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Siphulin, a Chromenone Lichen Acid

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A new type of lichen acid, for which the name siphulin is proposed, has been isolated from the lichen *Siphula ceratites* (Fr.) Th. Fr. Degradations together with NMR data indicate formula (1) for the acid.

Siphula ceratites (Fr.) Th. Fr. belongs to the imperfect lichens, so called because sporulating organs have never been observed in them. Its habitat appears to be disjunctive on the western rim of the Scandinavian peninsula and the northern rim of Kola.[1] The material used in these investigations was collected in Kongsmoen, about 200 km north of Trondheim.

The air dried and ground material, which contained a considerable amount of mineral contamination, was extracted for 24 h with ether; for details, see Experimental.

The acid showed an apparent double m.p.; it appeared to melt with decomposition at 185°, resolidified and finally melted at 229—230°. By low temperature percolation and isolation the acid exhibited only a single m.p., at about 180°(decomp.). The decomposition was interpreted as a decarboxylation and the resolidifying as due to the presence of pre-formed decarboxylation product. The former assumption was supported by isolation of the decomposition product, which indeed was a decarboxylation product (*cf.* below), and the latter by the behaviour shown on admixture of a small amount of decarboxylated product with the acid isolated by the percolation procedure.

The acid was optically inactive, and this was confirmed by optical rotatory dispersion measurement. It gave a violet colour with iron(III) chloride in ethanol and a blue colour with Gibbs's reagent in soda solution. Analyses indicated no methoxyl. By potentiometric titration the equivalent weight was determined as 425; the later established formula (1) requires 426.*

* In the preliminary note [2] a formula was given without a double bond in the pyrone ring. This was based upon the negative findings that siphulin was not hydrogenated in ethyl acetate in the presence of palladium-on-barium sulphate, and that its methyl ester trimethyl ether appeared saturated to potassium permanganate. As will be seen in the sequel, positive evidence to the contrary now has been obtained.

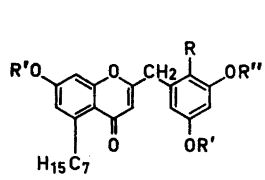
The acid was characterised by the following derivatives.

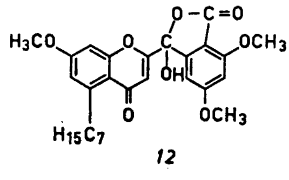
1. Triacetate (2), m.p. 145—146°.
2. Methyl ester (4), m.p. 208—209°.
3. Methyl ester triacetate (5), m.p. 132—133°.
4. Methyl ester dimethyl ether (6), m.p. 128—129°.
5. Methyl ester trimethyl ether (7), m.p. 77—78°.

The methyl ester dimethyl ether gave a bluish violet colour with iron(III) chloride in ethanol and a blue colour with Gibbs's reagent in aqueous-ethanolic soda solution. It also furnished a monoacetate (8), m.p. 123—124°.

In KBr siphulin exhibited a broad, indistinct band with a peak at about 1625 cm^{-1}. In tetrahydrofuran this band was somewhat more resolved, with peaks at 1658, 1615, and 1595 cm^{-1}. The infrared spectra of the methyl ester (4) and the methyl ester dimethyl ether (6) were no more informative, but the infrared spectra of the other derivatives pointed to the presence of two carbonyl functions in the molecule. The triacetate (2) had bands at 1785 (acetate), 1735 (carboxyl group), and 1650 cm^{-1} (conjugated carbonyl). The methyl ester triacetate (5) and the methyl ester dimethyl ether acetate (8) correspondingly showed bands at 1782, 1740, 1660, and at 1780, 1735, 1652 cm^{-1}, respectively, whilst the methyl ester trimethyl ether (7) had bands at 1730 and 1655 cm^{-1}. The idea that the bands at about 1655 cm^{-1} should be attributed to the presence of a carbonyl function in conjugation with a benzene nucleus was supported by the infrared spectra of decarboxysiphulin (9) and its di- (10) and trimethyl ethers (11), with bands at 1650, 1650, and 1660 cm^{-1}, respectively, the last value obtained in chloroform solution, and also by the facts that mild treatment of siphulin with alkali afforded only decarboxysiphulin (9), whilst siphulin methyl ester trimethyl ether (7) was recovered unchanged after treatment with methanolic sodium methylate.

To obtain another indication of the molecular composition, siphulin methyl ester trimethyl ether (7) was brominated with N-bromosuccinimide to give a monobromo derivative, m.p. 123—125°, bands in the infrared at 1730 and 1655 cm^{-1}.





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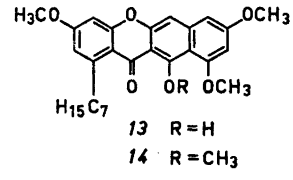


13 R=H
14 R=CH₃

1 R = COOH	R′ = H	R″ = H
2 R = COOH	R′ = Ac	R″ = Ac
3 R = COOH	R′ = CH_3	R″ = CH_3
4 R = $COOCH_3$	R′ = H	R″ = H
5 R = $COOCH_3$	R′ = Ac	R″ = Ac
6 R = $COOCH_3$	R′ = CH_3	R″ = H
7 R = $COOCH_3$	R′ = CH_3	R″ = CH_3
8 R = $COOCH_3$	R′ = CH_3	R″ = Ac
9 R = H	R′ = H	R″ = H
10 R = H	R′ = CH_3	R″ = H
11 R = H	R′ = CH_3	R″ = CH_3

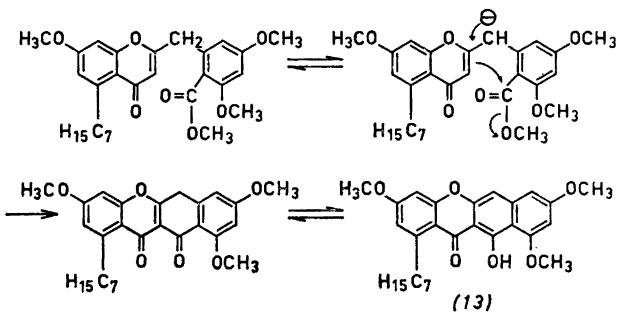
Alkaline degration of siphulin (1) furnished acetic acid, 3,5-dihydroxyphenylacetic acid (15), and sphaerophorol (29); for details, see Experimental. The compounds were identified by comparison with authentic specimens.

Similarly, alkaline degradation in methanol of siphulin methyl ester trimethyl ether (6) afforded several products; for details, see Experimental. Two weakly acidic products were a yellow solid and a liquid, obtained from the mother liquors of the yellow solid. The constitution of the yellow solid is discussed below. For the liquid is suggested the constitution as 2-hydroxy-4-methoxy-6-heptylacetophenone (38). The formulation appears reasonable in view of the isolation of sphaerophorol carboxylic acid 4-methyl ether as a degradation product of siphulin methyl ester trimethyl ether (see below), and it is in accordance with the NMR spectrum of the substance: An incompletely separated triplet with centrum at 9.14, a broad band at 8.71 ($-CH_2-$), a singlet at 7.43 ($COCH_3$), a triplet at 7.24 with coupling constant 7 c/s (benzylic CH_2), a sharp singlet at 6.31 (aromatic methoxyl), one at 3.72 (aromatic protons) and another at −2.90 (phenolic hydrogen).

The alkaline solution contained two more strongly acidic materials. In one case the isolated material was an acid (3) with m.p. 166—167° and bands in the infrared at 1725 and 1643 cm^{-1}, which on methylation with diazomethane furnished the starting material (7). In another case a different acid was isolated, m.p. 174.5—175°, which could be identified as 2-carboxy-3,5-dimethoxyphenylacetic acid (18).

These degradations established two parts of the molecule and the point of connection between them, and suggested formula (1) or the saturated equivalent for siphulin.

On the basis of (1) as the constitutional formula of siphulin, Dr. P. de Mayo suggested formula (13) for the yellow solid of m.p. 158—159° (above) formed by way of the reaction sequence

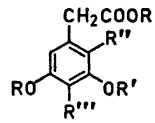


(13)

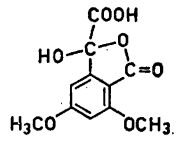
In agreement with this formulation, (13) could be monomethylated to give (14), m.p. 95—96°.

To obtain a confirmation of the assumed formula of siphulin its methyl ester trimethyl ether was oxidised with selenium dioxide to give a new substance, m.p. 167—168°, with carbonyl bands at 1775 and 1660 cm^{-1}. It appeared that the vicinity of the carbonyl group of the starting material had been left untouched, whilst the methylene group *ortho* to the ester grouping had been

oxidised to a keto group, which had reacted with the ester to form a five-membered ring lactol, most likely during the working up procedure. Accordingly the oxidation product is formulated as (12). This lactol was oxidised with potassium permanganate to give 3,5-dimethoxyphthalic acid, identified as the anhydride, and 2-hydroxy-4-methoxy-6-heptylbenzoic acid (sphaerophorol carboxylic acid 4-methyl ether) (32), m.p. 125—126°, identical with authentic material.



15 R = H	R′ = H	R″ = H	R‴ = H
16 R = Me	R′ = H	R″ = H	R‴ = H
17 R = H	R′ = Me	R″ = H	R‴ = H
18 R = H	R′ = Me	R″ = COOH	R‴ = H
19 R = Et	R′ = H	R″ = COOEt	R‴ = COOEt
20 R = Et	R′ = H	R″ = COOEt	R‴ = COOH
21 R = Me	R′ = H	R″ = COOMe	R‴ = COOH
22 R = Et	R′ = H	R″ = COOEt	R‴ = H
23 R = Me	R′ = H	R″ = COOMe	R‴ = H
24 R = H	R′ = Me	R″ = COOEt	R‴ = H
25 R = H	R′ = Me	R″ = COOEt	R‴ = Br
26 R = Me	R′ = Me	R″ = COOEt	R‴ = Br



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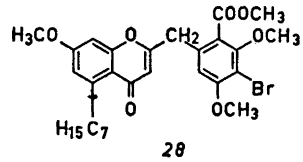

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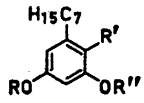
The lactol was subjected also to alkaline degradation and furnished the substance (38) and an acid. If the degradation was performed in air, the acid was 3,5-dimethoxyphthalic acid, whilst when carried out under nitrogen, an acid was isolated, which was oxidised by lead tetra-acetate to give 3,5-dimethoxyphthalic acid and carbon dioxide. The acid, therefore, presumably is 2-carboxy-3,5-dimethoxyphenylglyoxylic acid, which exists in the lactol form (27), since it gave rise to absorption bands at 1770 and 1660 cm^{-1}. Only this latter degradation experiment is recorded in Experimental.

Similar alkaline degradation of decarboxysiphulin trimethyl ether (11) afforded the acetophenone (38) and 3,5-dimethoxyphenylacetic acid (17).

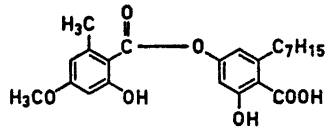
In Table 1 are recorded the ultraviolet absorption data of siphulin and its derivatives.

In Table 2 are found the ultraviolet absorption data of the various degradation products.

Table 3 contains the ultraviolet absorption data of sphaerophorol and synthesised compounds related to it, whilst Table 4 shows the ultraviolet



29	R = H	R′ = H	R″ = H
30	R = Me	R′ = H	R″ = Me
31	R = H	R′ = COOH	R″ = H
32	R = Me	R′ = COOH	R″ = H
33	R = H	R′ = COOMe	R″ = H
34	R = H	R′ = COOH	R″ = Me
35	R = H	R′ = COOMe	R″ = Me
36	R = Me	R′ = COOH	R″ = Me
37	R = Me	R′ = COOMe	R″ = Me
38	R = Me	R′ = $COCH_3$	R″ = H
39	R = Me	R′ = $COCH_3$	R″ = Me



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absorption data of orcinol and related, synthesised substances, all of which were used for comparison purposes. The shallow minimum observed with orcinol and its derivatives with substituents only in the methyl group is very characteristic and is faithfully reproduced by the recorder. With other substances prepared during this work shallow minima occasionally have been observed, but they are put on record as inflexions.

In Table 5 are found some NMR data of siphulin methyl ester trimethyl ether (7) and its bromoderivative together with those of a few model compounds. It is clear that both the two former compounds give rise to signals in the olefinic region. No signals indicative of the alternative, saturated formula could be seen in the recorded curves.

In the bromoderivative only the high-field aromatic proton signal was altered, relative to the signals in the spectrum of compound (7), and its area was about one half the area of the other aromatic proton signal. It appears, therefore, that the bromine atom has become attached to one of the aromatic nuclei. Tentatively it is suggested that the formula of the bromocompound is (28). The position between the methoxyl groups is analogous to the position of the bromine atom in the analogously prepared bromination product of (23), see formula (26) and Experimental. The corresponding position in the sphaerophorol nucleus of siphulin methyl ester trimethyl ether probably would be slightly less active.

EXPERIMENTAL

Ultraviolet absorption spectra were measured in ethanol on a Perkin-Elmer Model 13 and infrared absorption spectra on a Perkin-Elmer Model 21 spectrophotometer. Infrared absorption spectra were measured in potassium bromide unless stated to the contrary. Nuclear magnetic resonance spectra were recorded in deuterochloroform with tetra-

Table 1. Maxima and minima of the ultraviolet absorption spectra in ethanol of siphulin and derivatives.

Substance	λ_{Max}	λ_{Infl}	λ_{Min}	ε
Siphulin (1)		2425		29 500
			2480	28 000
	2510			29 000
			2590	19 500
	2640			21 000
			2745	17 500
	2930			23 000
Siphulin acetate (2)		2635		11 000
			2830	6 500
	2990			8 500
Siphulin trimethyl ether (3)		2500		25 000
			2610	9 000
	2870			20 500
Siphulin methyl ester (4)		2425		27 000
			2480	25 000
	2515			27 000
			2580	18 000
	2680			21 500
			2775	18 500
	2950			22 500
Siphulin methyl ester triacetate (5)		2630		12 000
			2830	8 000
	2980			10 000
Siphulin methyl ester dimethyl ether (6)			2480	27 000
	2515			28 000
			2575	20 500
	2660			23 500
			2750	19 500
	2920			22 000
Siphulin methyl ester dimethyl ether acetate (8)		2450		30 000
			2650	14 000
	2790			16 500
Siphulin methyl ester trimethyl ether (7)		2500		31 000
			2620	14 000
	2860			25 000
Decarboxysiphulin (9)		2415		30 000
		2490		26 500
			2605	8 500
	2865			23 000
Decarboxysiphulin dimethyl ether (10)		2490		21 000
			2600	8 000
	2830			18 500
Decarboxysiphulin trimethyl ether (11)		2495		20 000
			2595	7 500
	2815			18 000
Bromosiphulin methyl ester trimethyl ether (28)		2500		24 500
			2610	11 000
	2900			20 500

Table 2. Maxima and minima of ultraviolet absorption spectra in ethanol of degradation products of siphulin and derivatives.

Substance	λ_{Max}	λ_{Infl}	λ_{Min}	ε
Lactol (12)		2490		30 000
			2745	14 500
	2960			22 000
Benzoxanthone (13)			2400	18 500
	2530			46 500
			2620	28 000
	2920			49 500
			3205	9 500
	3260			11 500
			3340	8 500
	3410			12 500
			3600	1 600
	4200			10 000
Benzoxanthone methyl ether (14)			2350	23 500
	2530			42 000
			2620	33 000
	2720			54 000
			3185	7 000
	3410			10 000
			3585	4 500
	3885			7 000
2-Hydroxy-4-methoxy-6-heptylbenzoic acid (32)			2365	3 700
	2650			15 000
			2790	2 600
	3015			5 000
2-Hydroxy-4-methoxy-6-heptylacetophenone (38)			2480	2 900
	2700			5 800
2,4-Dimethoxy-6-heptylacetophenone (39)			2480	2 500
	2665			3 500
Sphaerophorol (3,5-dihydroxy-6-heptylbenzene (with 1 aq.)			2465	160
	2730			1 370
			2770	1 270
	2800			1 340
2-Carboxy-3,5-dimethoxyphenylglyoxylic acid (27)			2390	5 500
	2590			14 500
			2750	3 000
	2950			7 000
3,5-Dihydroxyphenylacetic acid (15)			2510	240
	2760			2 030
			2790	1 990
	2815			2 020
Methyl 3,5-dihydroxyphenylacetate (16)			2510	260
	2770			2 700
			2790	2 650
	2815			2 700
3,5-Dimethoxyphenylacetic acid (17)			2510	260
	2740			2 000
			2770	1 900
	2805			2 000

Table 3. Maxima and minima of ultraviolet absorption spectra in ethanol of sphaerophorol and derivatives.

Substance	λ_{Max}	λ_{Infl}	λ_{Min}	ε
Sphaerophorol (29)			2470	180
(with 1 aq.)	2730			1 570
			2770	1 500
	2800			1 570
Sphaerophorol dimethyl			2495	360
ether (30)	2715			1 700
			2750	1 600
	2780			1 700
Sphaerophorol carbox-			2390	4 000
ylic acid (31)	2625			15 500
			2830	3 800
	3015			6 500
Sphaerophorol carbox-			2400	4 000
ylic acid methyl	2650			16 500
ester (33)			2850	4 000
	3010			6 000
Sphaerophorol carbox-		2445		4 000
ylic acid 2-methyl			2690	2 000
ether (34)	2815			2 500
Sphaerophorol carbox-		2440		4 200
ylic acid methyl ester			2690	2 100
2-methyl ether (35)	2810			2 700
Sphaerophorol carbox-			2365	3 300
ylic acid 4-methyl	2615			16 000
ether (32)			2790	2 600
	3015			5 000
Sphaerophorol carbox-		2385		4 600
ylic acid dimethyl			2675	1 900
ether (36)	2800			2 200
Sphaerophorol carbox-			2665	2 000
ylic acid methyl ester	2800			2 500
dimethyl ether (37)				

Table 4. Maxima and minima of ultraviolet absorption spectra in ethanol of orcinol and related, synthetic substances.

Substance	λ_{Max}	λ_{Min}	ε
Ethyl 2-carbethoxy-4-carboxy-		2830	1 100
3,5-dihydroxyphenylacetate (20)	3155		3 200
Methyl 2-carbomethoxy-4-carboxy-	2240		21 800
3,5-dihydroxyphenylacetate (21)[a]	2380		17 100
	3200		5 500

Ethyl 2,4-dicarbethoxy-3,5-dihydroxyphenylacetate (19)	3125	2835	2 000 6 000
Ethyl 2-carbethoxy-3,5-dihydroxyphenylacetate (22)	2635 3025	2385 2820	3 200 15 500 3 700 6 000
Methyl 2-carbomethoxy-3,5-dihydroxyphenylacetate (23)[a]	2160 2650 3040		20 300 10 900 6 100
2-Carbethoxy-3,5-dimethoxyphenylacetic acid (24)	2510 2860	2365 2720	6 000 8 000 2 700 3 500
2-Carboxy-3,5-dimethoxyphenylacetic acid (18)	2500 2840	2370 2700	5 000 6 000 2 200 3 400
4-Bromo-2-carbethoxy-3,5-dimethoxyphenylacetic acid (25)	2910	2715	1 300 3 700
Methyl 4-bromo-2-carbethoxy-3,5-dimethoxyphenylacetate (26)	2935	2715	1 600 3 900
3,5-Dihydroxyphenylacetic acid (15)	2760 2815	2500 2790	210 2 040 2 010 2 040
Methyl 3,5-dihydroxyphenylacetate (16)	2770 2815	2505 2790	160 1 970 1 930 1 970
3,5-Dimethoxyphenylacetic acid (17)	2730 2795	2505 2760	220 1 940 1 870 1 960
Olivetol carboxylic acid (2,4-dihydroxy-6-pentylbenzoic acid)	2620 3010	2385 2810	2 800 13 000 2 600 4 500
Orcinol (3,5-dihydroxytoluene) (with 1 aq.)	2735 2810	2480 2780	180 1 700 1 600 1 700
2-Hydroxy-4-methoxy-6-methylbenzoic acid	2605 2985	2350 2780	3 500 16 500 2 800 5 500

Methyl 2-hydroxy-4-methoxy-6-methylbenzoate	2625	2360	2 600
			16 000
		2800	2 900
	3025		4 800
Ethyl 2-hydroxy-4-methoxy 6-methylbenzoate	2620	2360	3 000
			17 500
		2800	3 200
	3000		5 500
2,4-Dimethoxy-6-methylbenzoic acid	2800	2690	2 000
			2 400
Methyl 2,4-dimethoxy-6-methyl-benzoate	2800	2690	2 200
			2 600
2,4-Dimethoxy-6-methylaceto-phenone [b]	2670	2460	2 700
			5 500

[a] Data taken from W. R. Allison, G. T. Newbold, *J. Chem. Soc.* **1961** 2512.
[b] Specimen very kindly supplied by Dr. C. A. Wachtmeister, Stockholm, Sweden, m.p. 41–42°, carbonyl band in chloroform at 1700 cm^{-1}.

Table 5. Selected NMR absorption data of some derivatives of siphulin and model compounds in deuterochloroform.

Substance	Aromatic protons	Olefinic protons
Siphulin methyl ester trimethyl ether (7)	3.59	4.05
	3.36	
Bromocompound (28)	3.52	4.19
	3.39	
2,4-Dimethoxy-6-heptylbenzoic acid (36)	3.69	
Ethyl 2-hydroxy-4-methoxy-6-methylbenzoate [a]	3.65	
Methyl 2,4-dimethoxy-6-methylbenzoate	3.46	
2,4-Dimethoxy-6-methylacetophenone [b]	3.69	
2-Carbethoxy-3,5-dimethoxyphenylacetic acid (24)	3.58	
4-Bromo-2-carbethoxy-3,5-dimethoxyphenylacetic acid (25)	3.58	
Methyl 4-bromo-2-carbethoxy-3,5-dimethoxyphenylacetic acid (26)	3.51	

[a] Somewhat broadened band. [b] See Table 4.

methylsilane as internal standard on an Associated Electrical Industries Ltd. Type RS2 spectrometer. Chemical shifts are given as τ ppm. Most analyses are by Alfred Bernhard, Western Germany, others have been done by Mr. J. M. L. Cameron, Glasgow, Scotland, through the good office of Professor D. H. R. Barton, and still others are by the analytical laboratory of Dr. A. Wander AG, Bern, Switzerland, through the good offices of Drs. A. Aebi, and J. Schmutz.

The lichen material was collected on several occasions by Professor N. A. Sørensen in Kongsmoen, Nord-Trøndelag. Since it was found on readily corroded mountain ground, it contained considerable and variable amounts of inorganic material, about 50 % on the average of air dried material (about 10 % water content).

The air dried material was extracted for 24 h with ether in a soxhlet apparatus. The filtered ether solution was concentrated on the water-bath and extracted with sodium hydrogen carbonate solution. The extracted material was liberated by addition of sulphuric acid and isolated with ether. Thus 765 g of ash-containing lichen material gave 33 g of crude, crystalline, acidic matter. It was very soluble in ether, methanol, ethanol, acetone, and ethyl acetate, very sparingly soluble or insoluble in petroleum, benzene, and chloroform. With great losses a small amount of pure, crystalline *acid* was obtained from ether or from methanol, m.p. about 185° (decomp.), resolidifying and remelting at 228—229°. (Found: C 67.7; H 6.45. $C_{24}H_{26}O_7$ (426.47) requires: C 67.6; H 6.15). Potentiometric titration in ethanol-water (3:2) indicated an equivalent weight of 425 and a pK_a of 4.4.

Another portion of lichen material (100 g) was extracted by percolation with ether (about 2 litres), and the ethereal extract was concentrated *in vacuo* to a very small volume. The remaining solution was left for slow, spontaneous evaporation. The small amount of crystals formed was collected, m.p. 179—180° (decomp.). It did not solidify after melting, and gave no depression on admixture of the material above. The mixture solidified after melting and remelted at 228—229°. Also, the infrared spectra of the two materials were identical, but they were rather diffuse. When the material obtained by percolation was admixed with a trace of the decarboxylation product (below), it showed the double m.p. as described.

When the substance was heated and the evolved gasses passed into a solution of barium hydroxide in water, a white precipitate was formed which dissolved with effervescence on addition of hydrochloric acid.

Short reaction with diazomethane in ether readily gave a *methyl ester* (4), colourless needles, m.p. 208—209° from methanol or from acetone; absorption maxima in the infrared at 1653 and 1622 cm^{-1}. (Found: C 68.1; H 6.6; OCH_3 7.1. $C_{25}H_{28}O_7$ (440.50) requires: C 68.2; H 6.4; 1 OCH_3 7.0).

Acetylation of the methyl ester furnished a *methyl ester triacetate* (5), m.p. 132—133°, bands in the infrared in chloroform at 1780, 1740, and 1660 cm^{-1}. (Found: C 66.2; H 6.2; OCH_3 5.7. $C_{31}H_{34}O_{10}$ (566.61) requires: C 65.7; H 6.0; 1 OCH_3 5.5).

Acetylation of the acid afforded an *acid triacetate* (2), m.p. 145—146°, from acetone, bands in the infrared at 1785, 1732, and 1650, cm^{-1}. (Found: C 65.4; H 6.1. $C_{30}H_{32}O_{10}$ (552.58) requires: C 65.2; H 5.85).

Methylation of the acid with diazomethane in the presence of methanol with standing overnight gave a *methyl ester dimethyl ether* (6), m.p. 128—129°, from methanol or acetone, bluish violet colour with iron(III) chloride in ethanol, blue colour with Gibbs's reagent in aqueous-ethanolic soda solution, band in the infrared in chloroform at 1655 cm^{-1}. (Found: C 68.9; H 6.75; OCH_3 19.5. $C_{27}H_{32}O_7$ (468.55) requires: C 69.2; H 6.9; 3 OCH_3 19.4). Acetylation of this methyl ester dimethyl ether with acetic anhydride in pyridine with standing overnight at room temperature and working up with acid, water, sodium hydrogen carbonate, and ether afforded a *mono-acetate* (8), m.p. 123—124°, small, yellow, rhombic plates from chloroform-ether or from chloroform-acetone, no colour with iron(III) chloride or with Gibbs's reagent, bands in the infrared in chloroform at 1780, 1732 and 1655 cm^{-1}. (Found: C 68.6; H 6.9; OCH_3 17.95. $C_{29}H_{34}O_8$ (510.59) requires: C 68.2; H 6.7; 3 OCH_3 18.2).

Complete methylation of the acid was achieved in various ways.

1. Prolonged treatment of the acid or its methyl ester or the methylation product above with diazomethane in the presence of much methanol furnished the *methyl ester trimethyl ether* (7), rhombic plates from methanol or ether, m.p. 77—78°, no colour with iron(III) chloride or Gibbs's reagent, bands in the infrared in chloroform at 1730 and 1655 cm^{-1}. There was no indication of a band in the 3 500 cm^{-1} region.

2. Methylation of the acid or its methyl ester or the methyl ester dimethyl ether with dimethyl sulphate and potassium carbonate in acetone afforded the same substance (7). (Found: C 70.1; H 7.2; OCH_3 26.5. $C_{26}H_{34}O_7$ (482.58) requires: C 70.0; H 7.1; 4 OCH_3 25.7).
3. The methyl ester dimethyl ether (6) above (0.1 g), silver oxide (0.1 g) and methyl iodide (1 ml) in acetone (5 ml) were refluxed for 18 h. Isolation of the product gave the same methyl ester trimethyl ether (7) as above (m.p. and mixed m.p.).

Methyl ester trimethyl ether (7) (0.5 g) was refluxed for 2 h in methanol (80 ml) containing sodium methoxide (from 26 mg of sodium). The methanol was removed in a vacuum, and the residue was treated with ether and aqueous sodium hydroxide solution. The neutral fraction weighed 0.5 g and afforded crystals of m.p. 77—78° from a small amount of ether, no depression on admixture with the starting material.

The methyl ester trimethyl ether (7) also was recovered unchanged after treatment with hydroxylamine hydrochloride in pyridine on the water-bath for 1.5 h.

Decarboxysiphulin. (*1*) Siphulin (1) (0.5 g) in methanol (25 ml) was refluxed for 2.5 h with potassium hydroxide (2.5 g). Isolation of the reaction product with ether after acidification afforded a small amount of crystalline *decarboxysiphulin* (9), m.p. 229—230°, very soluble in the usual organic solvents except petroleum, benzene, chloroform, and carbon tetrachloride. (Found: C 72.0; H 7.1. $C_{23}H_{26}O_5$ (382.46) requires: C 72.2; H 6.85).

(*2*) Siphulin (0.5 g) in acetic acid (5 ml) was refluxed for 2 h with addition of 1 ml of hydrobromic acid (*d*, 1.49). Isolation of the product with ether furnished decarboxysiphulin, m.p. 229—230°, from a very small amount of acetone, no depression on admixture with the product obtained above.

Methylation of decarboxysiphulin. (*1*) Prolonged treatment of decarboxysiphulin with diazomethane in ether in the presence of methanol gave *decarboxysiphulin dimethyl ether* (10), m.p. 146—147°, fine, colourless needles from methanol, no colour with iron(III) chloride in ethanol, blue colour with Gibbs's reagent in aqueous-ethanolic soda solution. (Found: C 73.2; H 7.5; OCH_3 15.1. $C_{25}H_{30}O_5$ (410.41) requires: C 72.2. H 7.35; 2 OCH_3 15.1.

(*2*) Methylation of decarboxysiphulin with dimethyl sulphate and potassium carbonate in acetone afforded *decarboxysiphulin trimethyl ether* (11), m.p. 61—62°, plates or prisms from petroleum (seeding), no colour with iron(III) chloride or with Gibbs's reagent. (Found: C 73.9; H 7.5; OCH_3 21.7; C—CH_3 3.8. $C_{26}H_{32}O_5$ (424.54) requires: C 73.6; H 7.6; 3 OCH_3 21.9; 1 C—CH_3 3.5).

Bromination of siphulin methyl ester trimethyl ether. Siphulin methyl ester trimethyl ether (7) (0.5 g) was dissolved in carbon tetrachloride (50 ml). Part of the solvent was distilled off to remove any water present. N-Bromosuccinimide (0.3 g, calculated 0.19 g for one mole) and dry carbon tetrachloride (5 ml) were added, and the mixture was refluxed for 5 h. The reaction mixture was left for 4—5 days, when the precipitated imide was removed by filtration, and the filtrate was evaporated to dryness. Crystallisation from methanol (seeding) afforded faintly yellow prisms, m.p. 123—125°, which gave a positive Beilstein test. (Found: C 59.7, 59.9; H 5.9, 6.0; Br 14.1, 13.9, 13.9; OCH_3 21.6, 20.5, 20.4; C—CH_3 3.0, 4.2. $C_{29}H_{33}BrO_7$ (561.48) requires: C 60.2; H 5.9; Br 14.2; 4 OCH_3 22.1; 1 C—CH_3 2.7). Carbonyl bands in the infrared at 1730 and 1655 cm^{-1}.

Alkaline degradation of siphulin. Siphulin (1 g) and water (25 ml) were refluxed for a short time under pure nitrogen, and then sodium hydroxide (25 g) was added. Refluxing was continued for 20 min. To the alkaline reaction mixture sulphuric acid (17 ml, *d* 1.84) in water (100 ml) was added and 70 ml of liquid were distilled off. The distillate was neutralised with sodium hydroxide and evaporated to dryness. The residue showed an infrared spectrum identical with that of authentic sodium acetate. The residue (40 mg) was refluxed for 1 h in ethanol (35 ml) with *p*-bromophenacyl bromide (40 mg). The *p*-bromophenacyl ester of acetic acid crystallised on addition of a little water and prolonged standing, m.p. 84.5—85.5°, no depression on admixture with authentic ester of m.p. 85—86°; the infrared spectra were identical.

The distillation residue was extracted once with ether, which dissolved 0.8 g. This extract was refluxed with petroleum (500 ml), b. r. 60—70°, and filtered. The residue was refluxed with 45 ml of benzene in two portions, which dissolved 0.2 g, whilst 0.3 g were left. The benzene solution was evaporated to dryness, and the residue was dissolved in ether. The ether solution was extracted three times with water and then evaporated to dryness. The residue (0.2 g) furnished crystals from petroleum (with addition of a few

drops of water), m.p. 54—55°, no depression on admixture with authentic sphaerophorol (26). The infrared spectra in chloroform were identical.

The residue from the benzene treatment was refluxed for 1—2 h with benzene (500 ml) and filtered. On cooling crystals were deposited, m.p. 125—126° (0.1 g), no depression on admixture with authentic, anhydrous 3,5-dihydroxyphenylacetic acid (15), prepared according to Theilacker and Schmid.[3] (Found: C 57.0; H 4.85. $C_8H_8O_4$ (168.04) requires: C 57.2; H 4.8). The infrared spectra were identical with carbonyl band at 1700 cm^{-1}.

The acid was converted to its methyl ester by short treatment with diazomethane, m.p. 108—109°, from chloroform, carbonyl band at 1718 cm^{-1}. Ref. 3 gives m.p. 110—111°. (Found: C 60.3; H 5.8. $C_9H_{10}O_4$ (182.18) requires: C 59.3; H 5.5). The acid was converted to the dimethyl ether by methylation with dimethyl sulphate and potassium carbonate in acetone, m.p. 101.5—102.5°, from benzene or carbon tetrachloride, carbonyl band at 1698 cm^{-1}. Ref. 4 gives m.p. 99—100°. (Found: C 60.5; H 6.15. $C_{10}H_{12}O_4$ (196.20) requires: C 61.2; H 6.15). The derivatives showed no depression of the melting points on admixture with authentic specimens.

Alkaline degradation of siphulin methyl ester trimethyl ether. (*1*) Siphulin methyl ester trimethyl ether (7) (1 g) was refluxed under nitrogen for 45 min with potassium hydroxide (25 g) in methanol (25 ml). After cooling the reaction mixture was poured into water (500 ml) and extracted with ether. The ether solution contained 0.4 g of a yellow material which was crystallised from chloroform-methanol or methanol or acetone to give the benzoxanthone (13) with constant m.p. 158—159° (0.1 g). (Found: C 71.7; H 6.7; OCH_3 19.4. $C_{22}H_{30}O_6$ (450.54) requires: C 72.0; H 6.7; 3 OCH_3 20.7. The substance (in chloroform) exhibited no band in the infrared in the 3500 cm^{-1} region, but a carbonyl band at 1650 cm^{-1}.

Methylation of this substance with dimethyl sulphate and potassium carbonate in acetone afforded a new *compound* (14), m.p. 95—96°, yellow crystals from petroleum. (Found: C 72.5; H 7.1; OCH_3 26.0. $C_{28}H_{32}O_6$ (464.56) requires: C 72.4; H 6.9; 4 OCH_3 26.7). It gave rise to a carbonyl band at 1665 cm^{-1}.

The mother liquors from the crystallisation of the yellow substance, m.p. 158—159°, were evaporated to dryness, and the residue was extracted with boiling petroleum ether. The extracted material distilled at 110° and 0.01 torr (0.1 g), n_D^{21} 1.5339. Ultraviolet and infrared (neat) spectra were identical with those observed for the corresponding liquid degradation product with alkali from the lactol (below).

The alkaline solution (above) was acidified and extracted with ether to give 0.5 g of extract, which with ether furnished a small amount of crystalline material (0.1 g). Further crystallisations from chloroform-ether afforded stout, slightly yellow needles of an *acid*, m.p. 166—167°, carbonyl bands at 1725 and 1643 cm^{-1} in chloroform solution. (Found: C 68.6; H 6.9. $C_{27}H_{32}O_7$ (468.55) requires: C 69.2; H 6.9). Esterification of this acid with diazomethane regenerated the starting material, m.p. 77—78°, no depression on admixture.

(*2*) Siphulin methyl ester trimethyl ether (0.5 g) was refluxed for 45 min with potassium hydroxide (25 g) in methanol (25 ml). The hot solution was poured into distilled water, and sodium hydrogen carbonate (38 g) was added. The aqueous solution was extracted with ether and then evaporated to dryness on the waterbath. The residue was treated with a slight excess of hydrochloric acid (*d*, 1.19), and then extracted with acetone. The extract was evaporated to dryness, and the residue again extracted with acetone. Concentration of the acetone solution to a very small volume afforded colourless crystals (10 mg) which melted at 167—168°. A mixture with the acid of m.p. 166—167° (above) melted at 154—162°. Further crystallisations from chloroform, then from benzene and finally from acetone afforded 2-carboxy-3,5-dimethoxyphenylacetic acid (15), 5.5 mg, m.p. 174.5—175°, no depression on admixture with synthetic material (see below). The infrared spectra were also identical.

The material extracted with ether (0.3 g) was treated with petroleum. An oil was extracted, which distilled at 100° and 0.01 torr to give a colourless distillate, n_D^{20} 1.5350 (69 mg), 2-hydroxy-4-methoxy-6-heptylacetophenone (38) (*cf.* below). The distillation residue was discarded. The part which had been left undissolved by the petroleum, was crystallised from the same solvent to give yellowish crystals, m.p. 157.5—158.5° (50 mg), no depression on admixture with the yellow substance (13) of m.p. 158—159° (above).

Lactol (12). Siphulin methyl ester trimethyl ether (4.4. g) was refluxed for 2 h with selenium dioxide (1.2 g) in acetic acid (50 ml). The material isolated with ether was

treated with aqueous sodium hydroxide, and the resulting mixture was extracted with ether. The extract (0.6 g) was discarded. The dissolved material (3.8 g) was liberated with acid, extracted with ether and crystallised from carbon tetrachloride to give a colourless, crystalline powder of the *lactol* (12), m.p. 167–168°. The infrared spectrum in chloroform had bands at 1775 and 1660 cm^{-1}. (Found: C 67.1; H 6.2; OCH_3 19.3. $C_{27}H_{30}O_8$ (482.54) requires: C 67.2; H 6.25; 3 OCH_3 19.3.

Oxidation of the lactol (12) with potassium permanganate. The lactol (12) (1.1 g) was dissolved in dilute sodium hydroxide solution (from 0.7 g of sodium hydroxide), sodium hydrogen carbonate was added (1.5 g) and then the material was treated with potassium permanganate (1.0 g) in water. When all had been consumed, sodium sulphite and sulphuric acid were added. The acidic, aqueous solution was extracted once with ether. The extracted material (0.3 g) contained some starting material which could be removed by treatment with a small amount of ether, in which solvent it is sparingly soluble, m.p. 164–166° after one crystallisation from carbon tetrachloride. The ether had dissolved a small amount of a yellow oil, which deposited colourless, prismatic crystals from petroleum, m.p. 125–126° after three crystallisations from this solvent. The substance gave a violet colour with iron(III) chloride in ethanol and no depression on admixture with 2-hydroxy-4-methoxy-6-heptylbenzoic acid (32) (see below). (Found: C 67.4; H 8.3. $C_{15}H_{22}O_4$ (266.34) requires: C 67.6; H 8.3).

Thorough extraction of the aqueous solution with ether gave a material which deposited crystals from a concentrated ether solution, and which melted at 155–160°. Sublimation of this material in a vacuum furnished 3,5-dimethoxyphthalic anhydride, m.p. 149–150°, no depression on admixture with an authentic specimen. The infrared spectra were also identical.

Alkaline degradation of the lactol (12). (*1*) The lactol (235 mg) was refluxed with water (10 ml) and potassium hydroxide (2.5 g) for 2 h whilst nitrogen was passed through and into an aqueous solution of 2,4-dinitrophenylhydrazine perchlorate. No precipitate was obtained. The alkaline solution was acidified with sulphuric acid and 20 ml of water were distilled off. The distillate was neutral.

(*2*) The lactol (1.5 g) was refluxed as above. After cooling potassium hydrogen carbonate (25 g) was added. The aqueous solution was extracted with ether, which removed *2-hydroxy-4-methoxy-6-heptylacetophenone* (38) as a light yellow oil (0.73 g), which distilled at 120° at 0.01 torr, n_D^{18} 1.5372, one broad band at about 1600 cm^{-1} (neat). (Found: C 72.8; H 9.1; OCH_3 11.8; C–CH_3 10.5. $C_{16}H_{24}O_3$ (264.37) requires: C 72.7; H 9.15; OCH_3 11.7; 2 C–CH_3 11.4).

Methylation with dimethyl sulphate and potassium carbonate in acetone furnished *2,4-dimethoxy-6-heptylacetophenone* (39), a colourless liquid which distilled at 100° at 0.01 torr, n_D^{21} 1.5095, carbonyl band (neat) at 1694 cm^{-1}, no colour with iron((III) chloride in ethanol. (Found: C 72.3; H 9.35; OCH_3 21.5. $C_{17}H_{26}O_3$ (278.39) requires: C 73.3; H 9.4; 2 OCH_3 22.3).

The aqueous solution was evaporated to dryness, acidified and extracted with acetone as described above. The brownish extract was washed with ether which removed 0.45 g. The residue from the ether washing (0.37 g) was crystallised from a very small amount of acetone to furnish 0.2 g of colourless prisms of *2-carboxy-3,5-dimethoxyphenylglyoxylic acid* (27), m.p. 172–173°, carbonyl bands in the infrared at 1770 and 1660 cm^{-1}. (Found: C 48.6, 48.7; H 4.55, 4.50; OCH_3 22.7, 24.5; C–CH_3 5.8, 2.4. $C_{11}H_{10}O_7$ (254.20) requires: C 52.0; H 3.95; 2 OCH_3 24.4; C–CH_3 O. $C_{11}H_{10}O_7.H_2O$ (272.21) requires: C 48.5; H 4.45; 2 OCH_3 22.8).

On titration with lead tetra-acetate an amount of oxidant was consumed corresponding to a molecular weight of 260.

The acid (52 mg) was dissolved in hot water (5 ml) from which gasses had been removed by boiling. Periodic acid (41 mg) was added to the still warm solution, when part of the dissolved material started crystallising. The mixture was left for 2 h and then heated to boiling. The vapour was passed into a solution of barium hydroxide in water, when a colourless precipitate formed, which dissolved with effervescence on addition of hydrochloric acid. The aqueous solution on standing deposited colourless crystals, m.p. and mixed m.p. as for the starting material. The aqueous solution was left for spontaneous evaporation and then extracted with acetone. The extracted material was sublimed in a vacuum at 170° to give a sublimate which melted at 147–148° and which did not depress the m.p. of 3,5-dimethoxyphthalic anhydride.

Alkaline degradation of decarboxysiphulin trimethyl ether. Decarboxysiphulin trimethyl ether (11) (0.6 g) was refluxed for 45 min with potassium hydroxide (25 g) in methanol (25 ml). The reaction mixture was poured into water and sodium hydrogen carbonate (50 g, calc. 37.5 g) was added. The aqueous solution was extracted with ether and then evaporated to dryness.

The ether solution contained 0.3 g which at 110° and 0.01 torr gave a colourless distillate, n_D^{21} 1.5344, with ultraviolet and infrared (neat) spectra identical with those recorded for the liquid degradation product (38) from the lactol (12) (above).

The evaporated aqueous solution was treated with hydrochloric acid and acetone as above. Evaporation of the acetone solution left a felted mass of needles which was crystallised from petroleum, b. r. 60—70°, m.p. 102—103°, no depression on admixture with 3,5-dimethoxyphenylacetic acid (17) (*cf.* above). Also, the ultraviolet and infrared spectra were identical.

2-Hydroxy-4-methoxy-6-heptylbenzoic acid. Sphaerophorol carboxylic acid (0.1 g) (from sphaerophorin (40), isolated from *Sphaerophorus globosus* and from *S. fragilis*, m.p. 142—143°, carbonyl band at 1620 cm^{-1}, methyl ester, prepared with diazomethane, m.p. 74—75°, carbonyl band at 1638 cm^{-1}) was treated with diazomethane in ether-methanol mixture with standing for 4 h. Excess diazomethane was removed by evacuation, and the ethereal solution was extracted with dilute potassium hydroxide solution. The material remaining in the solution was hydrolysed by refluxing for 45 min with 0.2 g of potassium hydroxide in 10 ml of water. The alkaline solution was first extracted with ether, and then acidified and extracted with ether. The material in this final extract after three crystallisations from petroleum, b. r. 40—50°, gave 14 mg of *2-hydroxy-4-methoxy-6-heptylbenzoic acid* (32), m.p. 124—125°, carbonyl band at 1653 cm^{-1}. (Found: C 68.3; H 8.3. $C_{15}H_{22}O_4$ (266.34) requires: C 67.7; H 8.35).

4-Hydroxy-2-methoxy-6-heptylbenzoic acid. Sphaerophorin (40) (5 g), dimethyl sulphate (4 ml), potassium carbonate (15 g) and acetone (50 ml) were mixed and left overnight. A slight increase in temperature was noticed on mixing the components. Next day the mixture was refluxed for 1 h, filtered, evaporated and saponified as above. The treatment with potassium hydroxide caused slight hydrolysis of the depside linkage. The resulting product was treated with sodium methoxide in methanol with standing for 24 h under nitrogen. Organic matter was dissolved in ether and acidic materials were extracted with soda solution. They were hydrolysed by refluxing for 1 h with potassium hydroxide (3 g) in water (30 ml). The resulting acids were isolated with ether. Crystallisation from carbon tetrachloride furnished a low-melting (about 110°) and a high-melting (about 135°) fraction. The latter was impure 2,4-dimethoxy-6-methylbenzoic acid. The former was recrystallised from benzene until constant m.p. 110—110.5°, and was *4-hydroxy-2-methoxy-6-heptylbenzoic acid* (34). It showed a carbonyl band at 1702 cm^{-1}. (Found: C 67.6; H 8.15. $H_{15}H_{22}O_4$ (266.34) requires: C 67.7; H 8.35).

4-Hydroxy-2-methoxy-6-heptylbenzoic acid (34) was methylated with dimethyl sulphate and potassium carbonate in acetone, as above. The product was saponified by refluxing for 1 h with potassium hydroxide (10 g) in methanol (10 ml). The isolated acid, crystallised from petroleum, melted at 67—68° and showed no depression on admixture with *2,4-dimethoxy-6-heptylbenzoic acid* (36) which was prepared by the same procedure from sphaerophorol carboxylic acid (31), m.p. 67—68°, from petroleum, carbonyl bands in chloroform at 1753 and 1701 cm^{-1}. (Found: C 68.2; H 8.5. $C_{16}H_{24}O_4$ (280.34) requires: C 68.6; H 8.65).

Methyl 4-hydroxy-2-methoxy-6-heptylbenzoate (35) was prepared from the acid with diazomethane. It did not crystallise, and distilled at 120° and 0.01 torr, n_D^{24} 1.5123, carbonyl band in chloroform at 1725 cm^{-1}. (Found C 67.9; H 8.65. $C_{16}H_{24}O_4$ (280.34) requires: C 68.6; H 8.65).

Methyl 2,4-dimethoxy-6-heptylbenzoate (37) was prepared from the acid with diazomethane, b.p. 120° at 0.01 torr, n_D^{17} 1.5063, carbonyl band (neat) at 1738 cm^{-1}.

Ethyl 2-carbethoxy-4-carboxy-3,5-dihydroxyphenylacetate (20) was prepared according to Jerdan,[5] carbonyl bands at 1753, 1700, and 1650 cm^{-1}, m.p. 141—142°, Refs. 5, 6 141°; for constitution compare Asahina, Nogami [6] and Theilacker, Schmid.[3]

Ethyl 2-carbethoxy-3,5-dihydroxyphenylacetate (22) was prepared according to Nogami,[7] carbonyl bands at 1710 and 1660 cm^{-1}, m.p. 107—108°. Nogami [7] gives m.p. 108°.

2-Carbethoxy-3,5-dimethoxyphenylacetic acid. Ethyl 2-carbethoxy-3,5-dihydroxyphenylacetate [7] (22) (0.9 g) was refluxed for 1 h with dimethyl sulphate (5 ml) and a large excess

of freshly ignited potassium carbonate in acetone (50 ml). After filtration, acetone was removed, finally by distillation with methanol. To the remaining methanolic solution potassium hydroxide was added and the mixture was heated for a short time on the waterbath to hydrolyse excess dimethyl sulphate. Simultaneously the primary ester group was saponified. The reaction mixture was poured into water and extracted with ether. The aqueous solution was acidified and extracted with ether to give 0.8 g of crude *2-carbethoxy-3,5-dimethoxyphenylacetic acid* (24), m.p. 99—100°, raised to 102—103° by crystallisation from benzene; carbonyl band at 1725 cm^{-1}. (Found: C 58.0; H 5.9. $C_{13}H_{16}O_6$ (268.27) requires: C 58.2; H 6.0). A mixture with the starting material (m.p. 107—108°) melted at 80—90°, and a mixture with 3,5-dimethoxyphenylacetic acid (m.p. 102—103°) melted at 78—93°.

2-Carboxy-3,5-dimethoxyphenylacetic acid. 2-Carbethoxy-3,5-dimethoxyphenylacetic acid (0.2 g), potassium hydroxide (2.6 g), and water (10 ml) were refluxed for 30 min. To the alkaline solution sodium hydrogen carbonate (4 g) was added, and the solution was concentrated on the waterbath. The solution was acidified with concentrated hydrochloric acid, a large volume of acetone was added, and precipitated salt was removed by filtration. The filtrate was concentrated to a small volume, and finally water was removed by azeotropic distillation with ethanol and benzene. The residue was treated with acetone, and on seeding with the degradation product of m.p. 174.5—175° (above), crystals of *2-carboxy-3,5-dimethoxyphenylacetic acid* (18) were obtained, m.p. 174.5—175°, carbonyl band at 1700 cm^{-1}. (Found: C 54.5; H 5.1. $C_{11}H_{12}O_6$ (240.21) requires: C 55.0; H 5.05).

*Bromination of 2-carbethoxy-3,5-dimethoxyphenyl-acetic acid.** The bromination experiments were carried out in accordance with the directions given by Allison and Newbold [8] for introduction of bromine into the methyl group of 6-methyl-2-hydroxy-4-methoxybenzoic acid. In one series of experiments bromine was added to the acid in carbon tetrachloride solution with irradiation. In another series bromination was effected with N-bromosuccinimide with addition of benzoyl peroxide. In both cases a product was obtained which melted at 172—174°. (Found: C 44.3; H 4.3; Br 24.5. $C_{13}H_{15}BrO_6$ (347.17) requires: C 45.0; H 4.35; Br 23.0). Carbonyl band at 1710 cm^{-1}.

Attempts at resolving the product into optically avtive components by aid of morphine and brucine salts [9] gave only unchanged, optically inactive material.

Allison and Newbold have demonstrated [8] that 4,6-dibromo-5,7-dimethoxyphthalide can be selectively debrominated at the 4-position by hydrogenolysis in ethyl acetate in the presence of palladium-on-charcoal and magnesium oxide, whilst both bromine atoms are replaced by hydrogen in aqueous alkaline solution in the presence of palladium-on-calcium carbonate. In our case the former procedure furnished a crude hydrogenolysis product which melted at 150—170°; it gave a positive Beilstein test, and a mixture with the starting material melted at 168—173°. After one crystallisation from chloroform the product melted at 170—172° (40 mg from 145 mg). The latter hydrogenation procedure afforded pure 2-carbethoxy-3,5-dimethoxyphenylacetic acid, m.p. 101—102°, not raised by crystallisation; no depression on admixture with authentic material. The infrared spectra in potassium bromide also were identical. The bromination product, therefore, probably is a mixture with the 4-bromo derivative as the predominating component and no bromine in the side-chain.

Esterification of this bromo-acid with diazomethane in ether furnished the methyl ester, m.p. 116—116.5°, colourless needles from chloroform-petroleum, b. r. 40—50° (Found: C 47.0; H 4.35; Br 23.9. $C_{14}H_{17}BrO_6$ (361.20) requires: C 46.6; H 4.75; Br 22.1) Carbonyl band at 1725 cm^{-1}, broad.

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