benzyl phenyl sulphides,[1] the activity of the chlorobenzyl derivatives progressively decreased as the chlorine substituent occupied the *para*, *meta*, and *ortho* positions respectively. The *p*-nitrobenzyl compound again had little activity.

Both benzyl 4 : 6-dimethylpyrimid-2-yl sulphide and the *p*-chlorobenzyl derivative had similar, considerable activity but the *p*-nitrobenzyl compound was completely inactive.

The only general conclusion which can be drawn from these results is that a nitro group in the *para* position of the benzyl moiety reduced the activity of various, active benzyl heterocyclic sulphides to the red spider mite.

No general conclusion can be drawn concerning the effect on activity of substitution by chlorine in the *para* position of the benzene nucleus. Thus, the unsubstituted compound was more active than the *p*-chlorobenzyl derivative in the benzthiazol-2-yl and 4-phenylthiazol-2-yl benzyl sulphides but less active in the benzoxazol-2-yl, pyrid-2-yl and 4-methylthiazol-2-yl benzyl sulphides. A similar level of activity was found in the *p*-chlorobenzyl derivatives and in the unsubstituted benzyl 5-chlorobenzthiazol-2-yl, benzyl pyrid-4-yl, benzyl quinol-2-yl, and benzyl thiazolin-2-yl sulphides. Both the *p*-chlorobenzyl derivative and the unsubstituted compound were virtually inactive in the case of benziminazol-2-yl, 4-methylglyoxalin-2-yl and 4-phenylglyoxalin-2-yl benzyl sulphides.

The only sulphone which had any activity was *p*-chlorobenzyl pyrid-2-yl sulphone.

Of the heterocyclic-methyl phenyl sulphides only benzoxazol-2-ylmethyl *p*-chlorophenyl sulphide was appreciably active.

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Received 15 July, 1957

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THE TOXICITY OF ORGANIC SULPHIDES TO THE EGGS AND LARVAE OF THE GLASSHOUSE RED SPIDER MITE. VII.*—Benzyl Phenyl Sulphides (α-substituted)

By J. E. CRANHAM, D. GREENWOOD and H. A. STEVENSON

The synthesis of a number of benzyl phenyl sulphides, substituted in the α-position of the benzyl moiety, is described and their toxicities to the eggs and young mites of the glasshouse red spider (*Tetranychus telarius* L.) are tabulated.

* Part VI : preceding paper

Introduction

The activity against the red spider mite, in laboratory tests, of several series of benzyl phenyl sulphides containing substituents in the benzene nuclei has already been reported.[1-3] In order to complete the examination of the activity of these sulphides, it was of interest to synthesize and test a series containing substituents in the α-position of the benzyl moiety.

Experimental

Synthesis of compounds

The compounds containing an α-aryl substituent were prepared by condensing arenethiols with diphenylmethanol, or nuclear-substituted diphenylmethanol, as described by Finzi & Bellavita[4] and illustrated by the following example.

Diphenylmethanol (10 g.) and *p*-chlorobenzenethiol (8·5 g.) were stirred in acetic acid (100 c.c.). Concentrated sulphuric acid (34 g.) was added slowly, maintaining the temperature below 45°. Cooling, filtration, and recrystallization from ethanol gave 13·5 g. (80%) of p-*chlorophenyl diphenylmethyl sulphide* (Ref. No. 3955) as colourless needles.

Diphenylmethyl p-*fluorophenyl sulphide* (Ref. No. 4162), *di*-(p-*chlorophenyl*)*methyl phenyl sulphide* (Ref. No. 4005), *di*-(p-*chlorophenyl*)*methyl* p-*fluorophenyl sulphide* (Ref. No. 4163), and p-*chlorophenyl di*-(p-*chlorophenyl*)*methyl sulphide* (Ref. No. 4006) were prepared similarly.

2-(p-*Chlorophenylthio*)*phenylacetic acid* (Ref. No. 3957).—*p*-Chlorobenzenethiol (10 g.), followed by phenylchloroacetic acid (10 g.), was added to a solution of sodium (4 g.) in ethanol (200 c.c.). The solution was warmed slowly, and then refluxed for 2 hours. Cooling and addition of water gave a clear solution. Acidification precipitated the *product* which crystallized from alcohol as colourless needles (12·6 g.; 77%).

The *amide* (Ref. No. 4075) and *esters* (Ref. Nos. 4185, 4186) were prepared either from the acids by standard methods or by condensation of the arenethiols with the appropriate derivative of phenylchloroacetic acid. The preparation of 2-(p-*chlorophenylthio*)*phenylacetamide* (Ref. No. 4075) exemplifies the two methods.

Method 1.—2-(*p*-Chlorophenylthio)phenylacetic acid (5·6 g.) and thionyl chloride (3 c.c.) were refluxed in dry benzene (20 c.c.) for 2 hours. Removal of the solvent left a green, viscous oil which was added to ammonia solution (0·880, 100 c.c.). The solid which separated was recrystallized twice from ethanol to give 3·5 g. (63%) of colourless crystals.

Method 2.—*p*-Chlorobenzenethiol (6·5 g.), followed by phenylchloroacetamide (5 g.), were added to a cold solution of sodium (1·2 g.) in ethanol (120 c.c.). After refluxing the solution for 1½ hours, cooling and adding water, recrystallization gave the product (6·7 g.; 82%).

The *nitriles* (Ref. Nos. 4424, 4425) could not be obtained from phenylchloroacetonitrile and arenethiols, as disulphides and tars were formed. They were prepared by the action of phosphorus oxychloride in pyridine on the corresponding amides.[5]

αα-*Bis*-(p-*chlorophenylthio*)*toluene* (Ref. No. 3826).—Hydrogen chloride was passed into a solution of benzaldehyde (5·3 g.) and *p*-chlorobenzenethiol (16 g.) in acetic acid (50 c.c.) at 0° for 4 hours. The *product* separated as an oil which later solidified. Recrystallization from ethanol gave 14·7 g. (78%) of colourless needles.

The corresponding αα-*bis*-(p-*chlorophenylthio*)-p-*chlorotoluene* (Ref. No. 2873) was obtained similarly from *p*-chlorobenzaldehyde and *p*-chlorobenzenethiol.

An alternative method of preparing the last two substances (condensation of benzylidene chlorides and thiols) resulted in mixtures of the mercaptals with disulphides which could only be separated on an alumina column.

3-p-*Chlorophenylthio*-1 : 3-*diphenylpropan*-1-*one* (Ref. No. 3227).—Benzalacetophenone (2·3 g.) and *p*-chlorobenzenethiol (1·45 g.) were heated together at 100° for 2 hours and then cooled. The *product* crystallized from ethanol as colourless needles (2·6 g.; 74%).

1-p-*Chlorophenylthio*-1-*phenyl*-2-*phenylthioethane* (Ref. No. 3486).—Benzenesulphenyl chloride (7·3 g.) was added during 1 hour to a solution of styrene (5·2 g.) in carbon tetrachloride (25 c.c.) at −5°. The solution was then allowed to warm slowly to room temperature. Removal of the solvent and distillation gave 8·5 g. (68%) of 2-*chloro*-2-*phenylethyl phenyl sulphide*, b.p. 150°/1·5 mm. (Found: C, 67·6; H, 5·0. $C_{14}H_{13}ClS$ requires C, 67·6; H, 5·2%). This

compound was also prepared by a Ponndorf reduction of phenyl phenacyl sulphide followed by reaction with thionyl chloride. The intermediate *2-hydroxy-2-phenylethyl phenyl sulphide* (yield, 83%) had b.p. 173°/3 mm. (Found: C, 72·85; H. 6·3. $C_{14}H_{14}OS$ requires C, 73·0; H, 6·1%).

2-Chloro-2-phenylethyl phenyl sulphide (5·0 g.) and *p*-chlorobenzenethiol (3·5 g.) were refluxed for 2 hours in a solution of sodium (0·5 g.) in ethanol (40 c.c.). Cooling and addition of water gave an oil which was fractionated. The fraction of b.p. 165–175°/3 mm. (1·5 g.) was oxidized with hydrogen peroxide to give colourless needles of *2-ethoxy-2-phenylethyl phenyl sulphone*, m.p. 100–101° (Found: C, 66·55; H, 6·1. $C_{16}H_{18}O_3S$ requires C, 66·2; H, 6·2%). The fraction of b.p. 225–235°/3 mm. (3·2 g.) solidified and was recrystallized from alcohol to give 2·3 g. (32%) of 1-p-*chlorophenylthio*-1-*phenyl*-2-*phenylthioethane* as colourless needles. Oxidation gave the corresponding *disulphone*, colourless needles of m.p. 180° (Found: C, 57·4; H, 4·1. $C_{20}H_{17}O_4ClS_2$ requires C, 57·1; H, 4·0%).

Biological methods

The methods of testing have been described previously.[6] Compounds were tested at 0·1% and 0·025% of toxicant applied by the 'dipping' method.

Chlorbenside (*p*-chlorobenzyl *p*-chlorophenyl sulphide) was employed as a standard throughout the tests and, also, an 'untreated' control of 'suspension-medium' only. Percentage 'total mortalities' (i.e. kill of eggs plus kill of newly-hatched mites) were corrected for mortality in the formulation controls, which was generally less than 10%, and the results are shown in Table I.

Table I

Benzyl phenyl sulphides

$XC_6H_4{\cdot}CHR{\cdot}S{\cdot}C_6H_4Y$

Ref. No.	X	Y	R	% 'Total mortality' 0·1%	% 'Total mortality' 0·025%	M.p., °C or b.p., °C/mm.	Formula	Analysis Found % C	Analysis Found % H	Analysis Required % C	Analysis Required % H	Reference
4425	H	H	—CN	26	21	51–52	$C_{14}H_{11}NS$	74·8	4·8	74·7	4·9	*
3958	H	H	—CO_2H	14	1	103	$C_{14}H_{12}O_2S$	—	—	—	—	7
4161	H	H	—$CONH_2$	6	8	174	$C_{14}H_{13}ONS$	—	—	—	—	8
3956	H	H	—Ph	23	6	79	$C_{19}H_{16}S$	—	—	—	—	4
4162	H	*p*-F	—Ph	78	7	64–65	$C_{19}H_{15}FS$	77·1	5·3	77·55	5·1	*
4424	H	*p*-Cl	—CN	49	19	63–64	$C_{14}H_{10}NClS$	64·7	4·0	64·7	3·85	*
3957	H	*p*-Cl	—CO_2H	23	10	149–150	$C_{14}H_{11}O_2ClS$	60·5	4·0	60·3	3·95	*
4185	H	*p*-Cl	—CO_2Me	18	2	60	$C_{15}H_{13}O_2ClS$	61·6	4·5	61·5	4·4	*
4186	H	*p*-Cl	—CO_2Et	9	3	180/1·5	$C_{16}H_{15}O_2ClS$	62·2	5·0	62·6	4·9	*
4075	H	*p*-Cl	—$CONH_2$	6	6	186	$C_{14}H_{12}ONClS$	61·1	4·4	60·5	4·3	*
3955	H	*p*-Cl	—Ph	72	9	101–102	$C_{19}H_{15}ClS$	73·9	4·85	73·5	4·8	*
3826	H	*p*-Cl	*p*-ClC_6H_4S—	16	7	61	$C_{19}H_{14}Cl_2S_2$	60·1	3·65	60·5	3·7	*
3486	H	*p*-Cl	PhS·CH_2—	33	—	63	$C_{20}H_{17}ClS_2$	66·9	4·65	67·3	4·8	*
3227	H	*p*-Cl	PhCO·CH_2—	0	33	103	$C_{21}H_{17}OClS$	71·3	5·0	71·5	4·8	*
4005	*p*-Cl	H	*p*-ClC_6H_4—	51	14	72	$C_{19}H_{14}Cl_2S$	66·3	3·8	66·1	4·1	*
4163	*p*-Cl	*p*-F	*p*-ClC_6H_4—	53	12	62	$C_{19}H_{13}Cl_2FS$	62·9	4·0	62·8	3·6	*
4006	*p*-Cl	*p*-Cl	*p*-ClC_6H_4—	74	15	80–81	$C_{19}H_{13}Cl_3S$	60·2	3·3	60·1	3·4	*
2873	*p*-Cl	*p*-Cl	*p*-$ClC_6H_4{\cdot}S$—	49	20	61	$C_{19}H_{13}Cl_3S_2$	55·05	3·1	55·4	3·2	*

* Prepared by D. G.

Discussion of results

All the substances in this series can be regarded as benzyl phenyl sulphides containing, in addition to any nuclear substituents, a substituent in the methylene group of the bridge between the two benzene nuclei. The nuclear substituents, in all cases, were halogens, which have been shown to result in the most active substances in the previous series.[1–3] Nevertheless, none of the substances in the present series had any noteworthy activity.

Apparently, an unsubstituted methylene group in the bridge between the two benzene nuclei of the benzyl phenyl sulphides is essential for high activity against the red spider mite.

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Received 30 July, 1957

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DETERMINATION AND ISOLATION OF THE NON-VOLATILE ACIDS OF POME FRUITS AND A STUDY OF ACID CHANGES IN APPLES DURING STORAGE

By A. C. HULME and L. S. C. WOOLTORTON

A comprehensive scheme using ion exchange and partition chromatography is described for the determination of non-volatile organic acids of pome fruits. The method is used to investigate changes occurring in the acids of the peel and pulp of mature Bramley's Seedling apples during storage at 15°. These changes involve not only the aliphatic acids malic, citramalic and citric, but also the alicyclic acids quinic and shikimic.

Introduction

In recent years, acids other than citric and malic acids have been found in pome fruits[1] and this has prompted a reappraisal of the total acid metabolism of these fruits.

With the improvement of chromatographic methods of analyses, more and more ' acid spots ' are appearing on paper chromatograms of fruit extracts. The present authors (unpublished results) had detected as many as 30 such spots, each apparently representing a separate and distinct acid, in extracts of the banana ; in chromatograms of pear extracts, also, a considerable number of ' unknown ' acids are apparent. Interest is also increasing in the presence and ' role ' of such alicyclic acids as shikimic and quinic acids in plants generally. Although, as will be seen later, the amounts of these less common acids present in the apple may be extremely small, they show quite large percentage fluctuations. The numerous studies carried out over the past twenty years in the changes in total titratable acid, or more specifically malic acid, during the storage of apple fruits have not greatly advanced our knowledge of the essential contribution of ' acid ' to the acid metabolism of the fruits ; nor have they thrown any light on the causes of the physiological diseases to which apples and pears are liable during storage. Recently, however, it has been shown that one such disease, CO_2-injury, appears to be associated with the appearance of succinic acid which, while a likely intermediate on theoretical grounds in the metabolism of the fruit, has not been generally reported in apples or unfermented apple juice,[2] and which appears to be toxic to the apple even at low concentrations.[3]

It appears likely, therefore, that a number of acids, either present in very small amount or not even present at all in the free state under normal conditions may, nevertheless, play a most important part in the over-all metabolism of the tissue. Abnormal conditions may so interfere with the general acid metabolism that some of these acids may appear in measurable amounts. A prerequisite for the study of the acid metabolism of pome fruits in health and disease is, therefore, a comprehensive procedure for the detection and estimation of a whole range of organic acids. A technique for the determination of all the acids of the Krebs tricarboxylic acid cycle has been developed by Busch *et al.*[4] and adapted to a study of the acids