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Optical Resolution of some Auxin-active Thiocarbamates

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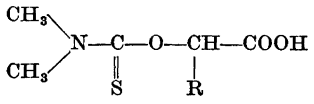
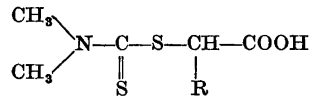
Several thiocarbamyl-derivatives of α-hydroxy- and α-thiocarboxylic acids have been synthesized and some of them resolved into optical antipodes. The compounds are of plant physiological interest and some of them show stereochemical specificity. The structural requirements for auxin activity have been modified to fit the results of the present investigation.

An interesting type of racemization has been observed. The acids are stable in the solid state but are rapidly racemized on melting. The theoretical considerations involved in this phenomenon will be discussed in a subsequent paper.

A few years ago a new type of plant growth regulators was discovered by van der Kerk and coworkers [1]. The structures of the new compounds, thiocarbamic esters of glycolic acid (I) or thioglycolic acid (II) are in part identical with the well-known α-aryloxyalkanoic acids (V). The fundamental



I



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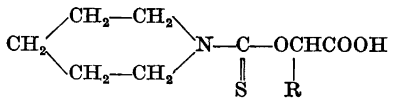

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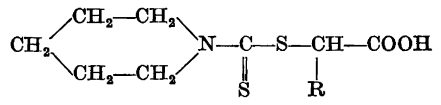

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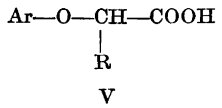

V

difference is the absence of a cyclic system in I and II; this is notable, as such a system, with a polar side-chain in a definite spatial position, has been generally accepted as a necessary requirement for auxin-activity [2].

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It has been found that the aryloxyalkanoic acids show stereochemical specificity, *i.e.* the auxin-activity is associated with a definite configuration (D—)[3-5]. It was thus of interest to find out whether the new compounds behaved in a similar way.

In the present study some acetic acids (R = H) and propionic acids (R = CH_3) of type I—IV have been synthesized. The propionic acids of type I—III have been resolved into optical antipodes. The growth-regulating properties have been studied by Professor B. Åberg. The acids of type I and II not only give typical auxin responses in several tests, but the propionic acids also show stereochemical specificity [6]. This fundamental physiological similarity between compounds of type I—II and type V may be regarded as evidence that they are all taking part in identical or similar reaction mechanisms within the cell. This view is further supported by the fact that the auxin activity is lowered when the C—O—C link in I is replaced by C—S—C. A similar lowering of the auxin activity has been found when the ether oxygen in α-(2-naphthoxy)propionic acid is replaced by sulphur [4].

In view of these facts a revision of the ring structure requirement seems to be inevitable. In fact van der Kerk *et al.* have pointed out that the C—N bond is likely to acquire some double-bond character due to internal electron shifts. A partial ring system is thus formed, with the side-chain in a distinct spatial position [1]. This argument has ben verified by infra-red investigation of a number of dithiocarbamates [7]. Some structurally similar O-alkylxanthates have been found to give physiological responses in spite of the fact that in these compounds resonance is much less probable [8]. However, the responses reported seem not to be of a true auxin type.

It is thus possible to apply the current structure-activity requirements to the new types of growth regulators, provided the ring requirement is stated as: A ring system or a partial ring system with the side-chain in a distinct spatial position.

The piperidylderivatives III and IV did not show auxin responses and the steric effects of the propionic acids were weak. For that reason the optical resolution was completed only for one of the acids.

During the optical resolution of the acids now investigated it was found that the optical activity increased very little or even decreased from one recrystallization to the next. These irregularities could be derived from thermal instability of the optically active forms. The behaviour of the antipodes was studied by melting point microscopy. In most cases new crystals were rapidly formed in the melt at a temperature just above the primary melting point. The phenomenon was not due to isomorphism, since the new crystals were optically inactive. Further, the melting points coincided with the melting points of the corresponding racemates, with which they are identical as proved by lack of melting point depression of mixtures. This racemization is rather rapid in the melt but seems not to occur in the crystalline state as the melting point is sharp and independent of the heating time. Even if racemization occurred to such a slight extent as a few percent it should be possible to detect by microscopy the formation of some eutectic melt at the lower, eutectic temperature. A racemization of this type seems not to have been reported previously. A theoretical discussion will appear in a paper to follow.

Table 1. Preparative and analytical data.

Compound				Method	Yield [a] (%)	Recryst. from	M. p.[b] (°C)	$[\alpha]_D^t$ (in acetone)	Equiv. weight	
Formula	Type	R	Isomer						Found	Calc.
$H_3)_2NCSOCH_2COOH$	I	H		A	43	BzH	115 −117.5[c]			
$_5H_{10})NCSOCH_2COOH$	III	H		A	34	aq. EtOH	118 −120.5		204.2	203.3
$H_3)_2NCSOCHCOOH$	I	CH_3	Rac.−	A	35	BzH	134 −136		175.7	177.2
			(+) −			BzH + petr.ether	122 −122.5	+75.9° (24°C)		177.2
			(−) −			» »	122 −122.5	−76.3° (20.5°C)	178.4	177.2
$_5H_{10})NCSOCHCOOH$	III	CH_3	Rac.−	A	35	aq. EtOH	145.5−147		218.8	217.3
			(+) −			BzH + petr.ether	98 − 99	+84.4° (21°C)	219.3	217.3
			(−) −			» »	98 − 99.5	−85.2° (21°C)	218.8	217.3
$H_3)_2NCS_2CH_2COOH$	II	H		B	46	Water	147 −149.3[d]			
$_5H_{10})NCS_2CH_2COOH$	IV	H		B	75	aq. EtOH	149 −151[e]		220.3	219.3
$H_3)_2NCS_2CHCOOH$	II	CH_3	Rac.−	B	38	» »	136 −138[f]		194.9	193.3
			(+) −			BzH + petr.ether		+76.9° (21°C)	195.0	193.3
			(−) −			» »	114.5−116	−77.4° (21°C)	194.4	193.3
$_5H_{10})NCS_2CHCOOH$	IV	CH_3	Rac.−	B	20	aq. EtOH	125 −130		234.1	233.4

[a] based on α-chlorocarboxylic acid in method A, on amine in method B. [b] hot stage microscope, corr. [c] Ref.[12] gives 116−117°C (uncorr.). [d] Ref.[12] gives 145−146°C (uncorr.). [e] Ref.[12] gives 145—147°C uncorr.). [f] Ref.[12] gives 134−135°C (uncorr.).

EXPERIMENTAL

The racemic acids were synthesized by one of the general procedures A and B, which are given below [9,12]. Further experimental details are found in Table 1.

Method A. An aqueous solution of 1 mole of an α-chlorocarboxylic acid is refluxed for 4 h with excess sodium carbonate in order to form the α-hydroxycarboxylic acid. After cooling to room temperature potassium hydroxide (1.2 mole) and carbon disulphide (1 mole) are added and the mixture shaken for 24−40 h. Excess carbon disulphide is removed *in vacuo* and 1 mole of chloroacetamide is added to the clear red solution. The mixture is stirred at room temperature for 6−7 h, filtered and carefully acidified with sulphuric acid. The yellow, crystalline intermediate is collected and added to an aqueous solution of 1 mole of the appropriate amine. After about 24 h at room temperature the solution is filtered and acidified with dilute hydrochloric acid to pH 2−3. The product is sometimes precipitated as an oil, which crystallizes rapidly on scratching.

Method B. Carbon disulphide (1 mole) is added to an aqueous solution of the amine (1 mole) cooled in ice. A concentrated aqueous solution of sodium hydroxide (1 mole) is added, followed by a neutralized solution of the α-chlorocarboxylic acid added at such a rate that the temperature is kept below 40°C. The solution is stirred for 2−4 h at room temperature and is then acidified. The product may come out as an oil which crystallizes on scratching.

Optical resolutions. Preliminary experiments were carried out with the following bases:

Strychnine	Quinidine	Cinchonidine
Brucine	Morphine	(+)-α-Phenethylamine
Quinine	Cinchonine	(−)-β-Phenylisopropylamine [10]

Ethyl acetate alone or with a small quantity of methanol was found to be the most effective solvent. The salt of the acid to be resolved with the optically active base was recrystallized several times. After each recrystallization a small sample of the salt was decomposed with hydrochloric acid, the acid isolated and the rotatory power determined.

Further details on the resolutions are found in Tables 2−6. The (+)-form of N-pentamethylenethiocarbamyllactic acid was obtained *via* the same base, brucine, as the (−)-form, which is notable. A small quantity of water (25 ml) was added to the mother liquor from crystallization No. 1a. A further crop of crystals was thus obtained (yield 18 %)

Table 2. Recrystallization of the (−)-β-phenyl*iso*propylamine salt of N,N-dimethylthiocarbamyllactic acid. Initial quantity: 0.07 mole.

Recryst. No.	Solvent (ml)		Yield of salt (%)	$[\alpha]_D$ of the acid
	EtAc	MeOH		
1	250	100	42.5	56.7°
2	125	75	32	65.0°
3	100	50	27	75.6°
4	80	40		74.7°
5	50	30	20	(71.4°)
6	50	30	18	74.1°

Table 3. Recrystallization of the cinchonidine salt of N,N-dimetylthiocarbamyllactic acid recovered from cryst. No. 1 and 2 above ($[\alpha]_D = -36°$). Initial quantity: 0.042 mole.

Recryst. No.	Solvent (ml)		Yield of salt (%)	$[\alpha]_D$ of the acid
	EtAc	MeOH		
1	150	15	67	−57.6°
2	150	20	49	−73.1°
3	100	18	35.5	(−70.9°)
4	75	15	22	−76.1°

Table 4. Recrystallization of the brucine salt of N-pentamethylenethiocarbamyllactic acid. Initial quantity: 0.2 mole.

Recryst. No.	EtAc (ml)	Yield of salt (%)	$[\alpha]_D$ of the acid	Note
1a	400	20	−56.7°	Cryst. No. 1 yielded two fractions; the second one (31 %) was recrystallized as No. 1b and then combined with the first one.
		31	−42.5°	
1b	200	26	−49.2°	
2	350	35	−77.1°	
3	300	31	−80.3°	
4	300	27.5	−80.3°	

Table 5. Recrystallization of the strychnine salt of N,N-dimethyldithiocarbamyllactic acid. Initial quantity: 0.075 mole.

Recryst. No.	Solvent (ml)		Yield of salt (%)	$[\alpha]_D$ of the acid
	EtAc	MeOH		
1	300	20	54	−54.4°
2	200	15	40.5	
3	175	15	25.5	−70.1°
4	150	15	21.5	−76.8°
5	125	15	12	−77.2

Table 6. Recrystallization of the (+)-β-phenyl*iso*propylamine salt of N,N-dimethyldithiocarbamyllactic acid recovered from cryst. No. 1 above. ($[\alpha]_D$ = +15°).

Recryst. No.	Solvent (ml)		Yield of salt (%)	$[\alpha]_D$ of the acid
	EtAc	MeOH		
1	160	40	44	50°
2	100	20	35	59.1°
3	75	20	30	71.7°
4	50	20	25	76.2°
5	50	20	22	75.0°
6	30	15	19.5	76.3°

and it was found to contain an almost pure (+)-acid ($[\alpha]_D$ = + 74.5°). The salt was recrystallized twice from ethyl acetate containing 2−5 % water. The rotatory power of the acid was + 81.3° and + 80.3°. Crystallization at −10°C gave a semi-solid salt but at room temperature the product was crystalline. The pure salts were analyzed, as may be seen from Table 7.

Table 7. Analyses of the pure salts.

Lactic acid derivative	Base	Formula	Calc. (%)			Found (%)		
			C	H	S	C	H	S
(+)-N,N-dimethyl-thiocarbamyl-	(−)-β-Phenyl*iso*-propylamine	$C_{15}H_{24}O_3N_2S$	57.66	7.74	10.26	57.8	7.88	10.8
(−)- —»—	Cinchonidine	$C_{25}H_{33}O_4N_3S$	63.67	7.05	6.80	63.6	7.07	6.89
(−)-N,N-Dimethyl-dithiocarbamyl-	Strychnine	$C_{27}H_{33}O_4N_3S_2$	61.45	6.30	12.15	61.2	6.51	11.6
(+)- —»—	(+)-β-Phenyl*iso*-propylamine	$C_{15}H_{24}O_2N_2S_2$	54.84	7.36	19.52	55.0	7.44	19.4
(+)-N-Penta-methylene-thiocarbamyl-	Brucine	$C_{32}H_{41}O_7N_3S$	62.83	6.76	5.24	62.6	6.90	5.07
(−)- —»—	Brucine	$C_{32}H_{41}O_7N_3S$	62.83	6.76	5.24	62.6	6.80	5.14

Thermal racemization. All melting points were determined with a hot stage microscope according to Kofler and Kofler [11]. On melting the optically active acids new crystals were usually formed in the melt. The recrystallization tendency increased in the following order: Pentamethylenethiocarbamyl $-<$Dimethylthiocarbamyl$-<$Dimethyldithiocarbamyllactic acid. Recrystallization of the last one was so rapid that the primary melting point could not be determined accurately.

After complete crystallization of the melt, the melting point of the new crystals was determined and found to be the same as the melting point of the corresponding racemic acid within 1°C. The optical activity had also disappeared and the melting point depression for a mixture of the racemate and the crystals from the melt was less than 1°C.

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