988. *The Chemistry of Fungi. Part XXX.** apo*Sclerotioramine and its Derivatives.*

By H. C. Fielding, N. B. Graham, Alexander Robertson, R. B. Travers, and W. B. Whalley.

Sclerotioramine, $C_{21}H_{24}O_4NCl$, which yields an *O*-acetate, $C_{21}H_{23}O_3NCl{\cdot}OAc$, and an *N*-methyl ether, $C_{21}H_{23}O_4Cl{>}NMe$, exhibits the properties of a pyridone, and on reduction by various methods gives, with the simultaneous elimination of two carbon atoms, an aromatic, amphoteric derivative, *apo*sclerotioramine, $C_{19}H_{22}O_2NCl$, forming a di-*O*-acetate, $C_{19}H_{20}NCl(OAc)_2$; dihydrosclerotioramine furnishes the analogous dihydro*apo*sclerotioramine, $C_{19}H_{24}O_2NCl$. From their properties it appears that these products are complex derivatives of *iso*quinolone, and in agreement with this the ozonolysis of di-*O*-acetyl*apo*sclerotioramine yields a monobasic *iso*quinolonecarboxylic acid, *apo*sclerotaminic acid, $C_{11}H_6O_2NCl(OAc)_2$. As a result of extensive investigation of these compounds, in conjunction with a comparative examination of the analogous products from *N*-methylsclerotioramine, tentative structural formulæ for *apo*sclerotaminic acid and *apo*sclerotioramine and their derivatives are proposed.

The weakly basic amine, sclerotioramine,[1] the salts of which readily give yellow solutions in concentrated acids, regenerating the base on dilution with water, is readily soluble in 2N-aqueous sodium hydroxide from which it is recovered unchanged on immediate acidification, thus indicating that the compound contains an enolic or phenolic hydroxyl group. In agreement with the view [1] that the nitrogen atom is present in a heterocyclic ring, the base, which does not react with 2 : 4-dinitrophenylhydrazine, is decomposed by boiling acid or alkali with the production of acetic acid but without liberation of ammonia, and on methylation gives *N*-methylsclerotioramine identical with the product formed by the interaction of sclerotiorin with methylamine.[1] This methyl derivative, which is insoluble in aqueous sodium hydroxide, cannot be acetylated and does not absorb in the 3μ region. On acetylation sclerotioramine gives *O*-acetylsclerotioramine, $C_{21}H_{23}O_3NCl{\cdot}OAc$, which is insoluble in dilute alkalis but readily forms a yellow solution in dilute hydrochloric acid; deacetylation of the acetate with ammonia, or with dilute aqueous sodium hydroxide or carbonate, regenerates the parent base. That this acetyl derivative is an *O*-acetate is demonstrated by, *inter alia*, the fact that (*a*) the melting point of the acetate is about 100° below that of the parent base, compatible with the generalisation that, whilst *N*-acetylation gives a product with a melting point higher than that of the parent base, *O*-acetylation has the converse effect, (*b*) acetylsclerotioramine is a stronger base than sclerotioramine, whereas *N*-acetylation would reduce the basicity, and (*c*) the acetate exhibits a new infrared absorption band at 1779 cm.$^{-1}$ which is indicative of a vinylogous acetate. The formation of alkali-insoluble products by *O*-acetylation or *N*-methylation of sclerotioramine is compatible with the postulate that the nitrogen atom is contained in a heterocyclic system, and probably one of the pyridone or potential pyridone type.

Reduction of sclerotioramine with zinc and acetic acid or sodium hydroxide is accompanied by extrusion of two carbon atoms as acetic acid (approximately one mol.) and the formation of an amphoteric substance dideoxydinorsclerotioramine, $C_{19}H_{22}O_2NCl$, which we name *apo*sclerotioramine; this compound, which is much more readily isolated as the sulphate, $(C_{19}H_{22}O_2NCl)_2H_2SO_4$, forms a diacetate, $C_{19}H_{20}NCl(OAc)_2$. That this derivative is a di-*O*-acetate and does not contain an *N*-acetyl residue is indicated by the fact that (*a*) its melting point is lower than that of *apo*sclerotioramine, (*b*) the infrared absorption at 1770 cm.$^{-1}$, which is assigned to aromatic or vinylogous acetyl vibrations,

* Part XXIX, preceding paper.

[1] Eade, Page, Robertson, Turner, and Whalley, *J.*, 1957, 4913.

is sufficiently strong to be attributed to the presence of two *O*-acetyl residues, and (*c*) the diacetate gives a hydrochloride, $C_{19}H_{20}NCl(OAc)_2,HCl$, showing that, compared with the parent compound, the basicity of the nitrogen has not been diminished; analysis of the hydrochloride shows that it contains an ionic and a non-ionic chlorine atom. From the general properties of di-*O*-acetyl*apo*sclerotioramine it appears that the parent base contains an aromatic nitrogen system with an aliphatic side chain and, further, the bathochromic shift of the ultraviolet absorption spectrum of the hydrochloride by 20—50 mμ for the various peaks (Fig. 1) indicates a quinoline or *iso*quinoline, and not a naphthylamine, nucleus.[2] Moreover, since the ultraviolet absorption spectrum of *apo*sclerotioramine does not show an appreciable shift in acidic or alkaline solution, the nucleus is probably in a quinolone or *iso*quinolone form.[2] in agreement with the pyridone character ascribed to the parent sclerotioramine.

Now, dihydrosclerotioramine, $C_{21}H_{26}O_4NCl$, which is formed by the action of ammonia on dihydrosclerotiorin,[1] is strictly analogous to sclerotioramine and on reduction with

FIG. 1. *Absorption spectra of* (*A*) *di*-O-*acetyl*-apo*sclerotioramine* [λ_{max} 225, 278, 320, 335 mμ ($\log_{10}$ ε 4·28, 4·36, 4·64, 4·62)], *and* (*B*) *di*-O-*acetyl*apo*sclerotioramine hydrochloride in* 0·1N-*hydrochloric acid* [λ_{max}. 220, 291, 359, 405 mμ ($\log_{10}$ ε 4·34, 4·66, 3·98, 3·76)].

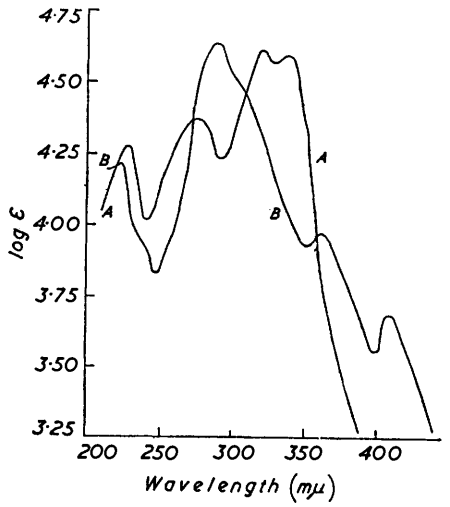
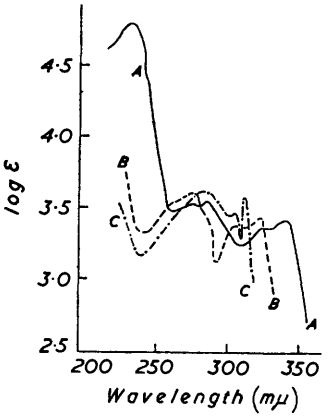


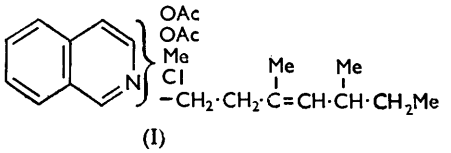
FIG. 2. *Absorption spectra of* (*A*) *di*-O-*acetyldihydro*apo*sclerotioramine* [λ_{max}. 231, 275, 284, 339 mμ ($\log_{10}$ ε 4·75, 3·52, 3·54, 3·48), (*B*) iso*quinoline, and* (*C*) *quinoline. In* 0·5N-*hydrochloric acid the major peak at* 231 mμ *for di*-O-*acetyldihydro*apo*sclerotioramine was shifted to* 245 mμ.



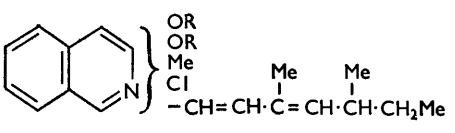
zinc dust and alkali furnishes dihydro*apo*sclerotioramine which is characterised as the diacetate, $C_{19}H_{22}NCl(OAc)_2$. For reasons advanced in the case of di-*O*-acetyl*apo*sclerotioramine, this derivative is a di-*O*-acetate and not *NO*-diacetyldihydro*apo*sclerotioramine. Since acetoxyl groups do not influence the ultraviolet absorption of aromatic systems [3] and the conjugated side-chain is now insulated from the aromatic chromophore the ultraviolet absorption of di-*O*-acetyldihydro*apo*sclerotioramine provides reasonably clear evidence regarding the *iso*quinoline nature of the nucleus present. Thus Fig. 2 shows that the absorption of this diacetate in neutral solution mimics that of *iso*quinoline (but not that of quinoline [4]) in intensity and in the relative position of the peaks but, as expected, at wavelengths longer by about 20 mμ. Consequently, on the pyridone hypothesis, di-*O*-acetyldihydro- and di-*O*-acetyl-*apo*sclerotioramine are in all probability *iso*quinolones, (I; R = Ac) and (II; R = Ac) respectively, containing in addition a nuclear *C*-methyl group. Collateral evidence for these views is provided below.

[2] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[3] Cooke, Macbeth, and Winzor, *J.*, 1939, 878.
[4] Ci. Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Ed. Arnold, London, 1954, p. 135.

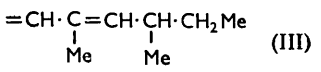
In agreement with earlier suggestions,[1] these partial formulæ imply that the alkyl side-chain of sclerotiorin is not involved in the formation of sclerotioramine and its analogues. This is substantiated by the formation of tetrahydrosclerotioramine, $C_{21}H_{28}O_4NCl$, from tetrahydrosclerotiorin and ammonia; this product is identical with the hydrogenation product of sclerotioramine and is converted, with the loss of two carbon atoms as acetic acid, by zinc and alkali into tetrahydro*apo*sclerotioramine analogous to *apo*sclerotioramine. Further, the ozonolysis of di-*O*-acetyl*apo*sclerotioramine involves the loss of eight carbon atoms corresponding to the residue (III) [five of which are accounted for by the isolation of (+)-α-methylbutyraldehyde[1]] with the formation of a monocarboxylic acid, $C_{11}H_6O_2NCl(OAc)_2$, which we name di-*O*-acetyl*apo*sclerotioraminic acid. This acid,



(I)

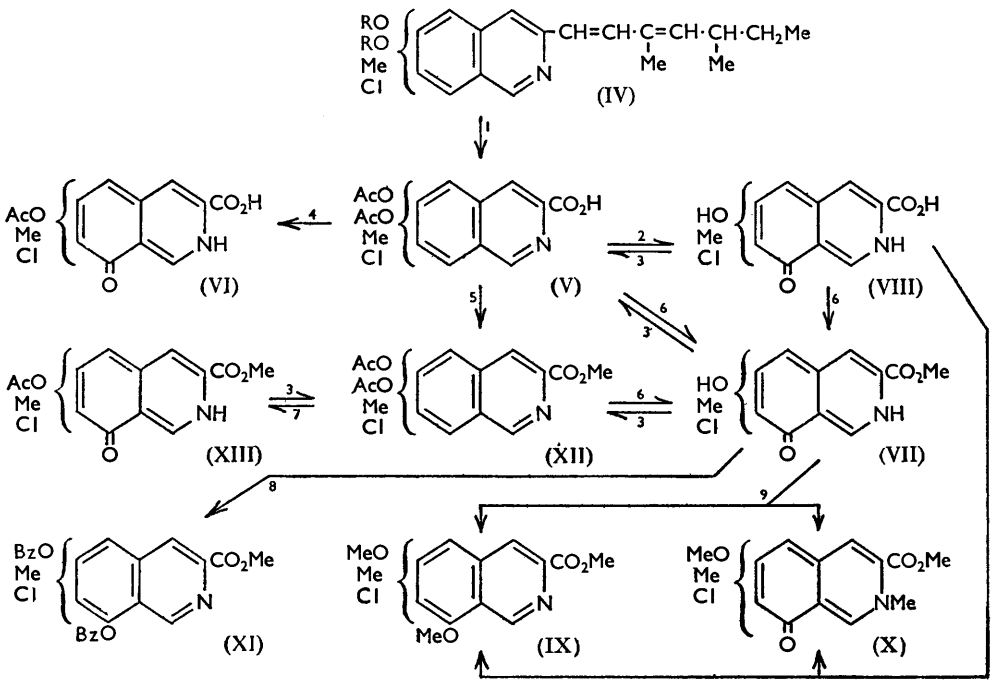


(II)



(III)

which must retain the *iso*quinolone nucleus of the precursor, forms a methyl ester and gives an intense red colour in alcohol with ferrous sulphate, indicating that the carboxyl group is conjugated with the aromatic residue and is in the *o*-position to the nitrogen atom,[5]



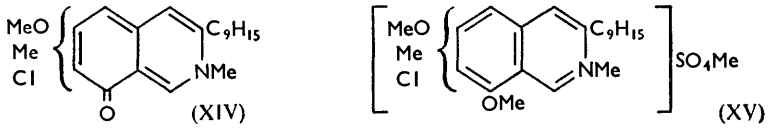
Reagents: 1, O_3. 2, NaOH. 3, Ac_2O–C_5H_5N. 4, NH_3. 5, CH_2N_2. 6, HCl–MeOH. 7, Chromatography. 8, BzCl–C_5H_5N. 9, MeI.

in agreement with previous hypotheses[1] concerning the nature of the progenitor of the nitrogen-containing ring in sclerotioramine. Consequently the partial formula (II; R = H) for *apo*sclerotioramine may be expanded to (IV; R = H), and di-*O*-acetyl*apo*-sclerotaminic acid and its methyl ester may be partially formulated as (V) and (XII)

[5] Ley, Schwarte, and Münnich, *Ber.*, 1924, **57**, 349.

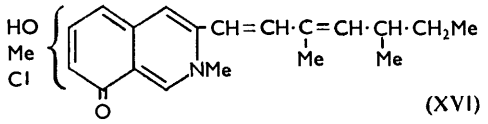
respectively. The infrared absorption spectra of di-*O*-acetyl*apo*sclerotaminic acid and its ester confirm their relationship: the acid (V) has a broad band at about 2500 cm.$^{-1}$ with separate peaks at 2558 and 2457 cm.$^{-1}$, without exhibiting absorption in the 3000 cm.$^{-1}$ region as would be expected if the acidity of di-*O*-acetyl*apo*sclerotaminic acid (V) was due to the presence of phenolic or enolic hydroxyl groups; the ester (XII) absorbs at 1783 (vs) (aromatic acetyl) and 1721 cm.$^{-1}$ (vs) (conjugated ester),[6] thereby confirming that the carboxyl group of (V) is attached directly to an aromatic nucleus. It follows that the conjugated-diene side-chain is also conjugated with the nucleus of *apo*sclerotioramine as in (IV) and hence probably with the nucleus of sclerotioramine.

On treatment with aqueous ammonia di-*O*-acetyl*apo*sclerotaminic acid (V) gives mono-*O*-acetyl*apo*sclerotaminic acid (VI), the composition of which together with the appearance of an additional band in the infrared spectrum at 1650 cm.$^{-1}$ are consistent with the hydrolysis of the *iso*quinolone acetyl residue attached to the oxygen atom of the hydroxyl group involved in the hydroxy*iso*quinoline–*iso*quinolone relationship (A), ·C(OH):Ċ·CH:N· ⇌ ·CO·Ċ:CH·NH·. Esterification of the acid (V) with methanol–hydrogen chloride is accompanied by deacetylation, giving rise to methyl *apo*sclerotaminate (VII) which on acetylation gives rise to the methyl di-*O*-acetyl*apo*sclerotaminate (XII). The ester (VII) is also obtained by deacetylation of the di-*O*-acetyl*apo*sclerotaminic acid (V) to *apo*sclerotaminic acid (VIII) followed by esterification with methanolic hydrogen chloride. When methyl di-*O*-acetyl*apo*sclerotaminate (XII) is allowed to remain in contact with aqueous solvents for several weeks or is chromatographed from methanol on aluminium oxide, one of the acetyl groups is removed by hydrolysis, giving methyl mono-*O*-acetyl*apo*sclerotaminate (XIII), which on acetylation regenerates the precursor (XII). From the fact that the product (XIII) exhibits a new infrared band at 1650 cm.$^{-1}$ (vinylogous amide) it is reasonably certain that the deacetylation involves only the acetoxy-group [7] of the hydroxy*iso*quinoline–*iso*quinolone relationship (A) above.

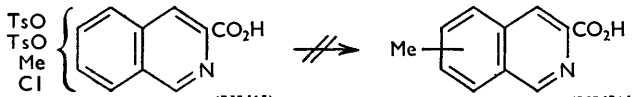


(XIV)

(XV)



(XVI)



(XVII) (XVIII)

(Ts = *p*-$C_6H_4Me·SO_2$)

Methylation of methyl *apo*sclerotaminate (VII) with methyl iodide and potassium carbonate gives the alkali-insoluble methyl di-*O*-methyl*apo*sclerotaminate (IX) as the chief product together with smaller amounts of the alkali-insoluble method *NO*-dimethyl-*apo*sclerotaminate (X). This simultaneous formation of *N*- and *O*-methyl ethers is an established characteristic of quinolones and *iso*quinolones.[8] Similarly, methylation of *apo*sclerotioramine sulphate with methyl iodide and potassium carbonate forms *NO*-dimethyl*apo*sclerotioramine (XIV), whilst methyl sulphate and potassium carbonate furnish *NOO*-trimethyl*apo*sclerotioramine methosulphate (XV). These products are

[6] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1956, p. 153.
[7] Gibson, Kynaston, and Lindsey, *J.*, 1955, 4340.
[8] Bogert and Seil, *J. Amer. Chem. Soc.*, 1907, **29**, 517.

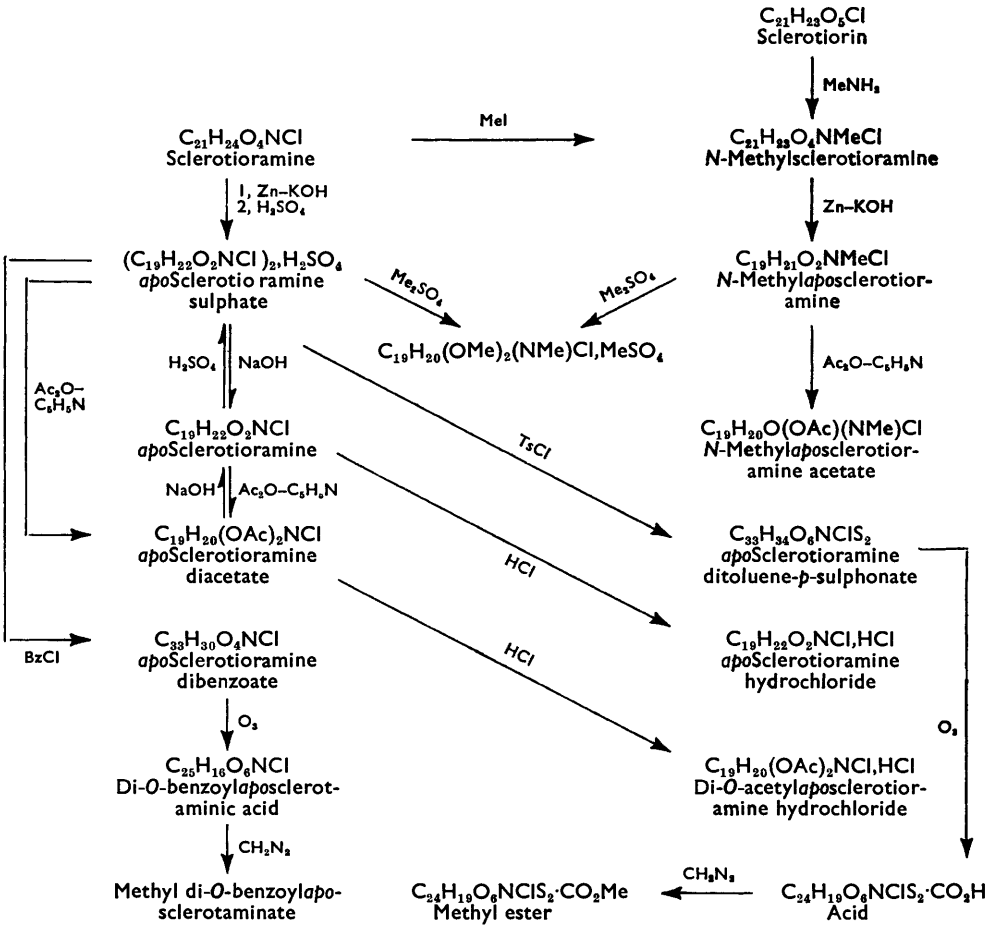
identical with the compounds obtained under similar conditions from *N*-methyl*apo*-sclerotioramine (XVI) (see below).

Benzoylation of *apo*sclerotioramine sulphate furnished the di-*O*-benzoate (IV; R = Bz), and on ozonolysis this product gave di-*O*-benzoyl*apo*sclerotaminic acid, which forms the methyl ester (XI), identical with the benzoylation product from methyl *apo*sclerotaminate (VII); this ester (XI) contains a *C*-methyl group, providing collateral evidence for the presence of this group in *apo*sclerotaminic acid and its derivatives. In agreement, a Kuhn–Roth estimation indicates the presence of three *C*-methyl residues in di-*O*-acetyl-*apo*sclerotaminic acid (V), *i.e.*, two from the acetyl groups and one in the nucleus.

Attempts to remove the halogen from *apo*sclerotaminic acid and its derivatives by a variety of methods failed: most of the starting material was always recovered.

*apo*Sclerotioramine (IV; R = H) gives a di-*O*-toluene-*p*-sulphonate (IV; R = *p*-$C_6H_4Me\cdot SO_2$) which is converted by ozonolysis into the di-*O*-toluene-*p*-sulphonate (XVII) of *apo*sclerotaminic acid, together with (+)-α-methylbutyraldehyde. Attempts to remove the halogen and toluene-*p*-sulphonyl residues by hydrogenation with Raney nickel,[9] (XVII) ⟶ (XVIII), were all unsuccessful. These reactions are summarised in Chart 1.

Chart 1.

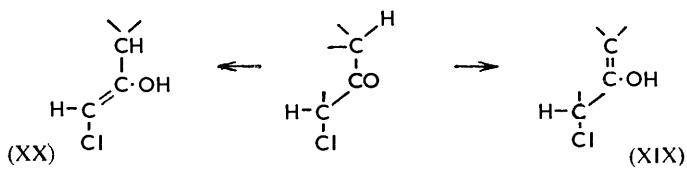


In experiments to determine whether *N*-methylsclerotioramine contains a lactone system, this compound, which is devoid of hydroxyl groups and is insoluble in aqueous

[9] Kenner and Murray, *J.*, 1950, 406; Cavillito and Haskell, *J. Amer. Chem. Soc.*, 1944, **66**, 1927.

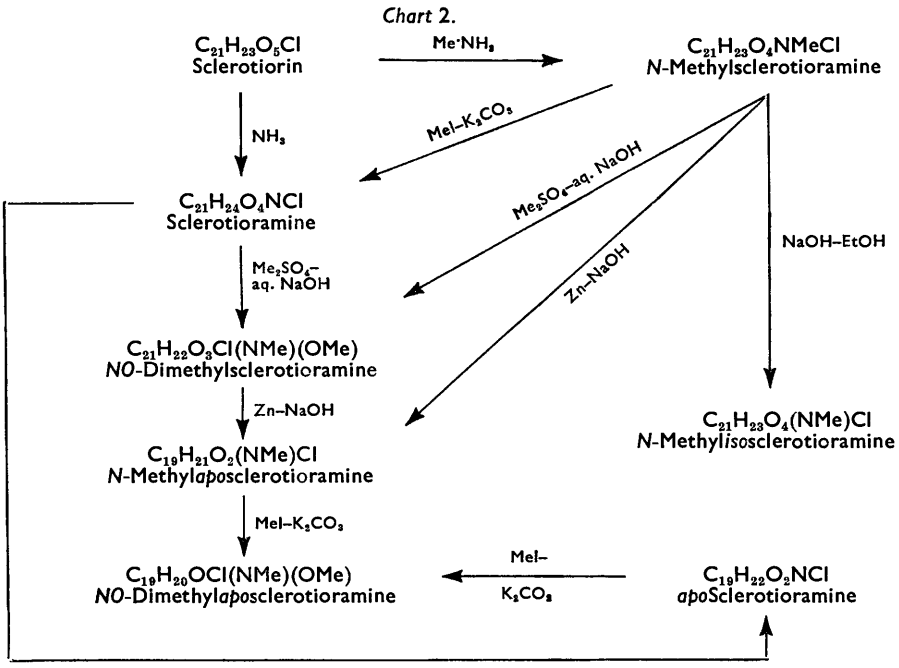
alkali, was dissolved in alcohol and treated with 2N-aqueous sodium hydroxide, giving a red solution. Dilution of this with water gave a somewhat unstable isomeride of the starting material, named *N*-methyl*iso*sclerotioramine, which exhibits strong absorption in the 3 μ region but has lost the carbonyl absorption at 1733 cm.$^{-1}$. Thus *N*-methyl*iso*-sclerotioramine is probably an enolic form of *N*-methylsclerotioramine, a view which is supported by formation of *NO*-dimethylsclerotioramine on methylation of sclerotioramine or of *N*-methylsclerotioramine with methyl sulphate and alkali. The infrared absorption at 1733—1745 cm.$^{-1}$ of, *inter alia*, sclerotiorin, dihydro- and tetrahydro-sclerotiorin, sclerotioramine, di- and tetra-hydrosclerotioramine, and *N*-methylsclerotioramine may be allocated provisionally to an α-chloro-ketone system,[10] and consequently the disappearance of this peak in *N*-methyl*iso*- and in *NO*-dimethyl-sclerotioramine may be attributed to enolisation of the type (XIX) or (XX).

Except in the *apo*-series all derivatives of sclerotiorin exhibit infrared absorption at 771—775 cm.$^{-1}$, which has been previously [1] assigned tentatively to the C–Cl stretching



frequency.[11] This absorption persists in *N*-methyl*iso*- and in *NO*-dimethyl-sclerotioramine (at 773 and 774 cm.$^{-1}$ respectively) and hence, if allocation of the absorption at 771—775 cm.$^{-1}$ is correct, it is likely that the enolisation proceeds by way of (XIX) rather than

Chart 2.



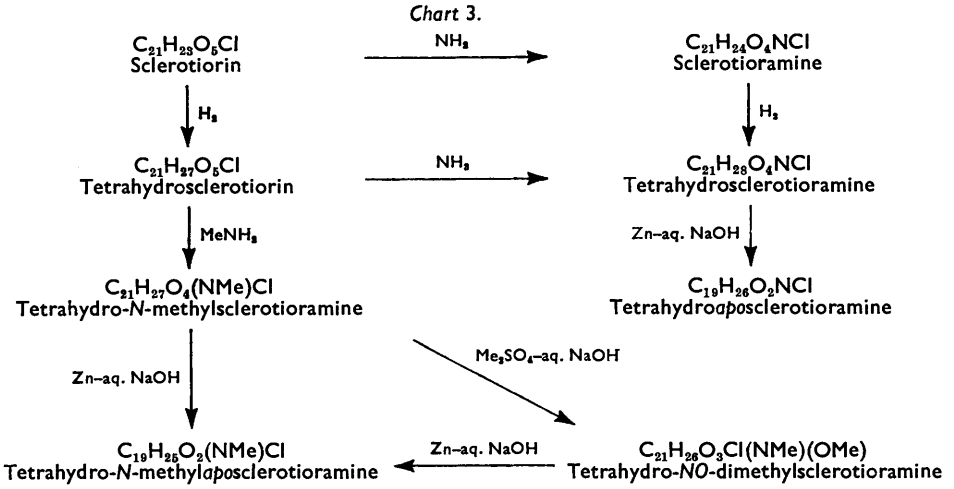
(XX), since in (XX) the C–Cl stretching frequency should undergo a considerable shift due to conjugation. Non-participation of the side-chain in this enolisation is shown by

[10] Ref. 6, p. 114.
[11] Ref. 6, p. 271.

(*a*) the formation of the analogous di- and tetra-hydro-*NO*-dimethylsclerotioramines from di- and tetra-hydrosclerotioramine respectively, (*b*) the production of 2 : 4-dimethylhexa-2-enaldehyde when *NO*-dimethylsclerotioramine is degraded with alkali, and (*c*) the reduction of both *N*-methyl- and *NO*-dimethyl-sclerotioramine with zinc–sodium hydroxide to give *N*-methyl*apo*sclerotioramine which is characterised as the monoacetate, $C_{22}H_{26}O_3NCl$. The formation of *NO*-dimethyl*apo*sclerotioramine (XIV) and of *NOO*-trimethyl*apo*sclerotioramine methosulphate (XV) from *apo*sclerotioramine and from *N*-methyl*apo*sclerotioramine provides additional evidence in support of the *iso*quinolone structures. These relations are summarised in charts 2 and 3.

On reduction with zinc and alkali tetrahydro-*N*-phenylsclerotioramine, which may be obtained from tetrahydrosclerotiorin [1] and aniline or by hydrogenation of *N*-phenylsclerotioramine, gave *N*-phenyl*apo*sclerotioramine.

Chart 3.



Experimental

O-*Acetylsclerotioramine*.—On being kept overnight a mixture of sclerotioramine (2 g.), acetic anhydride (20 ml.), and pyridine (0·5 g.) formed a deep red solution. After the removal of the excess of anhydride in a vacuum, the residue was dissolved in methanol (5 ml.) and slowly added to water (150 ml.), vigorously agitated. The precipitate was collected *immediately*, washed with water (150 ml.), and purified from methanol, giving O-*acetylsclerotioramine* in bright red needles (1·5 g.), m. p. 130° (Found: C, 63·6, 64·4; H, 6·3, 6·4; N, 3·4, 3·3. $C_{21}H_{23}O_3NCl{\cdot}OAc$ requires C, 64·0; H, 6·0; N, 3·2%). Very dilute acids, aqueous ammonia, or alkalis rapidly hydrolyse this acetate to sclerotioramine, m. p. and mixed m. p. 235° (decomp.).

N-*Methylsclerotioramine*.—Prepared from sclerotiorin and methylamine, this compound [1] was found to be dimorphous. Purification from aqueous solvents (*e.g.*, aqueous methanol) gave the base in purple needles, m. p. 225° (decomp.), whilst non-aqueous solvents (*e.g.*, alcohol) afforded red needles, m. p. 225° (decomp.) (Found: C, 65·8; H, 6·7. Calc. for $C_{22}H_{26}O_4NCl$: C, 65·4; H, 6·5%). A mixture of the two modifications had m. p. 225° and had identical infrared absorption spectra; the m. p. of the compound depended to some extent on the rate of heating.

Sclerotioramine [1] (1 g.) was methylated in boiling acetone (25 ml.) with potassium carbonate (5 g.) and methyl iodide (4 ml.) for 2 hrs. Repeated crystallisation of the product from aqueous methanol gave *N*-methylsclerotioramine in purple needles (0·9 g.), m. p. and mixed m. p. 218° (decomp.) (Found: C, 65·2; H, 6·2; N, 3·4; OMe, 0. Calc. for $C_{22}H_{26}O_4NCl$: C, 65·4; H, 6·5; N, 3·4%). Methylation of sclerotioramine (0·5 g.) by methyl sulphate–potassium carbonate for 45 min. gave *N*-methylsclerotioramine in purple needles (0·3 g.), m. p. and mixed

m. p. 218° (decomp.) after repeated crystallisation from aqueous methanol. The identity of the products obtained by the three methods was confirmed by comparison of their infrared absorption spectra.

Degradation of Sclerotioramine with Alkali or Acid.—When a solution of sclerotioramine (24 g.) in 10% aqueous sodium hydroxide (250 ml.) was heated under reflux in nitrogen for 3 hr., alkaline gas was not evolved. The cooled mixture was acidified with 2N-sulphuric acid, treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate, and distilled until a sample of the distillate was not acidic; the volume of liquid in the distilling flask was maintained by the addition of distilled water as required. After neutralisation with 2N-aqueous sodium hydroxide the distillate was evaporated, leaving colourless salts (8·5 g.), containing sodium acetate which on treatment with *o*-phenylenediamine in the usual manner gave 2-methylbenziminazole (3·3 g.), m. p. and mixed m. p. 172—174°.

The yellow solution formed by heating sclerotioramine (10 g.) with boiling 5N-sulphuric acid (250 ml.) for 32 hr. was decanted from a black solid, treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate to remove carbonyl compounds, and distilled, with the addition of water as required, until the distillate was neutral. Evaporation of the neutralised distillate and treatment of the residual salts (2·7 g.) with *o*-phenylenediamine in the usual manner gave 2-methylbenziminazole (0·1 g.), m. p. and mixed m. p. 174°.

apo*Sclerotioramine*.—When a solution of sclerotioramine (10 g.) in 2N-aqueous sodium hydroxide (150 ml.) was shaken with zinc dust (10 g.) for 15 min. the initial red colour changed to yellow; 5 min. later the mixture was filtered through a plug of glass wool into an excess of 2N-sulphuric acid at about 0°. The precipitated yellow solid was quickly isolated and purified by crystallisation from aqueous alcohol, giving apo*sclerotioramine sulphate* in bright yellow needles (*ca.* 5 g.) which did not melt but slowly decomposed at above 180° [Found: C, 58·8; H, 6·2; N, 3·2; Cl, 10·9. $(C_{19}H_{22}O_2NCl)_2,H_2SO_4$ requires C, 59·8; H, 6·0; N, 3·7; Cl, 9·3%]. The sulphate, which gave a positive test for sulphate ion, readily dissolved in 2N-aqueous sodium hydroxide, giving a yellow solution from which 2N-sulphuric acid reprecipitated the parent salt. 2N-Aqueous sodium hydroxide was added to a suspension of the sulphate (2 g.) in water (15 ml.) until a clear solution was formed. A stream of carbon dioxide then precipitated a brown solid which was collected, washed, and purified from methanol or alcohol, giving apo*sclerotioramine* in pale orange plates (0·8 g.), m. p. 237—238° (decomp.) (Found: C, 67·9; H, 6·6. $C_{19}H_{22}O_2NCl$ requires C, 68·7; H, 6·6%). This compound, which is soluble in the usual organic solvents and does not form a picrate, readily forms a yellow solution in 2N-aqueous sodium hydroxide which does not react with benzenediazonium chloride. Ozonolysis of *apo*-sclerotioramine under a variety of conditions gave (+)-α-methylbutyraldehyde (isolated and characterised as the 2 : 4-dinitrophenylhydrazone) as the only product.

Acidification of a solution of *apo*sclerotioramine (0·2 g.) in 2N-aqueous sodium hydroxide (10 ml.) with 2N-hydrochloric acid gave a bright yellow precipitate of apo*sclerotioramine hydrochloride* which separated from alcohol in yellow-green needles, m. p. 262° (decomp.) (Found: C, 60·3; H, 6·4; N, 3·8; Cl, 18·3. $C_{19}H_{22}O_2NCl,HCl$ requires C, 61·9; H, 6·3; N, 3·8; Cl, 19·3%). Prepared in a similar manner from the free base, the sulphate was identical with that obtained directly in the reduction of sclerotioramine.

Estimation of the Acids Produced by the Reductive Alkaline Degradation of Sclerotioramine.—All reagents employed in the following experiments on evaluations of the amount of acetic acid produced in the decomposition of sclerotioramine with zinc dust and alkali gave negative tests for chloride ions.

Sclerotioramine (23 g.) was reduced with zinc and alkali by the standard procedure and on isolation the solid product was acetylated, giving di-*O*-acetyl*apo*sclerotioramine (12 g.), m. p. and mixed m. p. 154°. The clear, aqueous acidic liquors were distilled from a large flask with an anti-splash device until the distillate was neutral to litmus (3 days); the volume of solution was maintained by intermittent addition of distilled water. A sample of the distillate, which had the smell of acetic acid and did not give a precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate, gave a copious white precipitate with silver nitrate–nitric acid. After neutralisation with aqueous sodium hydroxide (phenolphthalein) the main fraction of the distillate (*ca.* 5 l.) was evaporated on a steam-bath and the residue dried to constant weight (11·8 g.).

From trial experiments it became obvious that the salts contained sodium carbonate and sodium chloride and that the estimation and identification of the acetic acid as 2-methylbenziminazole was to some extent dependent on the concentration of the contaminants.

Consequently a number of comparative blank tests were performed with the object of defining the limits of accuracy of this estimation. The results are listed in the Table.

Na acetate and added salts	Crude yield (g.) and m. p.	Once crystallised yield (g.), m. p.	Twice crystallised yield (g.), m. p.
NaOAc (1 g.)	0·439 166—173°	0·305 170—174°	0·250 174—176°
NaOAc (1 g.) K_2CO_3 (1 g.)	0·364 172—174°	0·218 176—178°	0·126 176—178°
NaOAc (1 g.) Na_2CO_3 (1 g.) NaCl (1 g.)	0·465 150—154°	0·251 174—176°	0·177 175—176°
NaOAc (0·5 g.) Na_2CO_3 (1 g.) NaCl (0·5 g.)	0·60 90—100°	0·124 173—176°	0·080 175—176°

The following conditions were employed. A mixture of sodium acetate (1 g.), *o*-phenylenediamine (1·5 g.), added salts if any, concentrated hydrochloric acid (10 ml.), and distilled water (10 ml.) was heated under reflux for 1 hr., cooled, neutralised with ammonia (*d* 0·88), and cooled to −5°. The product which separated was purified by being twice crystallised from the minimum of hot water. On the basis of the tabulated results the extreme values for the yield of once recrystallised 2-methylbenziminazole from 1 g. of sodium acetate is 0·218—0·305 g. The same conditions were used for the preparation of 2-methylbenziminazole from the mixed sodium salts derived from sclerotioramine and the weight of mixed amounts of contaminants adjusted so that the mixture contained approximately 1 g. of sodium acetate, giving the following results:

Salts (g.)	Crude yield (g.)	Once crystallised yield (g.), m. p.	Twice crystallised yield (g.), m. p.
2·602	0·498	0·253, 176—177°	0·19, 175—176°
2·156	0·390	0·214, 175—177°	0·135, 176—177°

The number of mols. of acetic acid produced per mol. of sclerotioramine was calculated as follows: 1 mol. of sodium acetate being assumed to be produced per mol. of sclerotioramine, the wt. of sodium acetate formed would be 4·81 g. per 23 g. of sclerotioramine. The wt. of sodium acetate in the mixed salts is:

$$\frac{\text{yield of 2-methylbenziminazole from salts}}{\text{yield of 2-methylbenziminazole from 1 g. of NaOAc in standard mixture}} = A$$

Therefore, no. of mol. of sodium acetate formed is:

$$\frac{A\ (\text{total wt. of salts})}{\text{Wt. of salts taken for preparation of 2-methylbenziminazole}} \times \frac{1}{4{\cdot}81}$$

For the product once crystallised the extreme values of 0·78—1·14 mol. of sodium acetate per mol. of sclerotioramine were obtained.

The 2-methylbenziminazole obtained was identical with an authentic specimen [confirmed by conversion into the picrate, m. p. and mixed m. p. 211—213° (decomp.)].

Di-O-*acetyl*apo*sclerotioramine*.—A mixture of *apo*sclerotioramine (0·5 g.), acetic anhydride (10 ml.), and pyridine (6 drops) rapidly became homogeneous and 48 hr. later the solution was poured on ice (50 g.). Purified from alcohol, the solid gave *di*-O-*acetyl*apo*sclerotioramine* in needles (0·5 g.), m. p. 154°, which darkened slowly on being kept, were insoluble in cold 2N-aqueous sodium hydroxide, and had $[\alpha]_D^{20}$ +10·6° [Found: C, 66·7, 66·4; H, 6·3, 6·5; N, 3·4; Cl, 8·8; OAc, 20·5%; *M* (Menzies–Wright), 407, 422. $C_{19}H_{20}NCl(OAc)_2$ requires C, 66·3; H, 6·3; N, 3·4; Cl, 8·5%; *M*, 415·5]. An alcoholic solution of this acetate exhibits an intense violet fluorescence. The same diacetate (13 g.), m. p. and mixed m. p. 153—154°, was obtained when a solution from *apo*sclerotioramine sulphate (from 20 g. of sclerotioramine), acetic anhydride (200 ml.), and pyridine (15 ml.) was kept for 23 hr. and poured into water (500 ml.) with stirring.

When di-*O*-acetyl*apo*sclerotioramine (0·1 g.) was warmed for 1 hr. with 2N-alcoholic sodium hydroxide and the cooled solution acidified with 2N-sulphuric acid an orange precipitate separated which on purification from alcohol gave *apo*sclerotioramine sulphate (0·1 g.) in yellow needles, identical with an authentic specimen. Heating on the steam-bath with methanol (10 ml.) and hydrochloric acid (3 ml.), followed by evaporation of the yellow solution, converted

the diacetate (1 g.) into *di*-O-*acetyl*apo*sclerotioramine hydrochloride*, yellow needles (0·95 g.), m. p. 244—245° [Found: C, 61·1; H, 6·3; Cl, (ionic), 9·0; Cl (total), 17·7. $C_{19}H_{20}NCl(OAc)_2$,HCl requires C, 61·2; H, 6·0; Cl, (ionic), 8·0; Cl (total), 15·8%].

Dihydrosclerotioramine.—After addition of aqueous ammonia (5 ml.; *d* 0·88) to dihydrosclerotiorin [1] (1 g.) in methanol (20 ml.) the mixture was kept for 20 min. and poured into stirred 2N-sulphuric acid (250 ml.). Purified from methanol, the precipitate gave *dihydrosclerotioramine* in orange needles (0·85 g.), m. p. 171—172° (decomp.) (Found: C, 64·6; H, 7·0; N, 3·4. $C_{21}H_{26}O_4NCl$ requires C, 64·6; H, 6·6; N, 3·6%). This compound is readily soluble in cold 2N-aqueous sodium hydroxide from which it is precipitated unchanged.

Di-O-*acetyldihydro*apo*sclerotioramine.*—A solution of dihydrosclerotioramine (1·6 g.) in 2N-aqueous sodium hydroxide (100 ml.), containing zinc dust (2 g.), was shaken until the originally red solution had become colourless; it was then filtered through glass wool into 2N-sulphuric acid (200 ml.) at 0°. On acetylation by pyridine–acetic anhydride at room temperature for 12 hr., the crude precipitate gave *di*-O-*acetyldihydro*apo*sclerotioramine*, forming needles (0·8 g.) from aqueous alcohol which melted at 70°, resolidified at *ca.* 76°, and then melted at 140—146° (Found: C, 66·0; H, 6·4; N, 3·3; Cl, 9·1; OAc, 20·3; OMe, 0. $C_{23}H_{28}O_4NCl$ requires C, 66·1; H, 6·7; N, 3·4; Cl, 8·5; OAc, 20·60%).

Tetrahydrosclerotioramine.—A solution of sclerotioramine (2 g.) in acetic acid (50 ml.) was hydrogenated with a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) and the experiment interrupted after 32 min. when approximately 3 mols. of hydrogen had been absorbed. Purification of the product from aqueous alcohol gave *tetrahydrosclerotioramine* in orange prisms (0·2 g.), m. p. 185° (decomp.) (Found: C, 64·3; H, 7·1; N, 3·5; Cl, 10·1. $C_{21}H_{28}O_4NCl$ requires C, 64·4; H, 7·2; N, 3·6; Cl, 9·0%).

Tetrahydrosclerotiorin (m. p. 143—144°) (0·5 g.) slowly formed an orange-red solution in aqueous ammonia (20 ml.; *d* 0·88) and water (20 ml.), and on acidification with excess of hydrochloric acid this furnished a precipitate which, on purification from aqueous alcohol, gave tetrahydrosclerotioramine in orange prisms (0·3 g.), m. p. and mixed m. p. 186° (decomp.) (Found: C, 63·7; H, 7·1; N, 3·4; Cl, 10·0%). Tetrahydrosclerotioramine, which readily forms orange-red solutions in 2N-aqueous sodium hydrogen carbonate, has a negative ferric reaction in alcohol.

Di-O-*acetyltetrahydro*apo*sclerotioramine.*—(*a*) Reduction of tetrahydrosclerotioramine (0·5 g.) in acetic acid (15 ml.) with zinc dust (1 g.) gave *tetrahydro*apo*sclerotioramine* which separated from alcohol in golden prisms (0·35 g.), m. p. 196° (Found: C, 67·9, 67·6; H, 7·8, 7·8. $C_{19}H_{26}O_2NCl$ requires C, 68·0; H, 7·8%). Prepared by the acetic anhydride–pyridine method at room temperature for 12 hr., *di*-O-*acetyltetrahydro*apo*sclerotioramine* formed needles, m. p. 48°, from alcohol (Found: C, 66·0; H, 7·3. $C_{23}H_{30}O_4NCl$ requires C, 65·8; H, 7·2%).

(*b*) A solution tetrahydrosclerotioramine (1 g.) in acetic acid (50 ml.), containing a palladium–charcoal catalyst (from 1 g. of charcoal and 0·15 g. of palladium chloride), was agitated in hydrogen for 10 hr. Crystallised from alcohol the product gave tetrahydro*apo*sclerotioramine (0·15 g.), m. p. and mixed m. p. 196°. The remainder of the product was an intractable gum.

(*c*) Hydrogenation of tetrahydrosclerotioramine (1 g.) with platinum oxide (50 mg.) in alcohol (100 ml.) during 2 hr. gave tetrahydro*apo*sclerotioramine (0·1 g.), m. p. and mixed m. p. 196°.

Ozonolysis of Di-O-*acetyl*apo*sclerotioramine.*—A slow stream of ozone and oxygen was passed into a solution of the di-*O*-acetate (4 g.) in ethyl acetate at room temperature for 5 hr., the solvent was removed in a vacuum, and water (20 ml.) was added to the residue. Next day the aqueous liquor was decanted and the solid was purified from alcohol and dioxan, giving *di*-O-*acetyl*apo*sclerotaminic* acid in needles (1 g.), m. p. 243—245° (decomp.), $[\alpha]_D^{21}$ 0° [Found: C, 53·6; H, 3·8; N, 4·0; Cl, 10·0; OAc, 25·8; *C*-Me, 13·0. $C_9H_2NCl(Me)(OAc)_2{\cdot}CO_2H$ requires C, 53·4; H, 3·6; N, 4·2; Cl, 10·5; OAc, 25·5; *C*-Me, 13·3%]. This acid is very sparingly soluble in alcohol and dioxan, insoluble in 2N-aqueous sodium carbonate or 2N-hydrochloric acid, and readily soluble in 2N-aqueous sodium hydroxide or in concentrated hydrochloric acid to give a yellow solution. It does not react with Brady's reagent and has a negative ferric reaction in alcohol, but on the addition of a little solid ferrous sulphate gives a bright red colour in this solvent.

The aqueous liquor from the decomposition of the ozonide (from 12 g. of amine) was mixed with an excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate and next day the yellow precipitate was collected, dried, and purified by chromatography from alcohol on neutralised

aluminium oxide, giving (+)-α-methylbutyraldehyde 2 : 4-dinitrophenylhydrazone (0·7 g.), m. p. and mixed m. p. 132°. Admixed with the 2 : 4-dinitrophenylhydrazone of acetone, it had m. p. *ca.* 100°.

*Methyl Di-O-acetyl*apo*sclerotaminate*.—When excess of ethereal diazomethane was added to a suspension of di-*O*-acetyl*apo*sclerotaminic acid (2 g.) in methanol (40 ml.) a clear solution formed in 15 min. After the decomposition of the excess of reagent with acetic acid the solution was evaporated, the residue neutralised with 2N-aqueous sodium hydrogen carbonate, and the precipitate purified from methanol, giving the *methyl di-O-acetyl*apo*sclerotaminate* in needles (1·5 g.), m. p. 185° [Found: C, 54·5, 54·3; H, 4·5, 4·2; N, 3·9; Cl, 11·8; OMe, 8·6. 8·5; OAc, 23·6. $C_{11}H_5ONCl(OMe)(OAc)_2$ requires C, 54·4; H, 4·0; N, 4·0; Cl, 10·1; OMe, 8·8; OAc, 24·5%]. This ester has a negative ferric or ferrous sulphate reaction in alcohol and is insoluble in 2N-aqueous sodium hydroxide. Chromatography of this ester from methanol on neutralised alumina gave *methyl O-acetyl*apo*sclerotaminate*, forming almost colourless needles, m. p. 213—216° (decomp.), from methanol [Found: C, 54·9; H, 4·5; N, 4·5; Cl, 11·5; OAc, 13·8. $C_{12}H_9O_3NCl(OAc)$ requires C, 54·3; H, 3·9; N, 4·5; Cl, 11·4; OAc, 13·9%]. The same monoacetate of the ester (with an identical infrared absorption spectrum) separated when the parent methyl di-*O*-acetyl*apo*sclerotaminate was allowed to crystallise slowly from much aqueous methanol during 1—2 weeks. Admixed with the diacetate of the ester it had m. p. *ca.* 166—190° (decomp.) and on acetylation with pyridine–acetic anhydride at room temperature for 46 hr. quantitatively regenerated the diacetate of the methyl ester, forming needles, m. p. and mixed m. p. 182°, from methanol.

Aqueous ammonia solution (13 ml.; *d* 0·88) was added to di-*O*-acetyl*apo*sclerotaminic acid (1 g.) suspended in warm alcohol (15 ml.), and the resultant pale brown solution evaporated in a vacuum to a volume of *ca.* 5 ml. On being kept at 0° overnight, this deposited a semicrystalline ammonium salt (0·45 g.) which on dissolution in acetic acid (2 ml.) gave *O-acetyl*apo*sclerotaminic acid* in fawn-coloured prisms (0·4 g.), m. p. 280° (decomp.) with darkening from 230° [Found: C, 50·6; H, 4·0; N, 4·1; Cl, 11·1; OAc, 17·0. $C_{11}H_7O_3NCl(OAc),H_2O$ requires C, 50·0; H, 3·8; N, 4·5: Cl, 11·30; OAc, 13·7%].

Methyl apo*Sclerotaminate*.—A solution of di-*O*-acetyl*apo*sclerotaminic acid (2 g.) in methanol (200 ml.) and concentrated hydrochloric acid (10 ml.) was evaporated on the steam-bath to 50 ml., mixed with methanol (140 ml.) and concentrated hydrochloric acid (10 ml.), and again evaporated to 50 ml. Next day the crystalline product was purified from methanol, furnishing *methyl* apo*sclerotaminate* in yellow needles (1·2 g.), m. p. 244—245° (decomp.), insoluble in cold 2N-aqueous sodium hydroxide or in hot water [Found: N, 4·6; OMe, 9·9. $C_{11}H_7O_3NCl$·OMe requires N, 5·3; OMe, 11·6%]. Acetylation of this ester with pyridine–acetic anhydride at room temperature gave methyl di-*O*-acetyl*apo*sclerotaminate in needles, m. p. and mixed m. p. 185°, further identified by comparison of the infrared spectra (Found: C, 54·6; H, 4·1; N, 3·9. Calc. for $C_{16}H_{14}O_6NCl$: C, 54·4; H, 4·0; N, 4·0%).

A solution of di-*O*-acetyl*apo*sclerotaminic acid (0·5 g.) in 5% methanolic potassium hydroxide (20 ml.) was heated under reflux for 1 hr., cooled, and saturated with hydrogen chloride at 0°. After the removal of the inorganic salts the solution was concentrated to yield methyl *apo*sclerotaminate (0·25 g.) which separated from methanol in yellow needles, m. p. and mixed m. p. 245° (decomp.), having the requisite infrared spectrum.

apo*Sclerotaminic Acid*.—A solution of di-*O*-acetyl*apo*sclerotaminic acid (1·1 g.) in 2N-aqueous sodium hydroxide (75 ml.) was warmed on the steam-bath for 1 hr., cooled, and acidified with hydrochloric acid. Next day the semicrystalline product was collected and purified from methanol or dioxan, giving *apo*sclerotaminic acid in yellow needles, m. p. >300°, readily soluble in 2N-aqueous sodium hydrogen carbonate. By pyridine–acetic anhydride this was converted quantitatively into di-*O*-acetyl*apo*sclerotaminic acid, m. p. and mixed m. p. 242—243° (decomp.).

Methylation of Methyl apo*Sclerotaminate*.—Methylation of this ester (1·5 g.) (or of *apo*sclerotaminic acid, 0·5 g.) with methyl iodide (4 ml.) and potassium carbonate (5 g.) in boiling acetone (20 ml.) for 4 hr. gave *methyl* NO-*dimethyl*apo*sclerotaminate* which, on repeated purification from methanol, formed yellow needles (0·1 g.), m. p. 224° [Found: C, 57·1; H, 5·2; OMe, 21·2. $C_{12}H_8O_2NCl(OMe)_2$ requires C, 56·9; H, 4·7; OMe, 21·0%]. Dilution of the methanolic mother-liquors with water furnished a semi-crystalline product which on repeated purification from methanol furnished *methyl di-O-methyl*apo*sclerotaminate* in needles (0·25 g.), m. p. 168° [Found: C, 56·9; H, 4·5; N, 4·7; Cl, 12·0; OMe, 30·8. $C_{11}H_5ONCl(OMe)_3$ requires C, 56·9; H, 4·7; N, 4·7; Cl, 11·7; OMe, 31·5%].

NO-*Dimethyl*apo*sclerotioramine*.—Methylation of *apo*sclerotioramine sulphate (1 g.) with potassium carbonate (5 g.) and methyl iodide (4 ml.) in boiling acetone (25 ml.) for 1 hr. gave a gum which was purified by chromatography from benzene on neutralised aluminium oxide. After elution with benzene had removed a dark band from the column, elution with methanol gave NO-*dimethyl*apo*sclerotioramine* which formed yellow needles (0·1 g.), m. p. 246° (decomp.), from methanol [Found: C, 70·8; H, 7·2; N, 3·8; OMe, 8·6. $C_{19}H_{20}OCl(OMe)(NMe)$ requires C, 70·2; H, 7·1; N, 3·8; OMe, 8·6%].

NOO-*Trimethyl*apo*sclerotioramine Methosulphate*.—Methylation of *apo*sclerotioramine sulphate (2 g.) with potassium carbonate (5 g.) and methyl sulphate (2 g.) in boiling acetone (150 ml.) for 20 min. gave NOO-*trimethyl*apo*sclerotioramine methosulphate* which separated from benzene in pale yellow needles (1·2 g.), m. p. 212° (decomp.) [Found: C, 57·2; H, 6·5; N, 2·8; Cl, 7·2; OMe, 17·2. $C_{19}H_{20}Cl(NMe)(OMe)_2,MeSO_4$ requires C, 57·0; H, 6·6; N, 2·9; Cl, 7·3; OMe, 19·2%]; this product gives a positive test for sulphur.

*Ozonolysis of Di-*O*-benzoyl*apo*sclerotioramine*.—Benzoyl chloride (10 ml.) was added gradually to a well shaken solution of *apo*sclerotioramine (4·8 g.) in pyridine (20 ml.) at 0°, and the mixture was kept at room temperature for 4 hr., then poured into ice-water (150 g.). Purified from methanol–benzene, the product gave *di*-O-*benzoyl*apo*sclerotioramine* in needles (3·8 g.), m. p. 181°, $[\alpha]_D^{21}$ +19·3°, insoluble in 2N-aqueous sodium hydroxide or 2N-hydrochloric acid (Found: C, 73·7, 73·2; H, 5·7, 5·7; N, 2·5; Cl, 6·8, 6·8. $C_{33}H_{30}O_4NCl$ requires C, 73·4: H, 5·6; N, 2·6; Cl, 6·6%).

A stream of ozone and oxygen was passed into a solution of this dibenzoate (2·3 g.) in ethyl acetate (150 ml.) for 4 hr., the solvent was removed in a vacuum, and water (25 ml.) was added to the residue. Purification of the resulting solid from alcohol gave *di*-O-*benzoyl*apo*sclerotaminic acid*, m. p. 212—214° (decomp.) (Found: Cl, 8·1; *C*-Me, 0·9. $C_{25}H_{16}O_6NCl$ requires Cl, 7·7; *C*-Me, 3·1%).

*Ozonolysis of the Di-*O*-toluene*-p-*sulphonate of* apo*Sclerotioramine*.—Toluene-*p*-sulphonyl chloride (40 g.) was added to a solution of *apo*sclerotioramine sulphate (15 g.) in pyridine (100 ml.) at 0° and ½ hr. later the mixture was heated on the steam-bath for 15 min. and then poured, with stirring, into water. Repeated crystallisation of the solid from ethanol and then benzene–methanol gave the *di*-O-*toluene*-p-*sulphonate* of *apo*sclerotioramine in needles (12 g.), m. p. 153°, $[\alpha]_D^{21}$ +33°, readily forming a yellow solution in concentrated hydrochloric acid from which it was precipitated unchanged on dilution with water (Found: C, 62·1; H, 5·9; N, 2·0; Cl, 5·7. $C_{33}H_{34}O_6NClS_2$ requires C, 62·0; H, 5·4; N, 2·2; Cl, 5·5%).

A stream of ozone and oxygen was passed into a solution of this di-*O*-toluene-*p*-sulphonate (2 g.) in ethyl acetate (150 ml.) at room temperature for 4 hr. Decomposition of the ozonide with water (20 ml.) for 12 hr. followed by purification of the product from alcohol gave the *di*-O-*toluene*-p-*sulphonate* of *apo*sclerotaminic acid in plates (0·6 g.), m. p. 217° (decomp.), $[\alpha]_D^{22}$ 0° (Found: C, 53·3, 53·6, 53·5; H, 4·2, 3·9, 3·8; N, 2·5; Cl, 6·0, 6·0. $C_{25}H_{20}NClO_8S_2$ requires C, 53·4; H, 3·6; N, 2·5; Cl, 6·5%). The aqueous solution from the decomposition of the ozonide furnished (+)-α-methylbutyraldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 129°.

The foregoing acid (2 g.) suspended in methanol (50 ml.) was esterified with diazomethane, and the excess of reagent decomposed with acetic acid. After the removal of a little acidic material with 2N-aqueous sodium hydrogen carbonate the resulting *methyl ester* separated from methanol in prisms (1·4 g.), m. p. 158° (Found: C, 54·0, 54·6; H, 4·0, 4·0; N, 2·5; Cl, 5·7; OMe, 5·2. $C_{25}H_{19}NClO_7S_2$·OMe requires C, 54·2; H, 3·5; N, 2·4; Cl, 6·2; OMe, 5·4%). When this ester was heated with Raney nickel (W.4 grade) in boiling methanol the only product recovered was varying amounts of unchanged starting material.

A solution of di-*O*-toluene-*p*-sulphonate (1·2 g.) of *apo*sclerotaminic acid in methanol (50 ml.) containing Raney nickel (6 g. of W.4 grade) was boiled for 3 hr., filtered, and evaporated, leaving a pale green solid (0·5 g.). Purification of this by chromatography from benzene on neutralised aluminium oxide furnished a *complex* which separated from benzene in pale green needles (0·2 g.), m. p. >300°, insoluble in 2N-aqueous sodium hydroxide or 2N-hydrochloric acid, containing nickel and giving a positive test for sulphur [Found: C, 50·6; H, 3·8; N, 3·1; Cl, 6·7. $(C_{25}H_{19}NClO_8S_2)_2Ni$ requires C, 50·9; H, 3·2; N, 2·4; Cl, 6·0%].

N-*Methyl*iso*sclerotioramine*.—Addition of water to the dark violet solution formed by adding 2N-aqueous sodium hydroxide (5 ml.) to *N*-methylsclerotioramine (1 g.), dissolved in the minimum volume of alcohol, gave a violet precipitate which on purification from aqueous

methanol furnished N-*methyl*iso*sclerotioramine* in violet needles (0·5 g.), m. p. 120—125° (decomp.) (Found: C, 66·2; H, 6·8; N, 3·6; Cl, 9·3. $C_{22}H_{26}O_4NCl$ requires C, 65·4; H, 6·5; N, 3·5; Cl, 8·8%). When *N*-methylsclerotioramine was boiled with 30% sodium aqueous hydroxide solution for 3 days or with 50% sulphuric acid for 2 days, extensive decomposition occurred, but methylamine was not liberated.

NO-*Dimethylsclerotioramine* (with H. PAGE).—Methyl sulphate (2·5 ml.) was added gradually in 10 min. to an agitated solution of sclerotioramine (1 g.) in 2N-aqueous sodium hydroxide (50 ml.) at 0° and 15 min. later a deep red oil (which became solid 24 hr. later at −5°) separated from the alkaline solution. Purification of this solid by chromatography from methanol on neutral aluminium oxide furnished NO-*dimethylsclerotioramine* in purple plates (0·1 g.), m. p. 223° [Found: C, 66·5, 66·4; H, 6·9, 6·8; N, 3·7, 3·4; Cl, 8·9; OMe, 8·3, 8·0; *N*-Me, 6·0. $C_{21}H_{22}O_3Cl(NMe)(OMe)$ requires C, 66·1; H, 6·7; N, 3·4; Cl, 8·5; OMe, 7·4; *N*-Me, 7·0%]. Numerous variations of the reaction conditions failed to increase the yield of this product. Methylated by the same method, *N*-methylsclerotioramine (1 g.) gave *NO*-dimethylsclerotioramine, forming purple plates (0·15 g.) from methanol, m. p. and mixed m. p. 218°.

Tetrahydro-NO-*dimethylsclerotioramine.*—On dropwise addition of methyl sulphate (2 ml.) to a vigorously agitated solution of tetrahydrosclerotioramine (1 g.) in 2N-aqueous sodium hydroxide (50 ml.) at 0° in 10 min. an orange oil separated which solidified at 0° in 48 hr. and was then purified by chromatography from alcohol on neutral aluminium oxide, giving *tetrahydro*-NO-*dimethylsclerotioramine.* This crystallised from alcohol in orange-red plates (0·25 g.), m. p. 188° (Found: C, 66·1; H, 7·9; OMe, 8·0. $C_{22}H_{29}O_3NCl{\cdot}OMe$ requires C, 65·6; H, 7·7; OMe, 7·4%).

N-*Methyl*apo*sclerotioramine.*—Sufficient alcohol was added to *N*-methylsclerotioramine (2 g.) suspended in 2N-aqueous sodium hydroxide (10 ml.) to form a solution. Zinc dust (3 g.) was then introduced and the mixture shaken for about 10 min., until the initial purple colour changed to pale yellow, and then filtered into an excess of 2N-sulphuric acid at 0°. The dried precipitate was acetylated by pyridine–acetic anhydride at room temperature, giving O-*acetyl*-N-*methyl*apo*sclerotioramine* which separated from alcohol in pale yellow needles (1 g.), m. p. 230° (Found: C, 67·0; H, 6·7; N, 3·5; Cl, 9·4. $C_{22}H_{26}O_3NCl$ requires C, 67·0; H, 6·7; N, 3·6; Cl, 9·2%). The following method was somewhat more convenient for this preparation. On the addition of zinc dust (3 g.) to an agitated solution of *N*-methylsclerotioramine (2 g.) in acetic acid (25 ml.) the colour changed from red to pale yellow in 5 min. and the mixture was then filtered into ice-water. Purification of the yellow precipitate from aqueous alcohol gave N-*methyl*apo*sclerotioramine* in yellow needles (1·6 g.), m. p. 230—235° (decomp.) (Found: C, 68·7; H, 6·0; N, 3·4. $C_{20}H_{24}O_2NCl$ requires C, 69·5; H, 6·9; N, 4·1%). Acetylation of this with pyridine–acetic anhydride at room temperature furnished *O*-acetyl-*N*-methyl-*apo*sclerotioramine in pale yellow needles (1·5 g.), m. p. and mixed m. p. 229° (Found: C, 67·1; H, 6·7; N, 3·3; OAc, 13·7. Calc. for $C_{20}H_{23}ONCl{\cdot}OAc$: C, 67·0; H, 6·7; N, 3·6; OAc, 1·2%).

Reduction of *NO*-dimethylsclerotioramine with zinc and acetic acid or with zinc and alkali gave rise to *N*-methyl*apo*sclerotioramine, m. p. and mixed m. p. 230—235° (decomp.), giving the *O*-acetyl derivative, m. p. and mixed m. p. 229°. The compound and its acetate had the respective authentic infrared absorption spectra.

Distillation of the aqueous liquors remaining after the degradation of *NO*-dimethylsclerotioramine (0·2 g.) with boiling 2N-aqueous sodium hydroxide solution (10 ml.) for ½ hr., followed by acidification of the cooled solution and separation of the precipitate, furnished 2 : 4-dimethylhexa-2-enaldehyde, identified as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159°.

Methylation of *N*-methyl*apo*sclerotioramine (0·5 g.) by the methyl iodide–potassium carbonate method in boiling acetone gave a mixed product which was purified by chromatography from benzene–ether (1 : 1) on neutralised aluminium oxide. Washed with methanol, a deep red band (*a*) and then a yellow band (*b*) were eluted. Concentration of the eluate (*b*) gave *NO*-dimethyl*apo*sclerotioramine, forming yellow needles (0·25 g.), m. p. and mixed m. p. 250° (decomp.), from methanol, with the expected infrared spectrum. Crystallised from aqueous methanol, the eluate (*a*) furnished violet needles (*ca.* 20 mg.), m. p. 91°, which appeared to be a methiodide. Methylation of *N*-methyl*apo*sclerotioramine (0·5 g.) by the methyl sulphate–potassium carbonate method in boiling acetone gave *NO*-dimethyl*apo*sclerotioramine methosulphate which separated from benzene–methanol in pale yellow needles (0·3 g.),

m. p. and mixed m. p. 210° (decomp.) (Found: C, 57·3; H, 6·2; N, 2·9. Calc. for $C_{23}H_{32}O_6NClS$: C, 57·0; H, 6·6; N, 2·9%), having the requisite infrared absorption spectra.

Tetrahydro-N-*methylsclerotioramine*.—Treated with 30% aqueous methylamine (2·5 ml.), tetrahydrosclerotiorin (1 g.) in alcohol (10 ml.) rapidly formed a deep orange solution which gradually deposited crystalline *tetrahydro*-N-*methylsclerotioramine*. Purified from alcohol, this base formed orange plates (0·8 g.), m. p. 206° (Found: C, 64·7; H, 7·2; Cl, 8·9; N, 3·4. $C_{22}H_{30}O_4NCl$ requires C, 64·8; H, 7·4; Cl, 8·7; N, 3·4%).

O - *Acetyltetrahydro* - N - *methyl*apo*sclerotioramine*.—Tetrahydro - *N* - methylsclerotioramine (0·5 g.), dissolved in acetic acid (5 ml.), was reduced by zinc dust (1 g.) in 10 min. and the mixture filtered into ice-water, giving tetrahydro-*N*-methyl*apo*sclerotioramine which separated from alcohol in pale yellow needles (0·3 g.), m. p. 182° (decomp.). This compound, which contained varying amounts of water of crystallisation, did not give satisfactory analytical results and on acetylation gave O-*acetyltetrahydro*-N-*methyl*apo*sclerotioramine*, forming needles (0·25 g.), m. p. 126°, from alcohol (Found: C, 67·5; H, 7·8. $C_{22}H_{30}O_3NCl$ requires C, 67·4; H, 7·7%).

Reduction of tetrahydro-*NO*-dimethylsclerotioramine (0·5 g.) by the same method gave tetrahydro-*N*-methyl*apo*sclerotioramine (0·4 g.), m. p. and mixed m. p. 182°, forming the monoacetate, m. p. 126°.

Tetrahydro-N-*phenylsclerotioramine* (with Adelaide Harris).—A solution of *N*-phenylsclerotioramine (1 g.) in alcohol (200 ml.) containing a catalyst (from 0·7 g. of charcoal and 0·25 g. of palladium chloride) was shaken in hydrogen until (100 ml., 2·1 mols.) of gas had been absorbed. Purified from alcohol, the resulting *tetrahydro*-N-*phenylsclerotioramine* formed orange needles (0·8 g.), m. p. 180°, which on admixture with *N*-phenylsclerotioramine had m. p. 160—162° (Found: C, 69·4; H, 6·8; N, 3·0. $C_{27}H_{32}O_4NCl$ requires C, 69·1; H, 6·8; N, 3·0%). The same compound (0·9 g.), m. p. and mixed m. p. 180°, was prepared from tetrahydrosclerotiorin (1 g.) and aniline (0·5 g.) in alcohol (10 ml.) at room temperature for 48 hr. (Found: C, 68·9; H, 6·9; N, 2·8; Cl, 7·4%).

Tetrahydro-N-*phenyl*apo*sclerotioramine*.—Reduction of tetrahydro-*N*-phenylsclerotioramine (0·5 g.) in acetic acid (10 ml.) with zinc dust (1 g.) was complete in 2 mins., yielding *tetrahydro*-N-*phenyl*apo*sclerotioramine* which formed yellow plates (0·4 g.), m. p. 256° (decomp.) with darkening from 246°, from alcohol (Found: C, 72·6; H, 7·0. $C_{25}H_{30}O_2NCl$ requires C, 72·6; H, 7·3%). Prepared by the acetic anhydride–pyridine method, O-*acetyltetrahydro*-N-*phenyl*-apo*sclerotioramine* separated from alcohol in needles, m. p. 198° (Found: C, 71·4; H, 7·1. $C_{27}H_{32}O_3NCl$ requires C, 71·4; H, 7·3%).

Dihydro-NO-*dimethylsclerotioramine*.—Treatment of dihydrosclerotioramine (0·5 g.) in 2N-aqueous sodium hydroxide at 0° with methyl sulphate (2 ml., added dropwise) gave *dihydro*-NO-*dimethylsclerotioramine* which was purified by chromatography from methanol on neutralised aluminium oxide, followed by crystallisation from the same solvent, forming deep orange needles (0·1 g.), m. p. 166° (Found: C, 66·8; H, 7·7. $C_{23}H_{30}O_4NCl$ requires C, 65·9; H, 7·2%).

Dihydro-N-*methylsclerotioramine*.—Methylation of dihydrosclerotioramine (0·4 g.) in boiling acetone (15 ml.) with potassium carbonate (4 g.) and methyl iodide (2 ml.) for 2½ hr. gave *dihydro*-N-*methylsclerotioramine* which separated from methanol in orange plates (0·4 g.), m. p. 219—220 (decomp.) (Found: C, 65·2, 64·9; H, 7·1, 7·2; N, 3·4, 3·3; Cl, 9·2, 9·1; OMe, 0·2; *N*-Me, 9·2. $C_{21}H_{25}O_4ClNMe$ requires C, 65·1; H, 6·9; N, 3·5; Cl, 8·8; *N*-Me, 7·2%). This compound (0·4 g.), m. p. and mixed m. p. 220° (decomp.), was also obtained by the interaction of dihydrosclerotiorin (0·5 g.) and 30% aqueous methylamine (2 ml.).

The ultraviolet absorption spectra were measured in 95% alcohol with a Unicam S.P. 500 Spectrophotometer, and the infrared spectral data were obtained in Nujol on a Grubb-Parsons S.3. double-beam spectrophotometer. The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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[*Received, July 1st,* 1957.]