LXXI. STUDIES IN THE BIOCHEMISTRY OF MICRO-ORGANISMS

LXI. THE MOLECULAR CONSTITUTION OF GEODIN AND ERDIN, TWO CHLORINE-CONTAINING METABOLIC PRODUCTS OF *ASPERGILLUS TERREUS* THOM. PART II. DIHYDROGEODIN AND DIHYDROERDIN AND THE SYNTHESIS OF THEIR TRIMETHYL ETHERS

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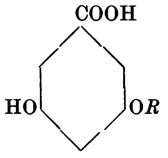
Raistrick & Smith [1936] showed that a strain of *Aspergillus terreus* Thom, when grown on Czapek-Dox solution containing glucose as sole source of carbon and KCl as sole source of chlorine, produced two new metabolic products, geodin, $C_{15}H_6O_5Cl_2(OCH_3)_2$, and erdin, $C_{15}H_7O_6Cl_2(OCH_3)$, each of which on catalytic reduction gave rise to a dihydro-derivative. Later, Clutterbuck *et al.* [1937] found that both dihydrogeodin and dihydroerdin yielded the same compound on complete methylation with diazomethane, viz. a neutral substance

$$C_{15}H_5O_2Cl_2(OCH_3)_5,$$

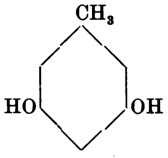
which on alkaline hydrolysis yielded a monobasic acid $C_{15}H_6O_3Cl_2(OCH_3)_4$, one methoxyl group having been lost. Since, as is shown later by synthesis, the latter compound contains a COOH group the formula of the neutral, fully methylated substance, may be expanded to $C_{14}H_5OCl_2(OCH_3)_4(COOCH_3)$ and the following experiment showed that this substance is undoubtedly dihydrogeodin trimethyl ether, the $COOCH_3$ group being already present in dihydrogeodin itself but absent from dihydroerdin. When dihydrogeodin and dihydroerdin are each fully ethylated with diazoethane and the resulting neutral compounds hydrolysed by aqueous alcoholic NaOH, the same monobasic acid is obtained in each case, viz. $C_{14}H_5OCl_2(OCH_3)(OC_2H_5)_3(COOH)$, which still retains the methoxyl group originally present in dihydroerdin. This substance is therefore dihydroerdin triethyl ether. The corresponding monobasic acid obtained by hydrolysis of fully methylated dihydrogeodin or dihydroerdin is therefore dihydroerdin trimethyl ether and a further consequence is that dihydrogeodin is the methyl ester of dihydroerdin.

Much light has been thrown on the detailed structure of dihydrogeodin and dihydroerdin by a study of the products of reductive and hydrolytic fission.

(*a*) *Reductive fission.* When dihydrogeodin was refluxed with hydriodic acid (*d*, 1·7) two molecules of methyl iodide and one of CO_2 were evolved, and the only non-volatile degradation products found were 3:5-dihydroxybenzoic acid (α-resorcylic acid) (I; $R=H$; $C_7H_6O_4$) and orcinol (II; $C_7H_8O_2$).



(I)



(II)

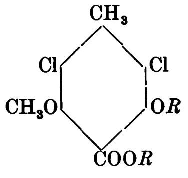
Since it is very unlikely that both these substances can arise from the same half of the molecule under the conditions of the experiment it follows that all the C atoms in dihydrogeodin are accounted for, and the action of HI may be summarized as $C_{17}H_{14}O_7Cl_2+3H_2O+4H=C_7H_8O_2+C_7H_6O_4+2CH_3OH$ (as $2CH_3I$) $+CO_2+2HCl$.

Dihydroerdin also yielded the same products (but with 1 mol. CH_3I in place of 2 mol.) and it is clear that the basal structure of each dihydro-compound consists of the orcinol nucleus linked in some way to the α-resorcylic acid nucleus. A consideration of the expanded formula $C_{14}H_5OCl_2(OCH_3)_4(COOCH_3)$ previously given for dihydrogeodin trimethyl ether reveals that only one oxygen atom is unaccounted for and it seemed probable therefore that this O atom is concerned in the link between the two nuclei. An obvious possibility is —CO— and this possibility was confirmed by hydrolytic fission.

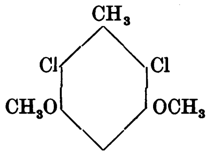
(*b*) *Hydrolytic fission.* Like many hydroxy-derivatives of benzophenone which undergo hydrolytic fission when heated with 80 % H_2SO_4 [cf. Graebe & Eichengrun, 1892] both dihydrogeodin and dihydroerdin are split by this reagent and give rise to the monomethyl ether of 3:5-dihydroxybenzoic acid (α-resorcylic acid) (I; $R=CH_3$; $C_8H_8O_4$) together with an acid $C_8H_6O_4Cl_2$, a fission which may be represented thus for dihydroerdin:

$$C_{16}H_{12}O_7Cl_2+H_2O=C_8H_8O_4+C_8H_6O_4Cl_2.$$

The chlorine-containing acid was obviously a derivative of orcinol and seemed to be a dichloro-derivative of either orsellinic or *p*-orsellinic acid. On complete methylation with diazomethane it yielded methyl 2:6-dichloro-3:5-dimethoxy-*p*-toluate (III; $R=CH_3$), identical in all respects with the compound prepared synthetically by the chlorination of methyl *p*-orsellinate dimethyl ether [Calam & Oxford, 1939]. The acid $C_8H_6O_4Cl_2$ is therefore *2:6-dichloro-3:5-dihydroxy-*p*-toluic acid* (III; $R=H$; $OCH_3=OH$).



(III)

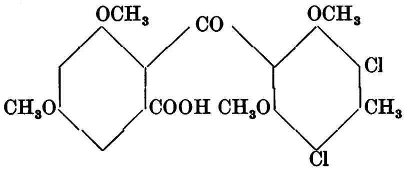


(IV)

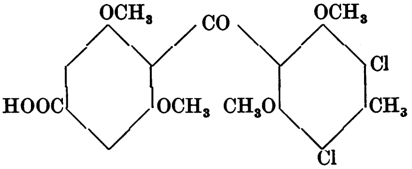
Dihydroerdin trimethyl ether also underwent a similar hydrolytic fission to yield 3:5-dimethoxybenzoic acid, CO_2, 2:6-dichloro-orcinol dimethyl ether (IV) and the monomethyl ether of dichloro-*p*-orsellinic acid (III; $R=H$).

Compound (IV) was also obtained in quite another way. The thermal degradation of geodin and erdin, as well as of dihydroerdin, at 250°, yielded a sublimate consisting essentially of a phenolic substance $C_7H_6O_2Cl_2$, *2:6-dichloro-orcinol*, which on methylation yielded IV ($C_9H_{10}O_2Cl_2$) identical in all respects with the dimethyl ether of 2:6-dichloro-orcinol prepared synthetically [Calam & Oxford, 1939].

The above evidence strongly suggests that dihydrogeodin and dihydroerdin are derivatives of benzophenone and, since two COOH groups appear in the fission products, one must be concerned in the union between the two benzene rings, dihydroerdin trimethyl ether being only a monobasic acid. The only possible links between the two rings are therefore —CO— and —CO.CH_2—. The latter must be incorrect since dihydroerdin trimethyl ether, when oxidized by boiling alkaline $KMnO_4$, forms a dibasic acid with the same number of C atoms but with two O atoms more and two H atoms less than the starting material. This can be explained only by the oxidation of CH_3 to COOH, hence the CH_3 group of the dichloro-orcinol half of the molecule must exist as such in the dihydro-compounds. The only possible link between the two benzene nuclei is therefore —CO—, and the failure of all our attempts to prepare derivatives of this carbonyl group is doubtless due to the steric effects of the adjacent OCH_3 groups. There are thus two possible structures for dihydroerdin trimethyl ether, viz.:



(V)

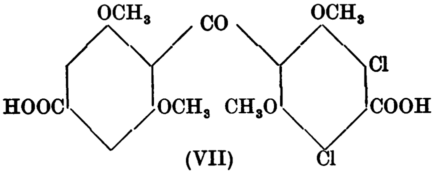


(VI)

for the free COOH group in this compound must be attached to the non-chlorinated benzene ring, there being no free position in the other ring. Each of these structures will yield 3:5-dimethoxybenzoic acid and 2:6-dichloro-3:5-dimethoxy-*p*-toluic acid or its degradation products on hydrolytic fission. Since no dimethoxy-phthalic or -terephthalic acid is formed in the fission, the evidence so far presented does not enable a decision to be made between (V) and (VI). Actually (V) is almost certainly correct for the following reasons.

(1) Dihydroerdin trimethyl ether can be acetylated to yield a neutral mono-acetyl derivative. This may be explained on (V) (a γ-keto-acid behaving as a γ-hydroxy-γ-lactone) for which there are many analogies including that of benzophenone-2-carboxylic acid [von Pechmann, 1881; Graebe, 1900], but cannot be explained convincingly on (VI).

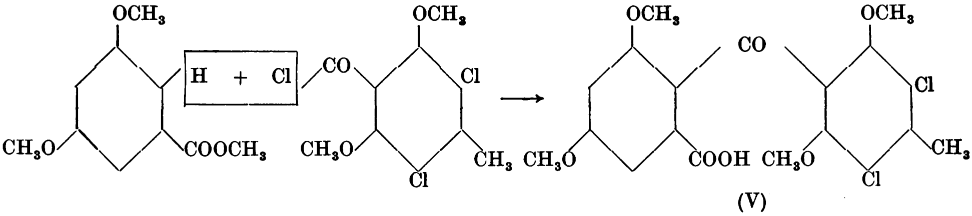
(2) The dibasic acid obtained by alkaline $KMnO_4$ oxidation of dihydroerdin trimethyl ether must be (VII) if derived from (VI). But such a structure is



(VII)

quite symmetrical about the —CO— link (except for the two Cl atoms, whose effect on the reactivity of the molecule is probably very small in comparison with that of the four methoxyl groups), and ought to yield both 3:5-dimethoxybenzoic acid and 2:6-dimethoxyterephthalic acid on hydrolytic fission. Actually 3:5-dimethoxybenzoic acid and 3:5-dichloro-2:6-dimethoxyterephthalic acid were the only hydrolytic products isolated.

(3) Dihydroerdin trimethyl ether has been synthesized by an application of the Friedel-Crafts reaction, 2:6-dichloro-3:5-dimethoxy-*p*-toluyl chloride being condensed directly with methyl 3:5-dimethoxybenzoate. From the known behaviour of resorcinol dimethyl ether towards acid chlorides in the Friedel-Crafts reaction it might be predicted with confidence that in the above more complex instance the entering group would also occupy the position *para* to one OCH_3 group and *ortho* to the other, to the almost total exclusion of the position *ortho* to each OCH_3 group. The presence of $COOCH_3$ *meta* to each OCH_3 would tend to strengthen this preference. Thus Jones & Robinson [1917], discussing the influence of a negative group on the directing effect of a positive group in benzene substitution, conclude "there is evidence that it is not merely *ortho* substitution which is favoured but that it is the particular *ortho* position situated between the positive and negative groups". There can be little doubt therefore that dihydroerdin trimethyl ether is *3′:5′-dichloro-4:6:2′:6′-tetramethoxy-4′-methylbenzophenone-2-carboxylic acid* (V). Since the hydrolytic fission of dihydroerdin itself yields the monomethyl ether of α-resorcylic acid, dihydroerdin is evidently either 3′:5′-dichloro-6:2′:6′-trihydroxy-4-methoxy- or 3′:5′-dichloro-4:2′:6′-trihydroxy-6-methoxy-4′-methylbenzophenone-2-carboxylic acid, but the evidence so far adduced offers no clue as to which structure is the correct one.



(V)

The methylation of synthetic dihydroerdin trimethyl ether with diazomethane yielded its methyl ester identical in all respects with dihydrogeodin trimethyl ether obtained by the complete methylation of dihydrogeodin, prepared by the catalytic reduction of geodin from *A. terreus*. Dihydrogeodin trimethyl ether is thus *methyl 3′:5′-dichloro-4:6:2′:6′-tetramethoxy-4′-methyl-benzophenone-2-carboxylate* (V; $COOH=COOCH_3$).

EXPERIMENTAL

Equivalents of dihydrogeodin and dihydroerdin. The compounds were dissolved in aqueous ethanol and titrated directly with 0·1 *N* NaOH, with phenolphthalein as indicator. *Dihydrogeodin:* Found, 322. $C_{17}H_{14}O_7Cl_2$ requires 401 (as monobasic acid) and 200·5 (as dibasic acid). *Dihydroerdin:* Found, 201. $C_{16}H_{12}O_7Cl_2$ requires 193·5 (as dibasic acid).

Dihydroerdin is thus clearly dibasic and dihydrogeodin more nearly monobasic than dibasic.

Ethylation of dihydrogeodin and dihydroerdin and subsequent hydrolysis to dihydroerdin triethyl ether

Dihydrogeodin (0·45 g.) was treated with excess of ethereal diazoethane for 30 min. The solvent was removed leaving a reddish gum (0·64 g.) which was hydrolysed by refluxing with ethanol (50 ml.) and *N* NaOH (25 ml.) for 1 hr. After removal of the ethanol *in vacuo* and acidification, the precipitated acid was collected (0·59 g.; M.P. 185°) and crystallized from benzene-light petroleum in colourless rectangular prisms, M.P. 211–213°. (Found: C, 55·95, 56·0; H, 5·2, 5·0; CH_3O, 24·9, 25·1 %. $C_{22}H_{24}O_7Cl_2$ (dihydroerdin triethyl ether) requires C, 56·05; H, 5·1; $CH_3O+3C_2H_5O$ (calc. as $4CH_3O$), 26·3 %. $C_{21}H_{22}O_7Cl_2$ (diethyldihydrogeodin) requires C, 55·1; H, 4·85; $2CH_3O+2C_2H_5O$ (calc. as $4CH_3O$), 27·1 %.) Dihydroerdin, treated in exactly the same way, gave identical rectangular prisms, M.P. 211–212°, alone or mixed with the acid obtained from dihydrogeodin. (Found: C, 56·2; H, 5·1; Cl, 14·8, 14·7; CH_3O, 25·1, 25·5 %. Equiv. 486. $C_{22}H_{24}O_7Cl_2$ requires C, 56·05; H, 5·1; Cl, 15·05; $CH_3O+3C_2H_5O$ (calc. as $4CH_3O$), 26·3 %. Equiv. 471.)

Acetyl derivative of dihydroerdin trimethyl ether

Dihydroerdin trimethyl ether (0·5 g.) was heated for 30 min. at 150–160° with anhydrous sodium acetate (1 g.), acetic anhydride (2 ml.) and glacial acetic acid (3 ml.). Water was then cautiously added to the cooled mixture, and the precipitated gum hardened after standing for several hours. The solid product was crystallized from light petroleum (B.P. 80–100°) and separated in rosettes of prisms (0·13 g.). Unlike the starting material it was not completely soluble in dilute $NaHCO_3$ solution. The $NaHCO_3$-insoluble portion (0·03 g.) was crystallized from CCl_4-light petroleum and formed compact square prisms, M.P. 208–210°. (Found: C, 53·5, 53·5; H, 4·15, 4·35; Cl, 15·1; hydrolysable $CH_3.CO$, 8·6; CH_3O, 24·85 %. $C_{21}H_{20}O_8Cl_2$ requires C, 53·5; H, 4·3; Cl, 15·05; $CH_3.CO$, 9·1; $4CH_3O$, 26·3 %.) The acetyl derivative is quite insoluble in cold caustic soda solution and dissolves only slowly on heating.

Hydrolysis. 0·02382 g. in 10 ml. EtOH + 5 ml. H_2O required only 0·004 ml. $N/10$ NaOH for neutralization to phenolphthalein. 1·891 ml. $N/10$ NaOH were then added and the corked flask kept at 37° overnight. Required: 1·034 ml. $N/10$ H_2SO_4 for back titration. Hence equiv. = 278. $C_{21}H_{20}O_8Cl_2$ titrating as a dibasic acid requires equiv. = 235·5.

Oxidation of dihydroerdin trimethyl ether to a dibasic acid containing the same number of carbon atoms

Dihydroerdin trimethyl ether, $C_{19}H_{18}O_7Cl_2$ (0·5 g.), was dissolved in 0·1 N NaOH (30 ml.) and the solution refluxed with slow dropwise addition of 5 % aqueous $KMnO_4$. A stable purple colour was reached after 30 ml. of the latter had been added during $2\frac{1}{2}$ hr. The liquid was cooled, decolored with SO_2 and acidified with dilute H_2SO_4. The precipitated acid separated as colourless needles (0·33 g., M.P. 229–231°), raised to 233–235° by recrystallization from hot water. (Found: C, 49·85; H, 3·6; Cl, 15·7, 15·25; CH_3O, 27·3 %. Equiv. 227. $C_{19}H_{16}O_9Cl_2$ requires C, 49·7; H, 3·5; Cl, 15·45; $4CH_3O$, 27·0 %. Equiv. 229·5 (titrating as a dibasic acid).)

Several attempts were made partially to methylate dihydroerdin with diazomethane and then to oxidize away the incompletely methylated parts of the molecule in the hope of isolating a recognizable dimethoxy-phthalic or -terephthalic acid, but even the product obtained by the addition of 2 mol. of diazomethane to dihydrogeodin was completely destroyed by $KMnO_4$ both in aqueous alkaline and in acetone solutions.

Reductive fission experiments

A. *Dihydrogeodin.* Dihydrogeodin (0·8487 g.) was heated with HI (15 ml.; *d*, 1·7) in a Zeisel apparatus in a stream of dry CO_2-free nitrogen, the bath temperature being maintained at 140–150°. The issuing gases were passed through bubblers containing alcoholic $AgNO_3$ and standard baryta solution respectively. The AgI produced in the former amounted to 0·9739 g. (calc. for $2CH_3O$, 0·9928 g.) whilst the CO_2 absorbed in the latter was equivalent to 44·05 ml. 0·1 *N* (calc. for 1 mol. CO_2, 42·3 ml. 0·1 *N*). The residual HI solution was washed into a continuous extractor and extracted with ether for 8 hr. The material left after removal of the solvent was dissolved in water and heated on the steam bath with red phosphorus to remove iodine, filtered and re-extracted with ether. The dried solid obtained from the final extract (0·635 g.; calc. 0·627 g.) was fractionally sublimed in a high vacuum, first at 80° to yield sublimate I (0·22 g.) and then at 160° to yield sublimate II (0·25 g.).

Sublimate I, after re-sublimation, was free from chlorine and melted at 108° alone or mixed with authentic anhydrous orcinol (M.P. 108°). In aqueous alcoholic solution it gave a violet colour with $FeCl_3$, identical with that given by orcinol. (Found: C, 68·0, 67·7; H, 6·5, 6·4 %. $C_7H_8O_2$ requires C, 67·7; H, 6·5 %.)

Sublimate II, after re-sublimation, was free from chlorine and melted at 236°, alone or mixed with authentic α-resorcylic acid (M.P. 236°) obtained by the HI demethylation of 3:5-dimethoxybenzoic acid. (Found: C, 54·8, 54·55; H, 4·1, 3·9 %. $C_7H_6O_4$ requires C, 54·5; H, 3·9 %.) On methylation with diazomethane and hydrolysis of the resulting methyl ester, 3:5-dimethoxybenzoic acid was obtained, M.P. 181–182°, alone or mixed with the authentic acid prepared by the hot alkaline $KMnO_4$ oxidation of orcinol dimethyl ether.

B. *Dihydroerdin.* Dihydroerdin (0·873 g.) under the same conditions gave CO_2 equivalent to 44·5 ml. 0·1 *N* (calc. for 1 mol. CO_2, 45·5 ml.) and CH_3I (as AgI) equivalent to one CH_3O group. From the HI was recovered 0·68 g. of crude solid material (calc. 0·64 g.) which was fractionally sublimed as before to yield orcinol (0·15 g.) and a small amount of α-resorcylic acid.

Hydrolytic fission experiments

A. *Dihydrogeodin.* Dihydrogeodin (1 g.) was gradually heated in a small flask on a wire gauze with a mixture of conc. H_2SO_4 (20 ml.) and water (10 ml.) with a thermometer in the liquid. At 120° the colour of the liquid suddenly became lighter, the heating was immediately stopped and the flask allowed to cool. Water (100 ml.) was then cautiously added and the precipitated solid collected, washed and dried (0·5 g.). The filtrate, after ether extraction, yielded a similar solid (0·5 g.). The combined products were repeatedly and fractionally sublimed in a high vacuum giving two main fractions.

Sublimate I sublimed at 110–120°, melted at 214° and gave an intense blue colour with $FeCl_3$. (Found: C, 40·7, 40·6; H, 2·7, 2·8; Cl, 29·4, 29·6 %. $C_8H_6O_4Cl_2$ requires C, 40·5; H, 2·55; Cl, 30·0 %.) It was shown to be *2:6-dichloro-3:5-dihydroxy-*p*-toluic acid* by complete methylation with diazomethane when methyl 2:6-dichloro-3:5-dimethoxy-*p*-toluate, M.P. 85–86°, was obtained, identical in all respects (crystalline form; mixed M.P.; solubilities) with the ester prepared synthetically [Calam & Oxford, 1939]. (Found: C, 47·7; H, 4·3; Cl, 25·2, 25·2; CH_3O, 33·7 %. $C_{11}H_{12}O_4Cl_2$ requires C, 47·3; H, 4·3; Cl, 25·4; $3CH_3O$, 33·3 %.) The above fission product, when heated above its M.P., lost CO_2 to yield *2:6-dichloro-orcinol*, M.P. 164°, identical with the chlorophenol obtained by thermal degradation of erdin (see later).

Sublimate II sublimed at 120–140°, and was finally obtained pure only after repeated fractional sublimation. It melted at 201° and did not contain chlorine, nor did it give any coloration with $FeCl_3$. It was soluble in $NaHCO_3$ solution with evolution of CO_2. (Found: C, 56·8; H, 4·9; CH_3O, 17·2 %. $C_8H_8O_4$ requires

C, 57·15; H, 4·8; $1CH_3O$, 18·4%.) It was shown to be the monomethyl ether of α-resorcylic acid (Mauthner [1927] gives M.P. 202–203°) by methylating it with diazomethane followed by hydrolysis of the resulting ester with aqueous alcoholic NaOH to yield 3:5-dimethoxybenzoic acid, M.P. 181–182°, alone or mixed with an authentic specimen.

B. *Dihydroerdin*. A more efficient and rapid method of separation of the fission products was devised in this case, advantage being taken of the sparing solubility of the sodium salt of the monomethyl ether of α-resorcylic acid in an excess of $NaHCO_3$ solution. Dihydroerdin (1·207 g.) and a mixture of conc. H_2SO_4 (22 ml.) and water (11 ml.) were heated together in a stream of CO_2-free nitrogen and the issuing gases passed through a bubbler containing standard baryta solution. The reaction flask was slowly heated in an oil bath and when the latter had reached 125° the red solution suddenly became nearly colourless, with simultaneous separation of a solid. The oil bath was at once removed and the reaction mixture cooled. The CO_2 evolved was equivalent to only 3·5 ml. 0·1 *N* NaOH. Water (65 ml.) was added to the reaction mixture and the precipitated solid was later collected, washed and dried. The crude product (1·02 g.) was shaken with a slight excess of saturated $NaHCO_3$ solution to neutralize it, and again filtered.

The filtrate on acidification gave an acid (0·42 g.), M.P. 200–205°, raised to 214° by a single sublimation in a high vacuum. This acid was identical with the acid, M.P. 214°, obtained in the hydrolytic fission of dihydrogeodin, and was therefore *2:6-dichloro-3:5-dihydroxy-*p*-toluic acid*. On methylation with diazomethane it yielded methyl 2:6-dichloro-3:5-dimethoxy-*p*-toluate identical in all respects with an authentic specimen of the ester prepared synthetically.

The $NaHCO_3$-insoluble residue was treated with dilute H_2SO_4 and extracted with ether, the extract being then shaken with dilute aqueous $NaHCO_3$. The non-acidic substance remaining in the ether (0·03 g.; calc. from CO_2 produced in the fission, 0·034 g.) gave on sublimation a product of M.P. 165°, identical with *2:6-dichloro-orcinol* obtained by thermal degradation of erdin (see later). The above bicarbonate extract was acidified and extracted with ether to yield a product (0·54 g.) which, when crystallized once from hot water, had M.P. 197–197·5°, and was free from chlorine. It was identical in all respects with the monomethyl ether of α-resorcylic acid obtained in the hydrolytic fission of dihydrogeodin. (Found: C, 56·7, 56·7; H, 4·95, 4·7; CH_3O, 17·15, 17·35%. $C_8H_8O_4$ requires C, 57·15; H, 4·8; $1CH_3O$, 18·4%.)

C. *Dihydrogeodin trimethyl ether*. The ether (1·0 g.) was heated with a mixture of conc. H_2SO_4 (20 ml.) and water (10 ml.) to 120° when the colour suddenly changed from deep orange to light brown. After cooling, water (40 ml.) was added and the precipitated solid (1·15 g.) collected later, washed and dried. It was covered with a slight excess of saturated $NaHCO_3$ solution, and, after standing for a while, filtered.

The filtrate, on acidification, yielded a crude product (0·59 g.) which after one recrystallization from benzene gave rather impure 3:5-dimethoxybenzoic acid (0·24 g.) (see below). The benzene mother liquor, on evaporation, yielded a different substance (0·17 g.) which was purified by sublimation followed by crystallization from aqueous alcohol. It formed hair-like needles, M.P. 201°, which contained chlorine and gave a violet colour with $FeCl_3$. (Found: C, 43·1, 43·1; H, 3·2, 3·15; CH_3O, 12·2%. $C_9H_8O_4Cl_2$ requires C, 43·0; H, 3·2; $1CH_3O$, 12·35%.) That it was 2:6-dichloro-3-hydroxy-5-methoxy-*p*-toluic acid (III, $R=H$) was shown by its identity with this substance prepared synthetically (Calam & Oxford [1939] who quote M.P. 202–203°) and by the fact that it yielded methyl 2:6-dichloro-3:5-dimethoxy-*p*-toluate (III; $R=CH_3$) on methylation with diazomethane.

The $NaHCO_3$-insoluble portion mentioned above was treated with 0·2 *N* NaOH (10 ml.), and the undissolved residue (0·12 g.) was recrystallized from light petroleum to yield prisms, M.P. 131–133°, not depressed on admixture with an authentic specimen of 2:6-dichloro-orcinol dimethyl ether (IV). The alkali-soluble material was recovered (0·25 g.) and proved to be chiefly 3:5-dimethoxybenzoic acid (0·49 g. in all). The combined specimens were recrystallized from hot water to yield needles, M.P. 181–182°, not depressed on admixture with an authentic specimen of 3:5-dimethoxybenzoic acid.

D. *The dibasic acid* $C_{19}H_{16}O_9Cl_2$ *obtained by oxidation of dihydroerdin trimethyl ether.* The acid (0·85 g.) was heated with conc. H_2SO_4 (17 ml.) and water (8 ml.) to 110° when the colour changed from orange to light brown. After cooling, an equal volume of water was added and the precipitated solid collected after an hour (0·55 g.). It gave only a faint violet coloration with $FeCl_3$.

After solution in dilute aqueous $NaHCO_3$ and filtration from a little tarry material it was reprecipitated (0·25 g.) and purified, by sublimation in a high vacuum at 100°, to yield chlorine-free 3:5-dimethoxybenzoic acid, M.P. and mixed M.P. 183°. (Found: CH_3O, 33·1 %. $C_9H_{10}O_4$ requires $2CH_3O$, 34·1 %.)

The original acid mother liquor from the fission and the filtrate from the above crude dimethoxybenzoic acid were extracted with ether and the combined crude products (0·44 g.) crystallized from ethyl acetate-light petroleum to give colourless needles, M.P. 236–238°, alone or mixed with authentic 3:5-dichloro-2:6-dimethoxyterephthalic acid, M.P. 235–237° [Calam & Oxford, 1939]. (Found: C, 40·1; H, 2·8; Cl, 24·7 %. Equiv. 143·5. $C_{10}H_8O_6Cl_2$ requires C, 40·7; H, 2·7; Cl, 24·1 %. Equiv. 147·5.)

Thermal degradation of geodin, erdin and dihydroerdin with production of 2:6-dichloro-orcinol

Geodin, erdin and dihydroerdin all give the same volatile product on thermal degradation. The following is a typical experiment: erdin (1 g.) was heated at 250° for 1¼ hr. in a long boiling tube fitted with a small condenser, when long, colourless needles sublimed (0·15 g.). This product, after resublimation, melted at 164°. (Found: C, 43·9, 44·1; H, 3·1, 3·2; Cl, 36·0, 36·3 %; mol. wt. (cryoscopic in camphor), 193, 189. $C_7H_6O_2Cl_2$ requires C, 43·5; H, 3·1; Cl, 36·75 %; mol. wt. 193.) It was soluble in caustic soda solution and contained two active H atoms as determined by the Zerewitinoff method (Roth). (Found: 1·8 active H atoms both in anisole at 19° and in pyridine at 95°.) It also contained one Me side chain, as determined by Kuhn-Roth oxidation. (Found: 0·947, 0·943 mol. of CH_3COOH per mol. of $C_7H_6O_2Cl_2$) and was therefore undoubtedly a dichlorodihydroxymethylbenzene. That it was *2:6-dichloro-orcinol* was proved by methylation with excess of ethereal diazomethane, when 2:6-dichloro-orcinol dimethyl ether (IV), M.P. 129°, was obtained, identical in all respects, including mixed M.P., with the authentic compound, M.P. 133–134°, prepared synthetically [Calam & Oxford, 1939]. (Found: C, 49·0, 48·8; H, 4·4, 4·55; Cl, 31·6, 31·6 %. $C_9H_{10}O_2Cl_2$ requires C, 48·8; H, 4·6; Cl, 32·1 %.) Dihydroerdin behaved very similarly to erdin, but with geodin the yield was smaller and the sublimate less pure.

Syntheses

A. *Dihydroerdin trimethyl ether.* (*3′:5′-Dichloro-4:6:2′:6′-tetramethoxy-4′-methylbenzophenone-2-carboxylic acid* (V).) A mixture of 2:6-dichloro-3:5-dimethoxy-*p*-toluic acid (5 g.) and thionyl chloride (7 ml.) was kept for an hour, after which excess of the latter was removed under reduced pressure. The resulting crude acid chloride, methyl 3:5-dimethoxybenzoate (5·5 g.) and powdered anhydrous aluminium chloride (5 g.), were placed in a long-necked round-bottomed flask, which, after displacement of the air by dry HCl gas, was fitted with a cork bearing a $CaCl_2$-tube. The mixture was heated on the steam bath for 10 min. until a homogeneous reddish-brown semi-solid mass had formed and was left at room temperature for 2 days. Water was added and unchanged methyl 3:5-dimethoxybenzoate removed by distillation in steam. The liquid was decanted from the residual gum which was methylated by treatment with acetone (30 ml.), methyl sulphate (10 ml.) and 2*N* NaOH (80 ml. in 8 successive portions of 10 ml.) with continuous shaking. The semi-solid product was washed by decantation several times and hydrolysed by refluxing with ethanol (50 ml.) and *N* NaOH (50 ml.) for 1 hr. After addition of water, cooling and filtration from a little oily impurity, the crude acid was precipitated by acidification (3·7 g.). After one crystallization from CCl_4-light petroleum it melted at 149–159° (1·6 g.) and from the mother liquor 1·4 g. of nearly pure 2:6-dichloro-3:5-dimethoxy-*p*-toluic acid were recovered, M.P. 107–112°. The product, M.P. 149–159°, was further purified by repeated crystallization from CCl_4 to yield colourless laminae, M.P. 177–179°, readily soluble in dilute aqueous $NaHCO_3$. (Found: C, 52·65; H, 4·1; Cl, 16·6, 16·8; CH_3O, 28·6, 28·8%. $C_{19}H_{18}O_7Cl_2$ requires C, 53·1; H, 4·2; Cl, 16·55; $4CH_3O$, 28·9%.) Clutterbuck *et al.* [1937] quote 168° for the M.P. of natural dihydroerdin trimethyl ether, but the M.P. of their material was raised after several recrystallizations from CCl_4 to 177–179° unaltered by admixture with the above synthetic product of the same M.P.

B. *Dihydrogeodin trimethyl ether.* (*Methyl 3':5'-dichloro-4:6:2':6'-tetramethoxy-4'-methylbenzophenone-2-carboxylate* (V; COOH = $COOCH_3$).) The above synthetic dihydroerdin trimethyl ether (M.P. 177–179°; 0·1 g.) was treated with excess of ethereal diazomethane, and the resulting ester crystallized from aqueous methyl alcohol to yield colourless needles, M.P. 110–112°, alone or mixed with dihydrogeodin trimethyl ether (M.P. 108°) prepared from natural dihydrogeodin. (Found: C, 53·65; H, 4·2; Cl, 16·05, 15·8; CH_3O, 34·3%. $C_{20}H_{20}O_7Cl_2$ requires C, 54·15; H, 4·55; Cl, 16·0; $5CH_3O$, 35·0%.)

C. *Decarboxydihydroerdin trimethyl ether.* (*3:5-Dichloro-2:6:2':4'-tetramethoxy-4-methylbenzophenone.*) Resorcinol dimethyl ether (5 g.) and anhydrous aluminium chloride (5 g.) were added to crude 2:6-dichloro-3:5-dimethoxy-*p*-toluyl chloride (5 g.) prepared as before (see above). The mixture was cooled, the air displaced by dry HCl gas, and the flask fitted with a cork bearing a $CaCl_2$-tube. After heating on the water bath until a homogeneous dark red mass had formed, the flask was kept for 2 days. The reaction mixture was decomposed with ice-water and the unchanged resorcinol dimethyl ether removed by steam distillation. The residual solid was taken up in ether, the extract washed with dilute aqueous $NaHCO_3$, and the solvent removed to yield a crude product (4·2 g.) which was dissolved in acetone (20 ml.) and treated with dimethyl sulphate (10 ml.) and 2*N* NaOH (80 ml. in ten successive lots) with continuous shaking. The solid product (4 g.) was crystallized from aqueous methyl alcohol to yield colourless parallelepipeds, M.P. 94–95°. (Found: C, 56·4, 56·3; H, 4·8, 4·7; Cl, 18·4; CH_3O, 31·5%. $C_{18}H_{18}O_5Cl_2$ requires C, 56·1; H, 4·7; Cl, 18·4; $4CH_3O$, 32·2%.)

Many attempts were made to decarboxylate dihydroerdin trimethyl ether in the hope of obtaining the above substituted benzophenone. These included heating in a sealed tube with water at 140° and with water and Cu bronze at

250°, heating the ether in the dry state in N_2 at 250–300° (practically no CO_2 evolved) and heating with quinoline and Cu chromite. All were fruitless, the material being either completely broken down or recovered unchanged.

D. *Homodecarboxydihydroerdin trimethyl ether.* (*3:5-Dichloro-2:6:2′:4′-tetramethoxy-4:6′-dimethylbenzophenone.*) The synthesis was carried out exactly as in the previous section save that orcinol dimethyl ether (5 g.) was used in place of resorcinol dimethyl ether. The crude product after methylation (3·5 g.) was purified by repeated crystallization from aqueous methyl alcohol. Large, colourless rectangular prisms, M.P. 105–106°. (Found: C, 57·1, 57·2; H, 5·1, 5·0; Cl, 17·95; CH_3O, 31·3, 31·15%. $C_{19}H_{20}O_5Cl_2$ requires C, 57·1; H, 5·05; Cl, 17·8; $4CH_3O$, 31·1%.)

In this preparation the $NaHCO_3$ extract of the ethereal solution of the crude product (after removal of unchanged orcinol dimethyl ether) yielded *2:6-dichloro-3:5-dihydroxy-*p*-toluic acid* on acidification; M.P. 214° after two sublimations in a high vacuum. This constitutes a synthesis of the chloro-acid obtained by the hydrolytic fission of dihydrogeodin and dihydroerdin (pp. 584–5).

Several attempts were made to oxidize both CH_3 groups in the above substituted benzophenone to COOH in the hope of obtaining the dibasic acid previously obtained by the oxidation of dihydroerdin trimethyl ether (p. 583). These included the action of $KMnO_4$ in alkaline and in acid solution; CrO_3 in acetic acid-acetic anhydride solution; $K_2Cr_2O_7$ in H_2SO_4 solution; and 25% aqueous HNO_3. All were fruitless, the compound being either completely destroyed or recovered unchanged.

SUMMARY

Geodin ($C_{15}H_6O_5Cl_2(OCH_3)_2$) and erdin ($C_{15}H_7O_6Cl_2(OCH_3)$), metabolic products of *Aspergillus terreus* Thom, each give rise to a dihydro-derivative on catalytic reduction, dihydrogeodin being the methyl ester of dihydroerdin. As a result of analytical and synthetic methods dihydrogeodin trimethyl ether, $C_{14}H_5OCl_2(OCH_3)_4COOCH_3$, has been shown to be *methyl 3′:5′-dichloro-4:6:2′:6′-tetramethoxy-4′-methylbenzophenone-2-carboxylate* and dihydroerdin trimethyl ether, $C_{14}H_5OCl_2(OCH_3)_4COOH$, to be *3′:5′-dichloro-4:6:2′:6′-tetramethoxy-4′-methylbenzophenone-2-carboxylic acid.*

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