1332. *The Chemistry of Fungi. Part L.*[1] *Rosenonolactone*

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The position of the carboxyl group in rosenonolactone (I) has been confirmed by the conversion of the metabolite into 1-ethyl-7-methylphenanthrene (V). Further examination of rosoic acid (XI), together with an investigation of the isomeric triols obtained by reduction of dihydrorosenono- and dihydroisorosenono-lactone, has substantiated the structure (I) of the metabolite and enabled the relative stereochemistry of rosenono- and isorosenono-lactone to be defined.

We previously provided [2] evidence for the formulation (I) (without stereochemical assignments) of rosenonolactone, a diterpenoid metabolite of *Trichothecium roseum* Link. Collateral support for this structure, together with the derivation of the relative stereochemistry of both rosenono- and isorosenono-lactone, is now reported. Part of this work has been the subject of a preliminary Communication.[3] The nomenclature is based upon

[1] Part XLIX, J. W. A. Simon, A. J. Hannaford, and W. B. Whalley, *J.*, 1965, 4164.
[2] A. Harris, A. Robertson, and W. B. Whalley, *J.*, 1958, 1799.
[3] B. Green, A. Harris, W. B. Whalley, and H. Smith, *Chem. and Ind.*, 1958, 1369.

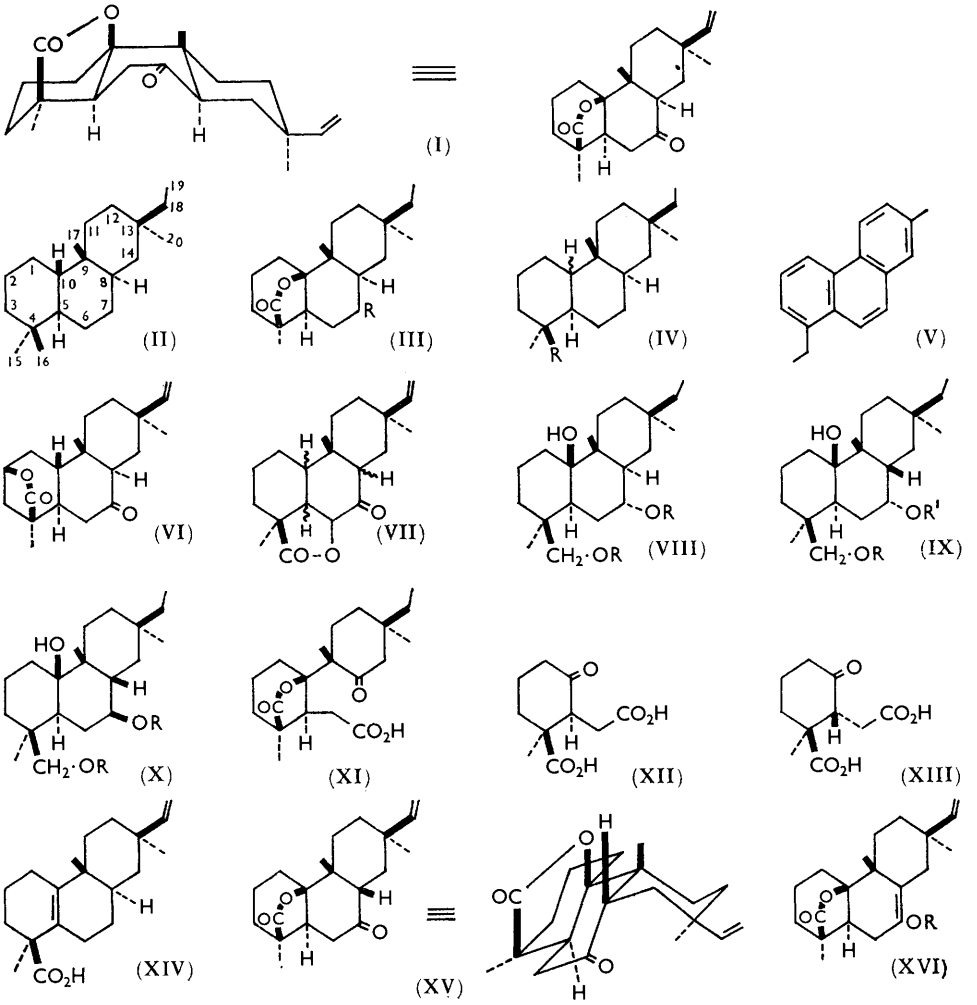
that of the parent hydrocarbon, rosane (II). Since the absolute stereochemistry of the metabolite has been determined [4] as in (I), the various formulæ illustrating relative configurations also represent the appropriate absolute configurations.

Although previous attempts to locate the tertiary carboxyl group in rosenonolactone were unsuccessful,[2] this has now been achieved. Thus, reduction of 10-hydroxyrosan-16-oic γ-lactone [2] (III; R = H_2) (see later for definition of stereochemistry) by the Clemmensen process gave rosan-16-oic acid (IV; R = CO_2H) which was converted, by way of the ester (IV; R = CO_2Me) into rosan-16-ol (IV; R = CH_2·OH). Dehydration of this alcohol with phosphorous pentachloride gave a halogenated hydrocarbon which, after successive treatment with boiling quinoline and then sodium, was dehydrogenated to yield 1-ethyl-7-methylphenanthrene (V). This result clearly locates the carboxyl residue of rosan-16-oic acid (and hence of rosenonolactone and its derivatives) at C-4, in agreement with previous conclusions.[2] Further, the γ-lactone system of the metabolite must terminate at C-2, C-6, or C-10. Whilst the evidence strongly supported formula (I) unequivocal exclusion of the alternatives (VI) and (VII) was desirable. This was effected as follows. Reduction of dihydrorosenonolactone with lithium aluminium hydride gave triol A, rosane-7α,10,16-triol (VIII; R = H) devoid of carbonyl absorption in the infrared spectrum, and containing three active hydrogens as measured by the Zerewitinoff technique. Acetylation of triol A gave 7α,16-diacetoxy-rosan-10-ol (VIII; R = Ac) having infrared absorption at 1709 (acetate), 1730 (acetate), and 3472 (hydroxyl) cm.$^{-1}$. Similarly, reduction of dihydroisorosenonolactone gave a mixture of almost equal amounts of two isomeric triols, B and C. Triol B, formulated (see later) as 8β-rosane-7α,10,16-triol (IX; R = R′ = H), furnished 7α,16-diacetoxy-8β-rosan-10-ol (IX; R = R′ = Ac) which has $\nu_{max.}$ at 1724 (acetate) cm.$^{-1}$. The infrared spectrum in Nujol and in carbon tetrachloride was devoid of an hydroxyl peak which must therefore be located in the very broad C–H absorption at *ca.* 2940 cm.$^{-1}$, since the presence of this hydroxyl residue is clearly indicated by elementary analyses and by the active hydrogen content of triol B and its di-*O*-acetate (IX; R = R′ = Ac). Lithium aluminium hydride reduction of (IX; R = R′ = Ac) regenerated triol B. Triol C is formulated as 8β-rosane-7β,10,16-triol (X; R = R′ = H) (see later) and yields 7β,16-diacetoxy-8β-rosan-10-ol (X; R = Ac) on acetylation. The infrared spectrum had $\nu_{max.}$ 1733 (acetate), 1712 (acetate), and 3484 (hydroxyl) cm.$^{-1}$. The triols A, B, and C were recovered quantitatively from attempted periodate oxidation. Hence, structure (VII), which would form an α-glycol on reduction, is excluded as a possible formula for rosenonolactone. This is in accord with the stability of the metabolite to zinc and acetic acid, a reagent which is specific for the scission of α-acyloxy-ketones [5] of type (VII). Further, the reduction of lactones of type (VI) and (VII) with lithium aluminium hydride would furnish triols containing one primary and two secondary hydroxyl groups. Such triols would form tri-*O*-acetates under the conditions used for the acetylation of triols A, B, and C. The production of di-*O*-acetates only from the triols A, B, and C clearly indicates the presence of one tertiary group in each triol in agreement with the structures (I) and (XV) for rosenono- and isorosenono-lactone, respectively.[2]

It is now possible to deduce the relative stereochemistry of rosenono- and isorosenonolactone. Thus, degradation of rosoic acid (XI) with alkali [2,6] gives (+)-5-ethyl-2,5-dimethylcyclohexanone together with (−)-2-carboxy-2-methyl-6-oxocyclohexylacetic acid (XIII). In a further investigation of this degradation two diastereoisomeric acids (XII) and (XIII) were isolated. Acid (XIII), which is stable to the action of bases and acids, is identical with that previously reported [2] and is now formulated as (−)-*trans*-2-carboxy-2-methyl-6-oxocyclohexylacetic acid (XIII). The isomeric acid which has infrared absorption at 1724 (carboxyl), 1689 and 1669 (hydrogen bonded acid and ketone) cm.$^{-1}$,

[4] W. B. Whalley, B. Green, D. Arigoni, J. J. Britt, and C. Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 5520.
[5] Cf. *e.g.*, F. M. Dean, J. Staunton, and W. B. Whalley, *J.*, 1959, 3004.
[6] A. Robertson, W. R. Smithies, and E. Tittensor, *J.*, 1949, 879.

is easily and irreversibly isomerised by base to (XIII). It is thus formulated as (+)-*cis*-2-carboxy-2-methyl-6-oxocyclohexylacetic acid (XII). This stereochemical assignment has received independent confirmation.[4] Since the unstable *cis*-acid (XII) must be the



initial product derived from ring A of dihydrorosenonolactone (by way of rosoic acid), whilst (XIII) is an artefact, it follows that the C-16 carboxyl group and the C-5 hydrogen must be *trans*-disposed in rosoic acid. In addition, because the C-16 carboxyl residue and the C-10 hydroxyl group must be *cis*-oriented, it follows that the C-10 hydroxyl and the C-5 hydrogen must be *trans*-disposed, *i.e.*, the A/B ring junction in rosenono- and in iso-rosenono-lactone must be *trans*.

The relative configuration of C-9 and C-10 can be deduced as follows. Lactonisation of ros-5(10)-en-16-oic acid (XIV), the structure of which has been confirmed by the absence of vinylic proton signals in the n.m.r. spectrum, gives two isomeric γ-lactones,[2] allo- and neo-hydroxyrosanoic lactones. Neither of these lactones is identical with, or antipodal with, 10-hydroxyrosan-16-oic γ-lactone (III; R = H_2) or the γ-lactones derived under identical conditions from the structurally associated dihydrodextro- and dihydroiso-dextro-pimaric acid.[7] The lactone (III; R = H_2) also differed from the γ-lactones derived from the resin acids. During the acid-catalysed formation of these various

[7] B. Green, A. Harris, and W. B. Whalley, *J.*, 1958, 4715.

γ-lactones the initial configuration at C-5 and C-8 may be perturbed to yield the most stable system. Further, since the configuration [7-9] of C-13 in allo- and neo-hydroxyrosanoic γ-lactone must be the same as that of C-13 in either dihydrodextro- or dihydroisodextropimaric acid it follows that our inability to equate these lactones with the γ-lactones from the resin acids must be ascribed to a difference in the relative disposition of C-16 and C-17, *i.e.*, C-16 and C-17 must be *cis*-disposed in allo- and neo-hydroxyrosanoic γ-lactones. It follows that C-9/C-10 must be *syn*-oriented in contrast to the usual *anti*-arrangement. In the dihydroresin acids C-16 and C-17 are *trans*, and lactonisation in this series yields a mixture of γ- and δ-lactones. Despite intensive search no corresponding δ-lactone has been detected among the products of lactonisation of ros-5(10)-en-16-oic acid (XIV). This is in agreement with a *syn*-disposition of C-9/C-10, since it is clear that lactonisation of the β-oriented carboxyl group on to C-9 would be prevented by the β-oriented C-17 methyl group.

The relative configuration of the B/C ring junction in rosenono- and isorosenono-lactone is derived from a consideration of the properties of triols A, B, and C. Thus, whilst the 7,16-diacetates of triols A and C were readily hydrolysed to the parent triols the 7,16-di-*O*-acetate of triol B gave a monoacetate, formulated as (IX; R = H, R′ = Ac) under the same hydrolytic conditions. This monoacetate readily regenerated the parent 7,16-di-*O*-acetate and was hydrolysed by more vigorous conditions to the triol B. Hence it may be concluded that the 7-hydroxyl group in triol B is axial; triol B is thus 8β-rosane-7α,10,16-triol (IX; R = R′ = H), the di-*O*-actate is (IX; R = R′ = Ac) and the monoacetate (IX; R = H, R′ = Ac). It further follows that in triols A and C the C-7 hydroxyl functions are equatorial: thus triol A is rosane-7α,10,16-triol (VIII; R = H) whilst triol C is 8β-rosane-7β,10,16-triol (X; R = H).

The formation from dihydrorosenonolactone of only one triol, the C-7 hydroxyl group of which is equatorial, indicates that the C-7 carbonyl residue is unhindered. Conversely, the production of two isomeric triols, B and C, from dihydroisorosenonolactone clearly demonstrates that the C-7 carbonyl residue in the precursor is sterically hindered. Models plainly show that this hindrance is produced by the C-13 substituents in the *trans-syn-cis* configuration, which is thus allocated to isorosenonolactone (XV); conversely, rosenonolactone is represented as the *trans-syn-trans* isomer (I). At this stage the stereochemistry of C-13 had not been defined; this has since been determined [10,11] as in (I).

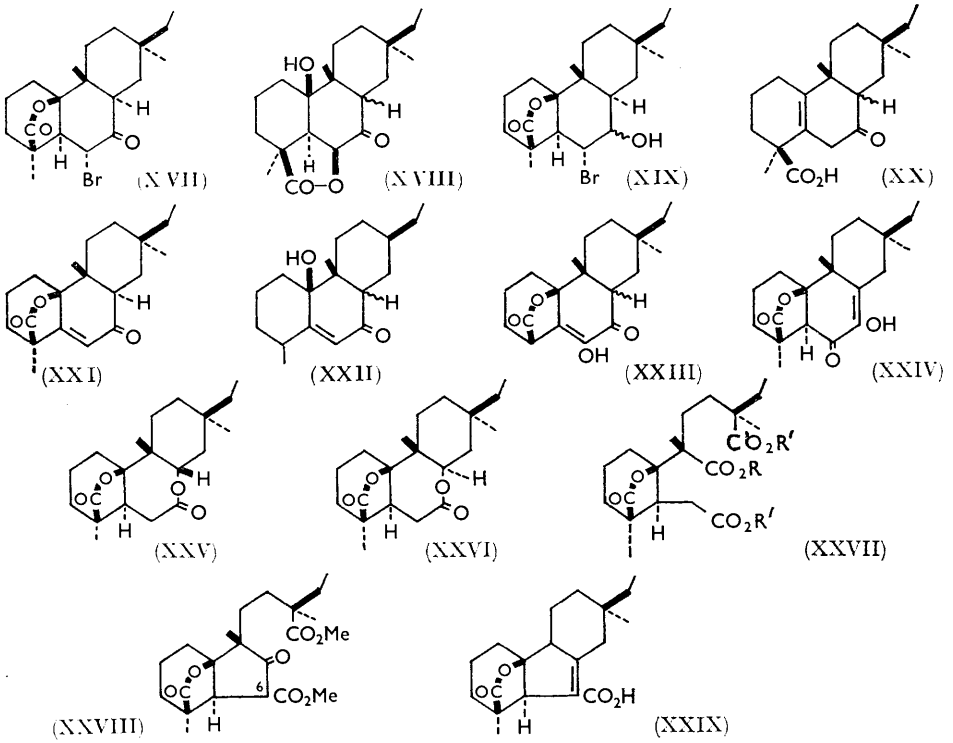
It is now clear that the interconversion of rosenono- and isorosenono-lactone proceeds by way of the enol (XVI; R = H) or the equivalent anion as previously suggested.[2] Whilst dihydroisorosenonolactone readily yields the enol acetate (XVI; R = Ac) dihydrorosenonolactone gives this derivative only under more vigorous conditions. This is in accord with the relative configuration at C-8 in the two series. The enol acetate was resistant to ozonolysis and thus could not be converted directly into rosoic acid.

When the γ-lactone ring has been opened the equilibrium between the rosenono-, isorosenono-series lies almost exclusively in favour of the iso-series (cf. the irreversible conversion of rosenono- into isorosenono-lactone by strongly alkaline reaction conditions which result in the opening of the γ-lactone ring [6]). However, when this interconversion is achieved by mildly basic conditions where the γ-lactone remains closed, the two series appear to have approximately equal stability and at the point of equilibrium, which is approachable from both sides, the product consists of approximately equal quantities of rosenono- and of isorosenono-lactone.

The stereochemistry of other derivatives of rosenonolactone may now be clarified. Thus, *e.g.*, the mercaptal (III; R = ·S·CH_2·CH_2·S·), which is formed [2] from either dihydrorosenono- or from dihydroisorosenono-lactone must belong to the rosenonolactone series

[8] O. E. Edwards and R. Howe, *Chem. and Ind.*, 1958, 629.
[9] E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.*, 1958, **80**, 2912.
[10] A. I. Scott, S. A. Sutherland, D. W. Young, I. Guglielmetti, D. Arigoni, and G. A. Sim, *Proc. Chem. Soc.*, 1964, 19.
[11] Part LI, following Paper.

in which the interaction between the substituents at C-13 and C-7 is absent; similarly the 2,4-dinitrophenylhydrazone which is produced [6] from both rosenono- and isorosenonolactone must belong to the 8α-series. It follows that the γ-lactone (III; R = H_2) and its various derivatives, *e.g.*, (IV), belong to the rosane series.



Various aspects of the stereochemistry of rosenonolactone have emerged from a study of the products of bromination and oxidation. Thus, whilst bromination of the enol acetate (XVI; R = Ac) gave an extremely unstable, 8-bromo-derivative, dihydrorosenonolactone formed a stable 6-bromo-derivative (XVII). This compound, which was also obtained, but in lower yield, from dihydroisorosenonolactone has infrared spectral absorption at 1789 (γ-lactone) and 1715 (ketone) cm.$^{-1}$, (in carbon tetrachloride), and shows $\lambda_{max.}$ 230 mμ, log ε 2·39. The ketonic frequency is thus 9 cm.$^{-1}$ lower, and the ultraviolet maximum 4 mμ lower than the corresponding absorption maxima of dihydrorosenonolactone. From these results it was therefore not possible to deduce the configuration of the C-6 halogen. It is not surprising, however, that these spectral data should be uninformative since the central ring of rosenonolactone has a rigid boat conformation in which the plane of the C-7 carbonyl group almost bisects the angle between the C-6 hydrogen and the C-6 bromine.

Whilst attempts to dehydrobrominate (XVII) with organic bases gave either unchanged ketone or an intractable, acidic mixture, the action of methanolic potassium hydroxide formed a product, $C_{20}H_{30}O_4$, having $\nu_{max.}$ 1709 (ketone), 1727 (lactone), and 3012 (hydroxyl) cm.$^{-1}$, and which could not be acetylated and had the properties of a lactone. This lactone is thus provisionally regarded as (XVIII) having been produced by internal attack of the carboxylate anion upon C-6. This view of the genesis of (XVIII) indicates that the halogen atom in (XVII) is α-oriented.

Reduction of the bromo-ketone (XVII) with potassium borohydride gave 6-bromo-7,10-dihydroxyrosan-16-oic-16,10-lactone (XIX) which had infrared absorption at 1789

(γ-lactone) and 3570 (hydroxyl) cm.$^{-1}$ (in carbon tetrachloride). Attempts to determine the orientation of the halogen by treatment of (XIX) with alkali furnished an intractable, acidic product, whilst reduction with zinc and acetic acid gave an acidic product which has $\lambda_{max.}$ 284 mμ, log ε 1·58 (isolated ketone), and $\nu_{max.}$ 1707 (isolated ketone and carboxylic acid), cm.$^{-1}$ and is provisionally formulated as (XX).

Oxidation of dihydrorosenonolactone with selenium dioxide gave the αβ-unsaturated ketone (XXI), which has $\nu_{max.}$ 1783 (γ-lactone) and 1672 and 1634 (αβ-unsaturated ketone) cm.$^{-1}$. The ultraviolet spectrum showed $\lambda_{max.}$ 235 mμ, log ε 4·04 (calculated, $\lambda_{max.}$ 240 mμ). In agreement with the structure (XXI), the action of methanolic potassium hydroxide gave the 16-nor-derivative (XXII), devoid of lactonic carbonyl absorption in the infrared spectrum but having $\nu_{max.}$ 1672 and 1624 (αβ-unsaturated ketone), and 3623 (hydroxyl) cm.$^{-1}$, and ultraviolet absorption at $\lambda_{max.}$ 238 mμ log ε 4·03. The resistance of (XXII) to acetylation provided collateral evidence for the tertiary hydroxyl residue. Selenium dioxide oxidation of dihydroisorosenonolactone gave a major product containing selenium together with a minor product which is regarded as the diosphenol * (XXIII) or (XXIV). This compound had infrared absorption at 1779 (γ-lactone) 1661 and 1623 (αβ-unsaturated ketone) and 3436 (hydroxyl) cm.$^{-1}$, is soluble in dilute alkali, exhibits an intense ferric reaction in alcohol and had $\lambda_{max.}$ 287 mμ, log ε 4·02. The diosphenol structure was supported by the properties of the *O*-acetate which had $\nu_{max.}$ 1786 (γ-lactone), 1776 (vinyl ester), 1675 and 1634 (αβ-unsaturated ketone) cm.$^{-1}$ and $\lambda_{max.}$ 254 mμ (calculated, 252 mμ), log ε 4·07, and thus exhibited the expected hypsochromic shift consequent upon acetylation of the enol.

In a search for an improved route to rosoic acid (XI), we investigated the Baeyer–Villiger oxidation of dihydrorosenono- and of dihydroisorosenono-lactone. Since this reaction usually proceeds with retention of configuration [12–14] the product from dihydroisorosenonolactone may be formulated as (XXV). The low yield of this dilactone which showed $\nu_{max.}$ 1775 (γ-lactone) and 1740 (ε lactone) cm.$^{-1}$, is compatible with the hindered environment of the C-7 carbonyl residue in the precursor. Confirmation of the structure (XXV) was provided by the identity of (XXV) with the dilactone produced by reduction of methyl rosoate [2] or of rosoic acid with sodium borohydride. The production of (XXV) is in agreement with general principles since reduction of the strongly hindered ketonic carbonyl group in methyl rosoate should give the corresponding axial alcohol and thence the dilactone (XXV). Dihydrorosenonolactone gave the epimeric dilactone (XXVI) in high yield, having $\nu_{max.}$ 1775 (γ-lactone) and 1750 (ε-lactone) cm.$^{-1}$. Collateral evidence for this structure was provided by oxidation of (XXVI) to rosoic acid.

A tricarboxylic acid, $C_{20}H_{30}O_8$, which is formulated as (XXVII; R = R′ = H) was obtained as a second product from this oxidation. The trimethyl ester (XXVII; R = R′ = Me) showed signals in the n.m.r. spectrum at τ 6·25, 6·31, and 6·35 (singlets, 3 × $COOCH_3$), 8·7, 8·85, and 8·95 (singlets, 3 × C–CH_3) and 9·18 (triplet, J = 7 c./sec., CH_2–CH_3). The infrared spectrum showed $\nu_{max.}$ 1780 (γ-lactone) cm.$^{-1}$. Hydrolysis of the trimethyl ester (XXVII; R = R′ = Me) gave an acidic ester, $C_{20}H_{29}O_7$(OMe) provisionally formulated as (XXVII; R′ = H, R = Me) which has $\nu_{max.}$ 1780 (γ-lactone), 1740 (ester) and 1720 (carboxyl) cm.$^{-1}$, together with a second compound, $C_{20}H_{26}O_5(OMe)_2$, which we formulate as (XXVIII). This has absorption at 1780 (γ-lactone) and 1740 (ester and cyclopentanone) cm.$^{-1}$. The n.m.r. spectrum has signals at τ 6·2 and 6·32 (singlets, 2 × $COOCH_3$), 8·8, 8·85, and 8·91 (singlets, 3 × C–CH_3) and 9·20 (triplet, J = 7 c./sec., CH_2·CH_3) and 7·04 [doublet, 1 proton, at C-6 in (XXVIII)]. Further support for this structure is provided by the formation of the same compound by treatment of (XXVII; R = R′ = Me)

* This compound, originally described by Dr. B. Green (Ph.D. Thesis, Liverpool, 1958), is probably identical with the derivative recently reported by Scott *et al.*[10]

[12] R. B. Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 878.
[13] K. Mislow and J. Brenner, *J. Amer. Chem. Soc.*, 1953, **75**, 2319.
[14] T. F. Gallagher and T. H. Kritchevsky, *J. Amer. Chem. Soc.*, 1950, **72**, 882.

with sodium methoxide [cf. the similar formation of anhydrorosoic acid,[6] which may now be formulated as (XXIX) from rosoic acid (XI)].

Several miscellaneous degradation products of rosenonolactone are described.

In collaboration with Mr. B. O. Handford we have isolated rosenonolactone from the mycelium of *T. luteum* Petch and of *T. cytosporium* Duddington when these organisms were grown upon Czapek–Dox medium. The last named organism also produced rosololactone.

Experimental

Degradation of Rosenonolactone to 1-*Ethyl*-7-*methylphenanthrene*.—A solution of 10-hydroxyrosan-16-oic γ-lactone (1 g.) in toluene (10 ml.) was added to a mixture of hydrochloric acid (5 ml.), water (5 ml.), acetic acid (0·25 ml.), and zinc amalgam (5 g.). The mixture was heated under reflux for 36 hr., with the addition of zinc amalgam (2·5 g.) after 24 hr., and of hydrochloric acid (7·5 ml.) every 2 hr. The combined ethereal extracts (2 × 50 ml.) of the cooled reaction mixture were washed with 0·1N-sodium hydroxide solution (50 ml.) and then with water (2 × 50 ml.). The sodium salt of the product separated at the interface but was removed by the subsequent water washings. Acidification of the alkaline washings followed by extraction with ether gave *rosan*-16-*oic acid* which formed prisms (0·5 g.), m. p. 133° (from methanol), $[\alpha]_D^{20}$ +17·5° (*c* 0·25 in $CHCl_3$) (Found: C, 78·4; H, 11·0. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%). The product gave no colour with tetranitromethane. The mixed m. p. with ros-5(10)-en-16-oic acid was *ca.* 118°.

The mother-liquors from the purification of rosan-16-oic acid (12 g.) gradually deposited a small quantity of a second *acid* which formed needles (0·15 g.), m. p. 206—207°, from aqueous alcohol (Found: C, 79·3; H, 11·5%). This acid gave a pale yellow colour with tetranitromethane in chloroform.

Esterification of rosan-16-oic acid (3·7 g.) in ether (80 ml.) at 0° with diazomethane furnished *methyl rosan*-16-*oate* as a pale yellow oil (3·4 g.), b. p. 175°/1 mm., $[\alpha]_D^{20}$ +27° (*c* 0·2 in chloroform) (Found: C, 78·6; H, 11·4. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·3%). A solution of this ester (2·6 g.) in ether (100 ml.) was added to a slurry of lithium aluminium hydride (2 g.) in ether (100 ml.) at a rate sufficient to maintain rapid ebullition. The mixture was then heated under reflux until reduction was completed (2½ hr.). After isolation in the usual manner *rosan*-16-*ol* formed needles (2·4 g.), m. p. 97° (from aqueous alcohol), $[\alpha]_D^{21}$ +20° (*c*, 0·15 in chloroform), having a negative tetranitromethane reaction in chloroform (Found: C, 82·4; H, 12·4. $C_{20}H_{36}O$ requires C, 82·2; H, 12·4%). The p-*nitrobenzoate* separated from alcohol in needles, m. p. 157° (Found: C, 73·3; H, 8·9; N, 3·2. $C_{27}H_{39}NO_4$ requires C, 73·4; H, 8·9; N, 3·2%). The *acetate* formed plates, m. p. 63° [from light petroleum (b. p. 40—60°)] (Found: C, 78·8; H, 11·4. $C_{22}H_{38}O_2$ requires C, 79·0; H, 11·5%).

Phosphorus pentachloride (1·5 g.) was added during 15 min. to a solution of rosan-16-ol (2 g.) in ether (150 ml.). Next day the resultant solution was boiled for 2 hr., cooled, decomposed by the addition of ice, washed, dried, and distilled. The pale yellow oily product was refluxed with quinoline (10 ml.) for 5 min., the cooled mixture dissolved in ether, and the ethereal extract washed free from quinoline with dilute hydrochloric acid. The residual red oil was distilled from sodium to yield a mixture of *rosenes* (1·25 g.), b. p. 170°/1·4 mm., having a negative Beilstein test for halogen and giving a yellow colour with tetranitromethane in chloroform (Found: C, 87·0; H, 12·3. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%). A mixture of these unsaturated hydrocarbons (3 g.) and powdered selenium (6 g.) was heated at 325—340° for 48 hr., with occasional stirring. After isolation with ether the crude product was purified by chromatography from light petroleum (b. p. 60—80°) on activated alumina to yield 1-ethyl-7-methylphenanthrene (0·4 g.) which separated from methanol in plates m. p. and mixed m. p. 81°, identical with an authentic specimen (Found: C, 92·4; H, 7·5. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). The mixture with 1,7-dimethylphenanthrene had m. p. *ca.* 65°. The picrate separated from methanol in yellow needles, m. p. 112°, identical with an authentic specimen. The *trinitrobenzeneate* separated from alcohol in yellow needles, m. p. 149°, identical with an authentic specimen (Found: C, 63·9; H, 4·6; N, 9·5. $C_{23}H_{19}N_3O_6$ requires C, 63·7; H, 4·4; N, 9·7%).

Rosane-7α,10,16-*triol*.—A solution of dihydrorosenonolactone (2·5 g.) in ether (250 ml.) was added during 2 hr., to a suspension of lithium aluminium hydride (1·3 g.) in gently refluxing ether (50 ml.). Reaction was completed by heating under reflux for 48 hr., and the product was then isolated in the usual manner and purified from alcohol and then ethyl acetate to yield

rosane-7α,10,16-*triol* in prisms (1·1 g.), m. p. 146°, $[\alpha]_D^{21}$ −54° (*c* 0·27 in chloroform) (Found: C, 73·8; H, 11·2. Active hydrogen, 1·0. $C_{20}H_{36}O_3$ requires C, 74·0; H, 11·2. Active hydrogen 3 × H, 0·93%).

Formed quantitatively by the action of acetic anhydride–pyridine at room temperature during 24 hr., 7α,16-*diacetoxyrosane*-10-*ol* formed needles, m. p. 137° (from aqueous methanol) (Found: C, 70·3; H, 10·0. $C_{24}H_{40}O_5$ requires C, 70·6; H, 9·9%). Hydrolysis of this acetate (0·1 g.) in methanol (5 ml.) containing 10% potassium hydroxide solution (1 ml.) during 15 min. furnished an almost quantitative yield of rosane-7α,10,16-triol, m. p. and mixed m. p. 146°, having the requisite infrared spectrum.

8β-*Rosane*-7α,10,16- *and* -7β,10,16-*triol*.—Reduction of dihydroisorosenonolactone (2·5 g.) in boiling ether (300 ml.) with lithium aluminium hydride (1·2 g.) occurred during 45 hr. After isolation in the usual manner, crystallisation of the product from ethyl acetate furnished 8β-*rosane*-7α,10,16-*triol* which was purified from ethyl acetate and then benzene to yield needles (0·6 g.), m. p. 184°, $[\alpha]_D$ +3° (*c* 0·09 in chloroform) (Found: C, 74·4; H, 11·1; Active hydrogen 0·98. $C_{20}H_{36}O_3$ requires C, 74·0; H, 11·2; Active hydrogen 3 × H, 0·93%). Formed quantitatively by the pyridine–acetic anhydride method at room temperature during 2 days the 7α,16-*di*-O-*acetate* separated from aqueous methanol in needles, m. p. 136° (Found: C, 70·3; H, 10·1; Active hydrogen, 0·40%; *M*, 351. $C_{20}H_{40}O_5$ requires C, 70·6; H, 9·9; Active hydrogen 1 × H, 0·32%; *M*, 360). A mixture with 7β,16-diacetoxy-8β-rosan-10-ol had m. p. 120—130°.

Hydrolysis of this acetate (0·5 g.) in methanol (25 ml.) containing 50% potassium hydroxide solution (1 ml.) at room temperature for 10 min. furnished 7α-*acetoxy*-8β-*rosane*-10,16-*diol* which formed needles (0·4 g.,) m. p. 196° (from alcohol) (Found: C, 71·7; H, 10·3; Active hydrogen, 0·52. $C_{22}H_{38}O_4$ requires C, 72·1; H, 10·4; Active hydrogen 2 × H, 0·55%). Reacetylation of this monoacetate furnished the parent diacetate, m. p. and mixed m. p. 136°, having the requisite infrared spectrum. Hydrolysis of the di-*O*-acetate (0·5 g.) with the quantity of reagents as above on the steam-bath during 30 min., furnished 8β-rosane-7α,10,16-triol (0·4 g.) having the requisite m. p., mixed m. p., and infrared spectrum. The same triol was also produced by the reduction during 2 hr., in boiling ether of the di-*O*-acetate with lithium aluminium hydride.

The mother-liquors from the purification of 8β-rosane-7α,10,16-triol gradually deposited 8β-*rosane* 7β,10,16-*triol* which separated from aqueous methanol in prisms (0·5 g.), m. p. 156°, mixed m. p. with the 7α,10,16-triol *ca.* 140° (Found: C, 73·6; H, 11·1; Active hydrogen, 0·84. $C_{20}H_{36}O_3$ requires C, 74·0; H, 11·2; Active hydrogen 3 × H, 0·93%). Prepared by the pyridine–acetic anhydride method during 2 days at room temperature, 7β,16-*diacetoxy*-8β-*rosan*-10-*ol* separated from aqueous methanol in prisms, m. p. 120° (Found: C, 70·2; H, 10·0. $C_{24}H_{40}O_5$ requires C, 70·6; H, 9·9%). Hydrolysis of this di-*O*-acetate at room temperature during 10 min., using the method previously described, furnished a quantitative yield of 8β-rosane-7β,10,16-triol having the requisite m. p., mixed m. p., and infrared spectrum.

Alkaline Degradation of Rosoic Acid.—A solution of rosoic acid (2·3 g.) in 0·5N-sodium hydroxide solution (80 ml.) was kept at room temperature for 3 days. An insoluble white precipitate was collected and purified from chloroform–methanol to yield a compound (0·3 g.) in plates, m. p. 257° (decomp.) (Found: C, 70·0; H, 9·0%). This compound was very sparingly soluble in the usual organic solvents except chloroform. The clear hydrolysate was diluted with water and extracted with ether to yield 5-ethyl-2,5-dimethylcyclohexanone (1·2 g.).[2,6] The alkaline solution remaining after extraction of the ketone was carefully acidified (cool) with 2N-sulphuric acid and extracted with ethyl acetate and the dried extract evaporated to yield a yellow gum (1 g.). Purification from ethyl acetate furnished (−)-*trans*-2-carboxy-2-methyl-6-oxocyclohexylacetic acid (0·3 g.), m. p. 205° (decomp.), identical (m. p., mixed m. p., and infrared spectrum) with a previously prepared specimen.[6] The ethyl acetate mother-liquors slowly deposited (+)-cis-2-*carboxy*-2-*methyl*-6-*oxocyclohexylacetic acid* which formed prisms (0·4 g.), m. p. 148°, $[\alpha]_D^{19}$ +24° (*c* 0·3 in water) (Found: C, 55·6; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·6%). A solution of this *cis*-acid (50 mg.) in 2N-sodium hydroxide solution (2 ml.) was kept at room temperature for 2 days, whereon acidification with cold 2N-sulphuric acid gave a quantitative yield of (−)-*trans*-2-carboxy-2-methyl-6-oxocyclohexylacetic acid having the requisite m. p., mixed m. p., rotation, and infrared spectrum. The (−)-*trans*-acid was unchanged under these conditions. A solution of (+)-*cis*-2-carboxy-2-methyl-6-oxocyclohexylacetic acid (0·3 g.) in ethanedithiol (4 ml.) was saturated with hydrogen chloride at 0°. Next day the semicrystalline mass was diluted with ethyl acetate and the product purified from ethyl

acetate to yield the *mercaptal*, plates (250 mg.), m. p. 237° (Found: C, 49·7; H, 6·3. $C_{12}H_{18}O_4S_2$ requires C, 49·7; H, 6·2%). Similarly the (−)-*trans*-acid (0·3 g.) furnished a *mercaptal* (0·25 g.), stout prisms, m. p. 217° (from ethyl acetate) (Found: C, 49·1; H, 6·1%). The mixed m. p. of the mercaptals was *ca.* 200°.

The Enol Acetate of Dihydrorosenonolactone.—(*a*) A mixture of dihydrorosenonolactone (1 g.), acetic anhydride (10 ml.), and fused sodium acetate (1·5 g.) was refluxed for 10 hr., cooled, and diluted with water. Next day the solid product was purified from alcohol to yield the enol acetate (0·7 g.) in prisms, m. p. and mixed m. p. with a previously prepared specimen, 183°.[6]

(*b*) Similarly dihydroisorosenonolactone (1 g.) furnished the same enol acetate (0·6 g.) having the requisite m. p., mixed m. p., and infrared spectrum.

The Interconversion of Rosenono- and Isorosenono-lactone.—(*a*) A solution of rosenonolactone (0·5 g.) in methanol (50 ml.) containing 2N-sodium hydroxide solution (0·1 ml.) was kept at 50° for 7 hr., cooled, and evaporated to 20 ml. under reduced pressure at 20°. Purification from benzene of the solid which separated furnished rosenonolactone (0·2 g.) in prisms, having the requisite m. p., mixed m. p., and infrared spectrum. The methanol solution remaining after separation of the rosenonolactone was diluted with water and the precipitate purified from aqueous alcohol to yield isorosenonolactone in needles (0·2 g.) having the requisite m. p., mixed m. p., and infrared spectrum.

(*b*) When isorosenonolactone (0·5 g.) was treated as in (*a*), separation of the products as in (*a*) furnished rosenonolactone (0·2 g.) and isorosenonolactone (0·2 g.).

(*c*) A solution of dihydrorosenonolactone (0·5 g.) in methanol (50 ml.) containing 2N-sodium hydroxide (0·1 ml.) was maintained at 50° during 6 hr. Evaporation gave mixed crystals which were separated mechanically to yield dihydrorosenonolactone in tablets, m. p. and mixed m. p. 184°, and dihydroisorosenonolactone in needles, m. p. and mixed m. p. 150°. A parallel experiment with dihydroisorosenonolactone gave a similar result.

Dihydrorosenololactone.—A solution of sodium borohydride (0·57 g.) in the minimum of water was added dropwise to dihydrorosenonolactone (0·43 g.) in methanol (100 ml.) at 35°. One hour later the solution was diluted with water and the precipitate purified from chloroform–benzene to yield *dihydrorosenololactone* in needles (1·2 g.), m. p. 196° (Found: C, 75·3; H, 10·3. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·1%).

6-*Bromodihydrorosenonolactone.*—(*a*) A solution of dihydrorosenonolactone (1 g.) in acetic acid (10 ml.) was treated with a solution of hydrobromic acid in acetic acid (0·1 ml.; 50% w/w) and bromine (0·50 g.) in acetic acid (1·5 ml.) at 50° in the dark in an atmosphere of nitrogen. After 45 min. at 50° the cooled solution was diluted with ether (100 ml.) washed with excess of 2N-sodium hydrogen carbonate solution water, dried, and evaporated to yield a pale brown gum, which crystallised on trituration with ether. Purification from ether or ether–chloroform furnished 6-*bromodihydrorosenonolactone* (0·12 g.) in plates, m. p. 222°, $[\alpha]_D^{20}$ −37·4° (*c* 0·15 in chloroform). This compound was very readily soluble in the usual organic solvents except light petroleum and was recovered unchanged after being refluxed for 1 hr. with pyridine: it had $\lambda_{max.}$ 278—296 mμ (log ε 1·52) (Found: C, 60·1; H, 7·4; Br, 20·7. $C_{20}H_{29}BrO_3$ requires C 60·4; H, 7·4; Br, 20·1%).

Acidification of the sodium hydrogen carbonate washings furnished an intractable gum (0·5 g.).

(*b*) Bromination of dihydroisorosenonolactone (1 g.) as in (*a*) furnished 6-bromodihydrorosenonolactone (0·02 g.). The acidic fraction was an intractable red gum.

6,10-*Dihydroxy*-7-*oxorosan*-16-*oic* 16,6- *Lactone.*—A solution of the previous lactone (0·13 g.) in methanol (10 ml.) containing potassium hydroxide (0·05 g.) was refluxed for 1 hr., cooled, and diluted with water. Isolated with ether, 6,10-*dihydroxy*-7-*oxorosan*-16-*oic* 16,6-*lactone* separated from light petroleum (b. p. 60—80°) or aqueous acetone in needles (0·1 g.), m. p. 156—157°, $[\alpha]_D^{20}$ +20° (*c* 0·07 in chloroform) (Found: C, 72·0; H, 9·2. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%).

6-*Bromo*-7-*hydroxyrosan*-16-*oic* γ-*Lactone.*—A slurry of potassium borohydride (0·05 g.) in methanol (10 ml.) was added during 20 min. to a solution of 6-bromodihydrorosenonolactone (0·1 g.) in methanol (40 ml.) at 35°. After 1 hr. the solution was diluted with water (50 ml.), and the resultant precipitate purified from methanol to yield 6-*bromo*-7,10-*dihydroxyrosan*-16-*oic* γ-*lactone* in needles (0·07 g.), m. p. 198°, $[\alpha]_D^{20}$ +62° (*c* 0·1 in chloroform) (Found: C, 60·0; H, 7·8; Br, 20·6. $C_{20}H_{31}BrO_3$ requires C, 60·1; H, 7·8; Br, 20·0%).

7-Oxoros-5(10)-en-16-oic Acid.—A mixture of zinc dust (0·4 g.), 6-bromodihydrorosenonolactone (0·07 g.), and acetic acid (8 ml.) was refluxed for 3 hr., when the solution was decanted from unchanged zinc, cooled, and diluted with water. Purification of the precipitate from aqueous alcohol gave *7-oxoros-5(10)-en-16-oic acid* in plates (0·046 g.), m. p. 185°, $\lambda_{max.}$ 284 mμ (log ε 1·58) (Found: C, 75·5; H, 9·8. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The mixed m. p. with dihydrorosenonolactone was *ca.* 160°. The product dissolved with effervescence in 2N-sodium hydrogen carbonate solution and exhibited a pale yellow coloration with tetranitromethane in chloroform solution.

7-Oxo-16-nor-ros-5(6)-en-10-ol.—A solution of dihydrorosenonolactone (0·14 g.) in acetic acid (30 ml.) containing selenium dioxide (0·14 g.) was refluxed for 2 hr., whereupon selenium (0·05 g.) was removed and the solvent removed by distillation under reduced pressure. The product was purified by chromatography from benzene on activated alumina and then by crystallisation from methanol to give *10-hydroxy-7-oxoros-5(6)-en-16-oic γ-lactone* in pale yellow needles (0·2 g.), m. p. 168°, $[\alpha]_D^{20}$ +5° (*c* 0·1 in chloroform), $\lambda_{max.}$ 235 mμ (log ε 4·04) (Found: C, 75·8; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%). A solution of this lactone (0·15 g.) in methanol (25 ml.) containing potassium hydroxide (2·5 g.) was refluxed for 1 hr., and diluted with water (100 ml.). Purification of the resultant precipitate from aqueous acetone gave *7-oxo-16-nor-ros-5(6)-en-10-ol* (0·1 g.) which formed plates, m. p. 134°, $\lambda_{max.}$ 238 mμ (log ε 4·03) (Found: C, 78·6; H, 10·4. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%).

Selenium Dioxide Oxidation of Dihydroisorosenonolactone.—A solution of dihydroisorosenonolactone (2 g.) in acetic acid (100 ml.) containing selenium dioxide (0·7 g.) was refluxed for 3 hr., whereafter selenium (0·25 g.) was removed and the solution evaporated under reduced pressure. Purification of the product by chromatography on activated alumina in light petroleum (b. p. 60—80°)–benzene (4 : 1) followed by crystallisation from light petroleum (b. p. 60—80°) furnished a *diosphenol* in needles (0·1 g.), m. p. 179°, having an intense brown ferric reaction in alcohol; $\lambda_{max.}$ 287 mμ (log ε 4·02) (Found: C, 71·9; H, 8·7. $C_{20}H_{28}O_4$ requires C, 72·2; H, 8·5%). Acetylation of this diosphenol (0·052 g.) with pyridine (10 ml.) containing acetic anhydride (2 ml.) during 24 hr. at room temperature furnished the O-*acetate* which formed needles (0·05 g.), m. p. 192° (from methanol), $\lambda_{max.}$ 254 mμ (log ε 4·07) (Found: C, 70·4; H, 7·9. $C_{22}H_{30}O_5$ requires C, 70·6; H, 8·1%). The petroleum mother-liquors from the purification of this lactone slowly deposited a second *compound* which formed red hexagonal prisms (0·16 g.), from light petroleum (b. p. 60—80°), m. p. 145°, with resolidification at 170° followed by remelting at 230° (decomp.). Crystallisation from aqueous methanol gave yellow needles, m. p. 240° (decomp.), $\lambda_{max.}$ 269 mμ (log ε 3·81) (Found: C, 60·8; H, 7·4; O, 12·15. $C_{20}H_{28}O_3Se$ requires C, 60·6; H, 7·1; O, 12·2%).

Rosoic Acid.—(*a*) A mixture of trifluoroacetic anhydride (2·5 ml.), methylene chloride (11 ml.), and 85% hydrogen peroxide (0·6 ml.) was stirred at 0° for 1 hr., and then added during 20 min. to a solution of dihydrorosenonolactone (0·5 g.) in methylene chloride (50 ml.) containing disodium hydrogen phosphate (7 g.) at 0°. After attaining room temperature the mixture was refluxed for 4 hr. Next day the inorganic salts were separated and washed with methylene chloride, and the combined methylene chloride solution washed with 2N-sodium carbonate solution. Evaporation gave the *dilactone* which separated in needles (0·37 g.), m. p. 267—270° (from alcohol), $[\alpha]_D^{20}$ −19·1° (*c* 3·66 in $CHCl_3$) (Found: C, 72·1; H, 9·0. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%).

A solution of chromic oxide (0·8 g.) in water (13 ml.) and concentrated sulphuric acid (10 ml.) was added to a solution of this dilactone (0·6 g.) in acetic acid (400 ml.), and the mixture stirred at room temperature during 12 hr. Excess of oxidising agent was destroyed by the addition of methanol; the solution was then concentrated *in vacuo*, diluted with water, and extracted with ether. The ethereal extract was washed with 2N-sodium hydrogen carbonate and the washing acidified and extracted with ether to yield rosoic acid (0·3 g.), identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen.

(*b*) Repetition of the chromic oxide oxidation described in (*a*) using the dilactone (2 g.) gave a mixture (1 g.) of rosoic acid and a tricarboxylic acid. A mixture of these acids (10 g.) was treated with 0·5N-sodium hydroxide [6] to yield 5-ethyl-2,5-dimethylcyclohexanone and a mixture of acids which was purified from ethyl acetate–light petroleum to yield a *tricarboxylic acid* (4 g.) in prisms, m. p. 242—244°, $[\alpha]_D^{20}$ +14·7° (*c* 4·08 in alcohol) (Found: C, 59·9; H, 7·4. $C_{20}H_{30}O_8$ requires C, 60·3; H, 7·6%). Prepared quantitatively by the action of diazomethane the *trimethyl ester* formed needles, m. p. 131° (from ethyl acetate–light petroleum), $[\alpha]_D^{20}$ +19·1°

(*c* 5·85 in $CHCl_3$) [Found: C, 63·0; H, 8·4; OMe, 20·9. $C_{20}H_{27}O_5(OMe)_3$ requires C, 62·7; H, 8·2; OMe, 21·1%].

A solution of this trimethyl ester (630 mg.) in methanol (20 ml.) containing potassium hydroxide (0·5 g.) was refluxed for 12 hr. The acidified solution was diluted with water and extracted with ethyl acetate. The crude product was chromatographed on silica from benzene. Elution with benzene–ether (1 : 1) gave the crude keto-ester (XXVIII) which was further purified by chromatography on neutral alumina from benzene–ether (1 : 1). Purification from ethyl acetate–light petroleum gave the *oxo-ester* (0·1 g.) in needles, m. p. 109—110°, exhibiting an intense violet reaction with ferric chloride, $[\alpha]_D^{19}$ −48·3° (*c* 6·17 in $CHCl_3$) [Found: C, 64·6; H, 8·2; OMe, 15·0. $C_{20}H_{26}O_5(OMe)_2$ requires C, 64·7; H, 7·9; OMe, 15·2%]. After removal of the oxo-ester from the column elution with ether gave a *monomethyl ester* (XXVII; R = Me, R′ = H) (0·1 g.) which was rechromatographed on silica from ether followed by crystallisation from ethyl acetate–light petrolum to yield needles, m. p. 205° (decomp.), $[\alpha]_D^{19}$ +15·9° (*c* 3·27 in alcohol) (Found: C, 60·8; H, 7·6. $C_{21}H_{32}O_8$ requires C, 61·2; H, 7·8%). This acid was readily soluble in sodium hydrogen carbonate solution and had a negative ferric reaction in alcohol.

Cyclisation of the trimethyl ester (XXVII; R = R′ = Me) (0·4 g.) in boiling benzene (25 ml.) containing sodium methoxide [prepared from sodium (60 mg.)] during 2 hr., gave the oxo-ester (120 mg.), identical (m. p., mixed m. p., and infrared spectrum) with the previously prepared specimen.

Dilactone from Dihydroisorosenonolactone.—Dihydroisorosenonolactone (0·5 g.) was oxidised with pertrifluoroacetic acid as previously described for dihydrorosenonolactone. Purification of the product by chromatography from benzene–light petroleum (b. p. 60—80°) (1 : 1) on neutral alumina followed by crystallisation from light petroleum (b. p. 60—80°) gave the dilactone (0·02 g.) in needles, identical (m. p., mixed m. p., and infrared spectrum) with the product previously derived from methyl rosoate [2] and from rosoic acid by reduction with sodium borohydride.

Potassium Borohydride Reduction of 18-Carboxy-10-hydroxy-7-oxo-19-nor-rosan-16-oic γ-Lactone.—A solution of potassium borohydride (0·125 g.) in the minimum quantity of water containing 2N-sodium hydroxide (0·1 ml.) was added to a solution of 18-carboxy-10-hydroxy-7-oxo-19-nor-rosan-16-pic γ-lactone (0·1 g.) [6] in methanol (50 ml.). One hr. later the mixture was diluted with water (50 ml.), extracted with ether, acidified, saturated with ammonium sulphate, and again extracted with ether. Purification of the acidic extract from water furnished *18-carboxy-7,10-dihydroxy-19-nor-rosan-16-oic 16,10-lactone* in plates (0·06 g.), m. p. 250—260° (decomp.) (Found: C, 68·1; H, 8·5. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4%).

18-Carboxy-10-hydroxy-7-oxo-19-nor-8β-rosan-16-oic γ-Lactone.—18-Carboxy-10-hydroxy-7-oxo-19-nor-rosan-16-oic γ-lactone (0·014 g.) dissolved in 5% aqueous potassium hydroxide (5 ml.) was warmed on the steam-bath for ½ hr. The solution was cooled and acidified to yield 18-carboxy-10-hydroxy-7-oxo-19-nor-8β-rosan-16-oic γ-lactone (0·12 g.), identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen.[6]

Methylation of this acid (0·4 g.) with ethereal diazomethane in chloroform–methanol (1 : 1) at 0° furnished the *methyl ester* which separated from aqueous methanol and then from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 145° (Found: C, 68·6; H, 7·9. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%). Reduction of this ester (0·12 g.) in methanol (10 ml.) with potassium borohydride (0·06 g.) in water (1 ml.) containing 2N-sodium hydroxide (0·1 ml.) during 2 hr. at room temperature furnished a colourless gum which was chromatographed on neutralised alumina in benzene solution. Elution with benzene–chloroform (6 : 1) furnished the *hydroxy-ester* which separated from benzene–light petroleum (b. p. 60—80°) in prisms (0·03 g.), m. p. 153° (Found: C, 68·7; H, 8·8. $C_{20}H_{30}O_5$ requires C, 68·5; H, 8·6%).

Ultraviolet spectra were determined in alcohol by using a Perkin-Elmer U.V. 137 spectrometer. Infrared spectra (unless indicated to the contrary) were determined in Nujol by using Perkin-Elmer 137 and 237 spectrometers. The n.m.r. spectra were determined in deuterochloroform by Miss J. Lovenack using a Varian A.60 spectrometer. We thank the Wellcome Trust for the provision of this instrument on permanent loan and Imperial Chemical Industries Limited, for a grant in aid of this investigation. One of us (G. A. E.) is indebted to the National Institutes of Health of the United States of America for a Post-Doctoral Fellowship.

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THE SCHOOL OF PHARMACY, THE UNIVERSITY, LONDON. [*Received, January 18th,* 1965.]