NMe_3\}OH$) by either rapid heating or vacuum-concentration of its methanolic solution at room temperature.



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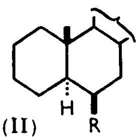

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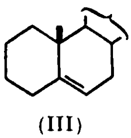
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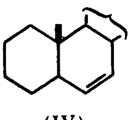
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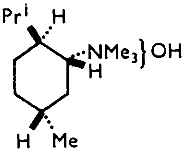

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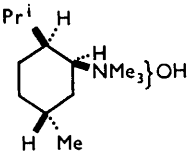

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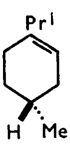

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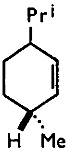

(VIII)

No cholestan-6-one was isolated after methylation of 6α-aminocholestane with formaldehyde and formic acid, and the related quaternary salt (I; $R = NMe_3\}I$) was stable in low-boiling organic solvents but lost methyl iodide on fusion. Pyrolysis of the quaternary hydroxide (I; $R = NMe_3\}OH$) gave 6α-dimethylaminocholestane (I; $R = NMe_2$) and a low yield of neutral product which was cholest-6-ene (IV) mixed with a considerable proportion of cholest-5-ene (III).

We believe that the formation of cholestan-6-one during formaldehyde–formic acid methylation of 6β- but not 6α-aminocholestane is related to the considerable steric interaction between the axial 10-methyl group and the axial basic centre. The same stereochemical feature appears to be responsible for the instability of the 6β-cholestanyltrimethylammonium salts, which in this respect resemble in their properties the metho-salts of Mannich bases. Shoppee and Howden [7] have shown that reaction of cholestan-6α-ol with phosphorus pentachloride or pentabromide yields the 6α-halides, but we have found that the 10-methyl group does not prevent Walden inversion in the reaction of cholestan-6α-yl toluene-*p*-sulphonate with the strong nucleophile dimethylamine (although extensive elimination yielding cholest-5-ene also occurs). There is an interesting analogy between these results and those of substitution at $C_{(3)}$ in 5 : 6-unsaturated steroids.[8, 9]

[4] Parham, Hunter, Hanson, and Lahr, *J. Amer. Chem. Soc.*, 1953, **75**, 5646; Grob, Kny, and Gagneux, *Helv. Chim. Acta*, 1957, **40**, 130.

[5] McKenna and Slinger, *J.*, 1958, 2759.

[6] Cf. Rapoport, Campion, and Gordon, *J. Amer. Chem. Soc.*, 1955, **77**, 2389.

[7] Shoppee and Howden, *Chem. and Ind.*, 1958, 414.

[8] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.

[9] Haworth, Lunts, and McKenna, *J.*, 1955, 986.

The direction of elimination in the Hofmann degradations reported is of some interest in that (*a*) formation of a considerable proportion of cholest-5-ene by fission of 6α-cholestanyltrimethylammonium hydroxide (5α-H) is obviously not a *trans*-elimination (relevant factors may be the rigidity of ring B and the equatorial disposition of the 6α-quaternary group) and (*b*) the apparently exclusive formation of cholest-5-ene from 6β-cholestanyltrimethylammonium salts does not correspond to anion-attack on hydrogen attached to the least alkylated β-carbon atom, which is $C_{(7)}$ (and carries a suitably oriented axial hydrogen atom). The results parallel those obtained with menthyl- (V) * and *neo*menthyl-trimethylammonium hydroxide (VI) which have been investigated and discussed by several groups of workers;[10] in particular, H. C. Brown and his collaborators regard the preponderant fission of the hydroxide (VI) to menth-3-ene (VII) rather than to menth-2-ene (VIII) as supporting their theory of the directive forces in bimolecular Hofmann eliminations. We have made no detailed kinetic study of any of the eliminations reported in this paper, but conditions in the formation of cholest-5-ene, at least from fused 6β-cholestanyltrimethylammonium hydroxide, would be expected to favour strongly a bimolecular elimination,[5] and the rate of fission of the 6β-quaternary iodide in boiling ethanol has been qualitatively shown to be sensitive to added alkali.

EXPERIMENTAL

Optical rotations refer to chloroform solutions at room temperature (17—23°) at concentrations (except where otherwise stated) of 1—3%. Light petroleum refers to the fraction of b. p. 40—60°.

6α- *and* 6β-*Aminocholestane*.—(*a*) Cholestan-6-one oxime (0·65 g.) in boiling pentanol (60 c.c.) was saturated with sodium during 1·5 hr. and the organic reduction products were treated with hydrochloric acid, yielding a mixture of 6α- (0·43 g.) and 6β-aminocholestane hydrochloride (0·18 g.), which were readily separated by utilising the remarkable fact that the 6β-hydrochloride is freely soluble, not only in ether (as in the 3 : 5-*cyclo*-analogue),[1, 9, 11] but also in light petroleum. After crystallisation from alcohol 6α-*aminocholestane hydrochloride* was obtained as rectangular prisms, m. p. 300°, $[\alpha]_D$ +34° (Found: C, 76·0; H, 12·0; N, 2·9. $C_{27}H_{50}NCl$ requires C, 76·5; H, 11·9; N, 3·3%), insoluble in water, ether, and light petroleum. 6α-Aminocholestane separated from methanol in prisms, m. p. 127—129°, $[\alpha]_D$ +38° (Found: C, 83·3; H, 12·7; N, 3·4. Calc. for $C_{27}H_{49}N$: C, 83·7; H, 12·7; N, 3·6%). The 6β-hydrochloride was recrystallised from acetone–ether and then converted into the amine, m. p. 108° undepressed on admixture with 6β-aminocholestane prepared by method (*b*).

6α-Aminocholestane was also obtained by reduction of 3β-chlorocholestan-6-one oxime as described above, and ethanol has been substituted for pentanol in each case; these earlier experiments, however, were carried out before we had noted the unusual solubility of 6β-aminocholestane hydrochloride in light petroleum, and this isomer was not therefore identified in reaction mixtures where it was probably present in small quantities.

(*b*) 6-Nitrocholest-5-ene (3 g.) in boiling ether (80 c.c.) was reduced with lithium aluminium hydride (1·5 g.) for 4 hr. and the resulting base (2·5 g.) converted into the hydrochloride, which was completely soluble in light petroleum. After recrystallisation of the salt from acetone–ether, the 6β-*aminocholestane hydrochloride* formed prisms, m. p. 190—192°, optically almost inactive ($[\alpha]_D$ *ca.* −1°; *c* 10%) (Found: C, 76·7; H, 11·6; N, 2·9; Cl, 8·5%. $C_{27}H_{50}NCl$ requires C, 76·5; H, 11·9; N, 3·3; Cl, 8·4%). 6β-Aminocholestane, prepared from the purified hydrochloride and recrystallised from ethanol, had m. p. 108°, $[\alpha]_D$ +11° (Found: C, 83·6; H, 12·7%).

(*c*) Reduction of cholestan-6-one oxime (1·1 g.) in boiling ether (100 c.c.) with lithium aluminium hydride (3 g.) for 48 hr. and purification of the basic product (1 g.) as described above

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* Formulæ (V—VIII) represent the quaternary hydroxides derived from (−)-menthylamine and (+)-*neo*menthylamine used in the investigations, and the isomeric derived (+)-menthenes.

[10] Brown and Moritani, *J. Amer. Chem. Soc.*, 1956, **78**, 2203; Cope and Acton, *ibid.*, 1958, **80**, 355; these authors give references to earlier work.

[11] Julian, Magnani, Meyer, and Cole, *ibid.*, 1948, **70**, 1834.

gave 6β-aminocholestane, m. p. 108° (undepressed with the compound derived from 6-nitrocholest-5-ene), $[\alpha]_D$ +13°.

The physical properties observed for 6α-aminocholestane agree with those given by other authors,[2, 12] but Shoppee, Evans, and Summers [2] have recorded m. p. 94—96°, $[\alpha]_D$ +6·3°, for 6β-aminocholestane.

Methylation of 6β-*Aminocholestane*.—(*a*) 6β-Aminocholestane (0·9 g.) was heated on a steam-bath with 40% aqueous formaldehyde (1·5 c.c.), 98% formic acid (1·5 c.c.), and water (3 c.c.) for 4 hr. After evaporation with excess of hydrochloric acid the products were separated with ether into 6β-dimethylaminocholestane hydrochloride (0·8 g.) and cholestan-6-one (0·1 g.). The latter was recrystallised from alcohol and identified by its m. p. and mixed m. p. (96°), infrared spectrum, and conversion into the oxime, m. p. and mixed m. p. 195°. 6β-*Dimethylaminocholestane hydrochloride* separated from acetone–chloroform in regular rectangular prisms, m. p. 255—257°, $[\alpha]_D$ +15° (Found: C, 76·6; H, 11·8; N, 3·2; Cl, 7·6. $C_{29}H_{54}NCl$ requires C, 77·0; H, 12·0; N, 3·1; Cl, 7·8%), soluble in water but not in dilute hydrochloric acid, ether, or light petroleum. 6β-*Dimethylaminocholestane*, obtained from the recrystallised hydrochloride, was an oil (resembling in this respect the 3 : 5-*cyclo*-analogue [9, 13]), b. p. 170° (bath)/0·005 mm., $[\alpha]_D$ −8° (Found: C, 83·6; H, 13·0. $C_{29}H_{53}N$ requires C, 83·9; H, 12·8%).

(*b*) A solution of 6β-aminocholestane (0·9 g.) in methyl iodide (8 c.c.) and methyl alcohol (3 c.c.) was refluxed gently with powdered anhydrous potassium carbonate (2 g.) for 6 hr., the mixture was evaporated to dryness under reduced pressure, and the residue extracted with cold chloroform (which does not dissolve tetramethylammonium iodide; cf. results described in the following paragraph). The extract was evaporated at *room temperature* under reduced pressure and the residue was separated with light petroleum into soluble (0·5 g.) and insoluble (0·5 g.) fractions. The former was treated with hydrochloric acid and the resulting mixture separated into 6β-dimethylaminocholestane hydrochloride (0·4 g.) which after recrystallisation from acetone–chloroform was identical in m. p. and infrared spectrum with the product prepared as in the preceding paragraph, and cholest-5-ene (0·1 g.), m. p. and mixed m. p. 91—92° after recrystallisation from ethanol. The petroleum-insoluble product was 6β-*cholestanyltrimethylammonium iodide*, which had m. p. 120—140° (rapid heating) after drying at 20°/0·005 mm.; the melting range (which was lowered on storage) appears to be due to partial Hofmann fission, and the ready similar degradation in hot organic solvents (see following paragraphs) discouraged attempts at recrystallisation, but the freshly prepared salt appeared to be pure (Found: N, 2·7; I, 22·5. $C_{30}H_{56}NI$ requires N, 2·5; I, 22·8%).

Hofmann Fission of 6β-*Cholestanyltrimethylammonium Salts*.—(*a*) The ready degradation of 6β-cholestanyltrimethylammonium iodide was first encountered during attempts to prepare the salt from the tertiary base in the usual manner. For example, the tertiary base (0·5 g.) was refluxed overnight with acetone (10 c.c.) and methyl iodide (5 c.c.), the solution was evaporated, and the residue was separated with light petroleum into soluble (0·20 g.) and insoluble (0·39 g.) fractions. The former was identified as cholest-5-ene by m. p. (90—91° before recrystallisation, 92° after recrystallisation from alcohol), mixed m. p., infrared spectrum, and specific rotation ($[\alpha]_D$ of unpurified product, −52°). The petroleum-insoluble solid was separated with boiling acetone into soluble (0·3 g.) and insoluble (90 mg.) fractions, and the latter, m. p. >360° after recrystallisation from aqueous acetone, was identified as tetramethylammonium iodide (Found: I, 62·8. Calc. for $C_4H_{12}NI$: I, 63·2%) by its infrared spectrum. The acetone-soluble compound after recrystallisation from the same solvent formed regular rectangular prisms, m. p. 258—260°, and was identified as 6β-*dimethylaminocholestane hydriodide* * by conversion into the oily tertiary base and formation therefrom in the usual manner, infrared comparison with an authentic specimen, and analysis (Found: C, 64·0; H, 9·9; I, 22·9. $C_{29}H_{54}NI$ requires C, 64·1; H, 9·9; I, 23·4%).

(*b*) 6β-Cholestanyltrimethylammonium iodide (150 mg.) in chloroform (2 c.c.) was refluxed for 3 hr.: a heavy precipitate began to appear during the first few minutes' heating. The solvent was evaporated and the residue was extracted with ether which removed cholest-5-ene

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* These results prompted re-examination of the salt obtained [9] together with cholesteryl iodide and tetramethylammonium iodide from 6β-dimethylamino-3 : 5-*cyclo*cholestane by treatment with methyl iodide in acetone, and previously described as the methiodide. This salt is also in fact a hydriodide. The chemistry of 3 : 5-*cyclo*-bases will be discussed further in a later communication.

[12] Vanghelovici and Vasiliu, *Bull. Soc. chim. România*, 1935, **17**, 249 (*Chem. Abs.*, 1936, **30**, 7119).

[13] Šorm, Lábler, and Černý, *Chem. Listy*, 1953, **47**, 418.

(90 mg.); the residue was then washed with chloroform, and the insoluble product (50 mg.) was recrystallised from acetone. It had m. p. 230—240° (Found: I, 67·8. Calc. for $C_3H_{10}NI$: I, 67·9%) and its infrared spectrum was identical with that of authentic trimethylammonium iodide.

(*c*) Quaternary iodide (0·12 g.) in methanol (10 c.c.) and water (2 c.c.) was shaken for 8 hr. with excess of silver oxide, silver salts were filtered off, and the filtrate was evaporated overnight in a vacuum-desiccator (solid KOH). When the desiccator was opened a strong odour of volatile amine was noted; the waxy residue was therefore washed with ether which removed cholest-5-ene (50 mg.), m. p. and mixed m. p. 88—89° before, 91—92° after, recrystallisation from ethanol, $[\alpha]_D$ $-55°$ (purified sample). Infrared spectroscopic examination of the crude sample gave no indication of the presence of cholest-6-ene. The ether-insoluble residue fused with evolution of volatile base when heated rapidly to 100—140°; ether then extracted more cholest-5-ene (5 mg.), m. p. and mixed m. p. 88—89° before, 91—92° after, recrystallisation from ethanol.

(*d*) The quaternary iodide was cleaved nearly quantitatively into cholest-5-ene and trimethylammonium iodide by being heated for 4 min. at 170°.

Effect of Base on Rate of Hofmann Fission of 6β-*Cholestanyltrimethylammonium Iodide in Ethanol*.—The following is typical of several groups of experiments. The same reflux apparatus was used throughout, and boiling was always attained by immersion in a boiling water-bath to just above the level of the methiodide solution.

(*a*) A solution of the methiodide (20 mg.) in 0·5N-ethanolic potassium hydroxide (1 c.c.) was refluxed for 10 min. and cooled to 15°; crystals (cholest-5-ene) were deposited. The mixture was diluted with light petroleum (4 c.c.), water (4 c.c.) was added, and after shaking and separation of the phases the aqueous-alcohol layer was extracted three times further with light petroleum (4 c.c.). The total petroleum extract yielded cholest-5-ene (13 mg.; theoretical).

(*b*) A solution of the methiodide (20 mg.) in ethanol (1 c.c.) deposited no significant quantity of crystals when refluxed even for 20 min., cooled to 15°, and seeded with cholest-5-ene. Application of the extraction technique described in the preceding paragraph, however, yielded cholest-5-ene (5 mg.). Undecomposed methiodide (12 mg.) was then extracted by chloroform from its suspension in the aqueous-alcohol layer.

(*c*) A solution of the methiodide (20 mg.) in ethanol (1 c.c.) gave a quantitative yield of cholest-5-ene after being refluxed for 2 hr.

Methylation of 6α-*Aminocholestane*.—Methylation of the primary amine with formaldehyde and formic acid gave 6α-*dimethylaminocholestane*, which separated from acetone in prisms, m. p. 64—65°, $[\alpha]_D$ $+50°$ (Found: C, 84·2; H, 13·0; N, 3·3. $C_{29}H_{53}N$ requires C, 83·9; H, 12·8; N, 3·4%); the tertiary base was best purified *via* the *hydrochloride*, irregular leaflets (from chloroform–ether), m. p. 260—265°, $[\alpha]_D$ $+41°$ (Found: C, 77·1; H, 12·3. $C_{29}H_{54}NCl$ requires C, 77·0; H, 12·0%). This salt was soluble in water but not in dilute hydrochloric acid, ether, or light petroleum. When the tertiary base was refluxed in acetone with methyl iodide, or when the primary base was refluxed in methanol with methyl iodide and potassium carbonate, the only organic product was 6α-*cholestanyltrimethylammonium iodide*, m. p. 140—200° (Found: N, 2·5; I, 22·9. $C_{30}H_{56}NI$ requires N, 2·5; I, 22·8%); the m. p. range was not reduced on recrystallisation and appears to be due to partial decomposition during heating (see next paragraph).

Hofmann Fission of 6α-*Cholestanyltrimethylammonium Salts*.—(*a*) The quaternary iodide (60 mg.) was heated at 200—210° for 4 min., and the mixture was then cooled and extracted with ether. The extract contained a neutral oil (6 mg.) and 6α-dimethylaminocholestane (29 mg.), m. p. and mixed m. p. 62—64° after recrystallisation from acetone.

(*b*) The methiodide (0·3 g.) was converted in the usual manner into the quaternary hydroxide which was decomposed at 175—195°/0·02 mm. Extraction with ether gave 6α-dimethylaminocholestane (175 mg.), m. p. (from acetone) 62—64°, and a neutral fraction (15 mg.) which were separated by hydrochloric acid treatment. The neutral fraction had m. p. 55—65° (raised to 70—72° by recrystallisation from methanol) and $[\alpha]_D$ $-67°$ (the specific rotations of cholest-5-ene and cholest-6-ene have recently been given [14] as $-55°$ and $-84°$ respectively. The strongest band in the C–H deformation area was at 770 cm.$^{-1}$, and this is attributed to cholest-6-ene,[15] but bands at 797 and 836 cm.$^{-1}$ due to cholest-5-ene [16] were also prominent. Reduction

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[14] Turner, Meador, and Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.

[15] Henbest, Meakins, and Wood, *J.*, 1954, 800.

[16] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.

of the mixture with hydrogen and platinium in acetic acid–ether gave cholestane which was pure after a single recrystallisation from methanol, having m. p. and mixed m. p. 79—80°.

*Reaction of Cholestan-*6α*-yl Toluene-*p*-sulphonate with Dimethylamine.*—The ester,[17] m. p. 108° (109 mg.), was heated in a steel autoclave with an excess of dimethylamine at 120° for 4 days, the mixture was treated with excess of aqueous sodium hydroxide and extacted with ether, and the ether was evaporated. Treatment of the residue with hydrochloric acid gave the ether-insoluble 6β-dimethylaminocholestane hydrochloride (18 mg.) which after recrystallisation from carbon tetrachloride–chloroform had m. p. 258—260°, $[\alpha]_D$ +13° (Found: C, 77·3; H, 11·9. Calc. for $C_{29}H_{54}NCl$: C, 77·0; H, 12·0%). The infrared spectrum of this salt was identical with that of samples prepared from 6β-aminocholestane, and likewise the derived tertiary base was degraded to cholest-5-ene on attempted quaternisation with methyl iodide in boiling acetone.

The neutral product from the autoclave experiment was crude cholest-5-ene, which had m. p. and mixed m. p. 88—89° after purification by chromatography on alumina; when the reaction was run at 100° for 16 hr., however, some of the ester was also recovered, and the yield of tertiary base was correspondingly reduced.

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THE UNIVERSITY, SHEFFIELD. [*Received, August 28th,* 1958.]

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[17] Karrer, Asmis, Sareen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022; Shoppee and Summers, *J.*, 1952, 1786.