

Synthetic Plant Hormones

III.* Sulphur Analogues of 2,4-Dichlorophenoxy- and
4-Chloro-2-methylphenoxy-acetic Acids

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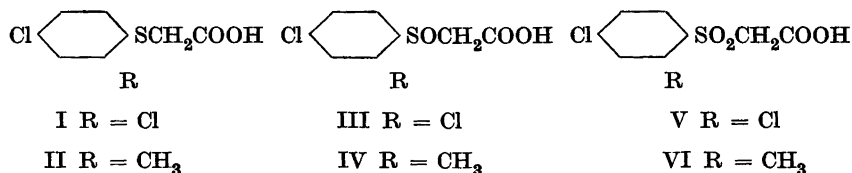
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The preparation of the sulphur analogues of 2,4-dichlorophenoxy- and 4-chloro-2-methylphenoxy-acetic acids, *viz.* 2,4-dichlorophenylmercaptoacetic acid (I) and 4-chloro-2-methylphenylmercaptoacetic acid (II), and the corresponding sulphinyl- and sulphonyl-acetic acids (III, IV respectively V, VI) was mentioned in part I of this series¹. These compounds were prepared in order to study the influence of successive oxidation of the sulphur atom on the plant hormone activity of the acids, and the theoretical background of the investigation was discussed at that time, and it is the purpose of this communication to discuss the activity of the 4-chloro-2-methyl compounds, and to describe the preparative methods used for the whole series. The results of the testing of the 2,4-dichloro-compounds have been discussed elsewhere by Wilske and Burström². A study on the activity of 2,4-dichlorophenylmercaptoacetic acid as well as some other substituted phenylmercaptoacetic acids has been published by Thompson, Swanson and Norman³.

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The phenylmercaptoacetic acids, which have been synthesised earlier by other methods, were prepared by the general method of Kalle and Co⁴ from the corresponding anilines by diazotisation, conversion to the thiophenols via the xanthates and finally coupling with chloroacetic acid in alkaline solution. The sulphinylacetic acids were obtained by oxidation of the mercaptoacetic acids with hydrogen peroxide in glacial acetic acid at room temperature, and oxidation with potassium permanganate in the presence of sodium carbonate gave the corresponding sulphonylacetic acids. When an attempt was made to oxidise 2,4-benzenesulphinylacetic acid with potassium permanganate at elevated temperatures the product obtained was methyl 2,4-dichlorophenylsulphone and not the expected sulphonylacetic acid.

EXPERIMENTAL *

2,4-Dichlorophenylmercaptoacetic acid. 2,4-Dichloroaniline (38 g) in ice cold dilute (1 : 6) hydrochloric acid (350 ml) was diazotised by the addition of sodium nitrite (17 g). When this solution was poured into a solution of potassium ethyl xanthate (46 g) and sodium carbonate (25 g) in water (160 ml) at 70° C, a red oil separated immediately. When the evolution of nitrogen had ceased, the mixture was cooled to room temperature, acidified with dilute sulphuric acid and extracted twice with ether. The ether extracts were combined and evaporated and the ethyl 2,4-dichlorophenyl xanthate was dissolved in a mixture of alcohol (75 g) and 35% aqueous sodium hydroxide (46 g). The mixture was heated under reflux for four hours. Then a solution of chloroacetic acid (35 g) in 35% aqueous sodium hydroxide (42 g) was added, and the mixture was boiled for a further four hours. The alcohol was distilled off, and the residual yellow material dissolved in water. The solution was filtered and acidified with hydrochloric acid. The yellowish crystalline precipitate (50 g, 90%) was collected and recrystallised repeatedly from water and then formed colourless prisms.

M.p. 122–123° C.

$C_8H_6SO_2Cl_2$	Calc.	C 40.5	H 2.55	Cl 29.9	Equiv. weight 237.1
	Found »	39.9	» 2.52	» 29.3	» » 238

The synthesis of this acid has been reported in a patent⁵, but no data were given of its physical properties.

4-Chloro-2-methylphenylmercaptoacetic acid. This acid was prepared analogously from 2-amino-5-chlorotoluene and after three recrystallisations from water melted at 127–128° C in agreement with value reported by Herz, Bauer, Steiger, Albrecht and Dereser⁶. The yield of crude product was 82% of the theoretical.

$C_9H_9SO_2Cl$	Calc.	S 14.8	Cl 16.4
	Found »	14.7	» 16.2

2,4-Dichlorobenzenesulphinylacetic acid. 2,4-Dichlorophenylmercaptoacetic acid (10 g) was dissolved in glacial acetic acid (40 ml), and 30% hydrogen peroxide (12 g) was added. After a short time colourless crystalline material began to separate. The reaction mixture was kept at room temperature for about twelve hours, and the product (6 g) was collected

* All melting points uncorrected.

by filtration and repeatedly recrystallised from water, forming colourless needles of m.p. 145–146° C (decomp). Further material could be obtained by evaporation of the original mother liquor, the total yield of crude product being 89 % of the theoretical.

$C_8H_8SO_3Cl_2$	Calc.	C 38.0	H 2.39	Equiv. weight 253.1
	Found	» 37.8	» 2.40	» » 252

4-Chloro-2-methylbenzenesulphonylacetic acid. 4-Chloro-2-methylphenylmercaptoacetic acid (4 g) was oxidised with 30 % hydrogen peroxide (4.8) in glacial acetic acid (15 ml) as described for the 2,4-dichloro compound. The yield of crude product was 3.5 g (82 %) and after four crystallisations from water the compound had m.p. 128–129° C (decomp.).

$C_9H_9SO_3Cl$	Calc.	C 46.5	H 3.90	Equiv. weight 232.7
	Found	» 46.4	» 4.00	» » 230

2,4-Dichlorobenzenesulphonylacetic acid. An aqueous solution of 2,4-dichlorophenylmercaptoacetic acid (3 g) and sodium carbonate (0.7 g) was treated at 30° C with a solution of potassium permanganate (4 g) in water. The solution was saturated with sulphur dioxide until the manganese sludge had dissolved. The sulphonylacetic acid separated as a colourless oil, that crystallised on stirring. Yield 1.8 g (56 %). Three recrystallisations from water yielded the pure product. M.p. 150–151° C.

$C_8H_6SO_4Cl_2$	Calc.	C 35.7	H 2.25	Equiv. weight 269.1
	Found	» 35.7	» 2.24	» » 267

4-Chloro-2-methylbenzenesulphonylacetic acid. 4-Chloro-2-methylphenylmercaptoacetic acid was oxidised as described above for the 2,4-dichloro compound. The yield of crude product from 2 g of 4-chloro-2-methylphenylmercaptoacetic acid was 1.5 g (65 %). The product was recrystallised three times from benzene and then melted at 147–148° C.

$C_9H_9SO_4Cl$	Calc.	C 43.5	H 3.66	Equiv. weight 248.7
	Found	» 43.6	» 3.65	» » 247

Methyl-2,4-dichlorophenylsulphone. 2,4-Dichlorobenzenesulphonylacetic acid (2 g) and sodium carbonate (0.5 g) were dissolved in water and oxidised at 60° C with an aqueous solution of potassium permanganate (1.3 g). The manganese sludge was removed by filtration and the solution was evaporated almost to dryness. On cooling a neutral compound separated as long colourless needles (0.56 g) which after recrystallisation from water melted at 74–75° C.

$C_7H_6SO_2Cl_2$ (189.6)	Calc.	C 37.3	H 2.69
	Found	» 37.2	» 2.68

PHYSIOLOGICAL PART

The physiological activity of the acids was studied in simple growth tests using *Lepidium* seedlings.

Seeds were germinated in 20 cm Petri dishes. Two day old seedlings, selected for uniformity with roots *ca.* 10 mm long, were transferred to 7 cm petri dishes, containing five sheets of filter paper wetted by 5 ml of the test solutions, prepared by dissolving the acids in a nearly equivalent amount of potassium hydroxide, and adjusting the pH to 7. Each dish contained 10 seedlings and all experiments were run in quintuplicate. The dishes were placed in the dark at 20° C and the root lengths were recorded after two days. The mean error of the growth determinations amounted to ± 4 per cent.

The results are given in Table 1. For convenience the following abbreviations are used for the acids:

Table 1. Elongation of *Lepidium* roots in two days in solutions of (the given) acids and a phosphate buffer of pH 7. — Mean error ± 1 mm.

Concentration <i>M</i>	Acid tested				Phosphate buffer
	4-C-2-M	4-C-2-MS	4-C-2-MSO	4-C-2-MSO ₂	
0	26.3	26.3	26.3	26.3	26.3
10 ⁻⁸	30.0	—	—	—	—
10 ⁻⁷	27.2	32.6	—	—	—
10 ⁻⁶	15.6	24.4	25.7	29.6	—
10 ⁻⁵	2.9 *	10.6	25.6	22.9	23.1
10 ⁻⁴	0.1 **	0.9 *	13.1	28.2	23.6
10 ⁻³	—	0 **	0.3 *	20.6	24.4
10 ⁻²	—	—	—	10.4	13.8

* Typical "auxin-roots"; no elongation but swelling of the roots and excessive formation of root hairs.

** Roots dead.

4-chloro-2-methylphenoxyacetic acid	4-C-2-M
4-chloro-2-methylphenylmercaptoacetic acid	4-C-2-MS
4-chloro-2-methylbenzenesulphonylacetic acid	4-C-2-MSO
4-chloro-2-methylbenzenesulphonylacetic acid	4-C-2-MSO ₂

A regularly decreasing growth retardation was obtained with increasing substitution from the phenoxy- to the sulphonylderivatives. In 10⁻⁵ *M* 4-C-2-M, 10⁻⁴ *M* 4-C-2-MS, and 10⁻³ *M* 4-C-2-MSO there appeared symptoms which regularly accompany an auxin excess, *i.e.* inhibited elongation, root swellings, and excessive formation of root hairs. No signs of this kind were encountered with 4-C-2-MSO₂, even in 10⁻² *M* solution: the root elongation was certainly retarded but not much more than by a phosphate solution of the same strength. Thus it may be concluded that the sulphonyl derivative is lacking in specific growth inhibiting action.

The phenoxyacetic acid derivatives are all comparatively strong acids, and it was assumed by Wilske and Burström² that they might be regarded as completely dissociated, so that in comparing them the dissociation could be neglected. However, it has been found with other acids⁷ that growth inhibition of this kind parallels the concentration of undissociated acid, even if this concentration is low. Whether this is due to the mode of action of the acids

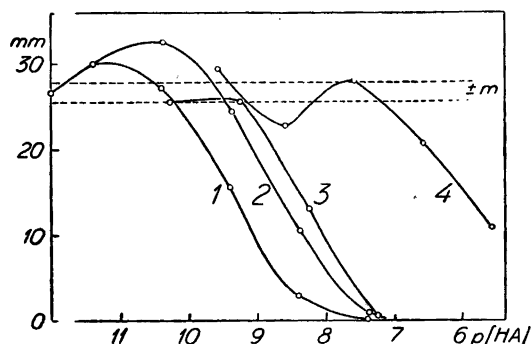


Fig. 1. The relationship between root elongation and concentration of undissociated acid for 1) 4-C-2-M, 2) 4-C-2-MS, 3) 4-C-2-MSO, and 4) 4-C-2-MSO₂. $\pm m$ denotes the mean error for the control roots.

on the root surface or to their permeation cannot be decided. It is, anyway, necessary to pay due attention to the dissociation, in evaluating the relative activity of the acids.

The dissociation constants for the acids in question were determined from the titration curves of the sulphinyl- and sulphonylacetic acid derivatives, and for the two less soluble compounds from pH-determinations of saturated solutions using a glass electrode. These determinations were carried out by Miss E. Welin-Berger, Botanical Laboratory, Lund, and the following (average) results were obtained:

Acid	pK_{20°
4-C-2-M	3.62
4-C-2-MS	3.89
4-C-2-MSO	2.82
4-C-2-MSO ₂	2.68

If root elongation is plotted as a function of the concentration of undissociated acid, the graph shown in Fig. 1 is obtained. There is still a difference between the phenoxy- and the thiophenoxy-compounds, which implies a marked decrease in activity if oxygen is substituted for sulphur, but the graphs for the thiophenoxy- and sulphinylacids fall close together. The most obvious conclusion is that no considerable decrease in the activity occurs until the sulphur atom is completely oxidised. — It must also be born in mind that the decreasing activity at the highest concentrations of the sulphonyl compound obviously does not depend specifically upon the acid.

The mean error for the control roots has also been plotted in the figure, and it shows that little significance can be attributed to the increase in root

lengths observed at the lowest concentrations of the phenoxy- and thio-phenoxy-compounds. Much larger samples of seedlings would be required to reveal a statistically significant growth promotion by these acids.

The conclusion can be drawn that the results on the specific growth retardation give considerable supports to the hypothesis advanced by Erdtman¹, concerning the relationship between structure and activity. The agreement is much better than that obtained in a different test with the corresponding 2,4-dichlorophenylmercaptoacetic acid derivatives². However, a confirmation of the theory requires that it could be shown to hold true for growth accelerating as well as growth inhibiting activity.

SUMMARY

The sulphur analogues of 2,4-dichlorophenoxy- and 4-chloro-2-methylphenoxy-acetic acid have been prepared and oxidised to the corresponding sulphinyl- and sulphonylacetic acids. The action of the 4-chloro-2-methyl-substituted acids upon *Lepidium* seedlings has been studied and compared with that of 4-chloro-2-methylphenoxyacetic acid. The mercapto- and the sulphinyl-acetic acid derivatives retard growth to a smaller extent than the phenoxyacetic acid derivative, whereas the sulphonylacetic acid derivative has no specific growth inhibiting activity.

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