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THE REACTION OF THE PERIODATE-OXIDATION PRODUCTS OF 1,4-ANHYDROERYTHRITOL AND OF SOME RELATED PYRROLIDINE GLYCOLS WITH THIOSEMICARBAZIDES

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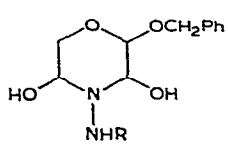
ABSTRACT

Simple analogues of the dialdehyde formed by periodate oxidation of benzyl β-L-arabinopyranoside have been prepared Oxydiacetaldehyde may be condensed with one or two moles of substituted thiosemicarbazides, whereas *N*-aryliminodiacetaldehydes give only bis(thiosemicarbazones) The oxidation of *N*-arylpyrrolidine-3,4-diols with one equivalent of periodate is straightforward if electron-attracting aromatic substituents are present, but, otherwise, some cleavage of N–C bonds in the pyrrolidine ring can be demonstrated The crystalline hemialdal, 2,6-dihydroxy-4-phenylmorpholine, was isolated The rates of conversion of some α-functionally-substituted thiosemicarbazones into glyoxal derivatives have been compared

INTRODUCTION AND DISCUSSION

In a recent study[1] of the structure of the thiosemicarbazide derivatives of periodate-oxidised polysaccharides, one of us used, as model compounds the oxidation products of some simple sugars The mode of action of certain hydrazides on these monosaccharide derivatives was determined, and one group of products, from benzyl β-L-arabinopyranoside[2], proved to have the cyclic structure **1** This led us to examine



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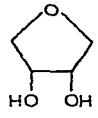

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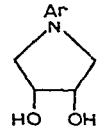

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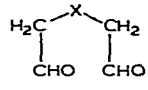
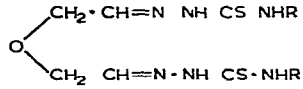
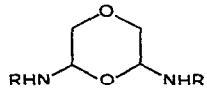


7 X = *p*-ClC$_6$H$_4$N
8 X = *p*-MeOC$_6$H$_4$N

4 X = O
5 X = S
6 X = PhN



9 R = Me
10 R = Pr
11 R = CH$_2$Ph



12 R = NH CS NHMe

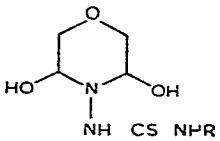
still simpler dialdehydes of comparable structure, derived, respectively, from 1,4-anhydroerythritol (**2**) and the pyrrolidine glycols (**3**), and we now report on the

reactions of these oxo-compounds with thiosemicarbazides Some preliminary work with the dialdehydes **5** and **6** was carried out earlier[3]

Oxydiacetaldehyde (**4**) was first prepared, as the bis-acetal, by means of a conventional ether synthesis[4] Periodate oxidation of the appropriate glycol **2** is more convenient Klosterman and Smith[5] compared the rate of consumption of this reagent by the *cis*- and *trans*-isomers, but isolated neither the dialdehyde nor any derivative The oxidation product has since been used[6] to prepare the oxygen analogue of Ψ-pelletierine

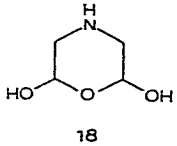
We have obtained bis(thiosemicarbazones) **10** and **11** in 80–95% yield by using the appropriate 4-substituted thiosemicarbazide The yield of 4-methylthiosemicarbazone (**9**) was somewhat lower due to its water-solubility In the presence of water, this compound exists as a monohydrate, which evidently has the cyclic structure (**12**), since the u v absorption spectrum has a maximum at 246–247 nm, and not at 270 nm which is characteristic of C=N in this context[1] The *p*-dioxane **12** can be dehydrated readily to the bis(thiosemicarbazone)

When one equivalent of thiosemicarbazide was used, the expected analogues (**13–17**) of the benzyl β-L-arabinopyranoside derivative **1** were obtained in yields



13 R=H
14 R=Me
15 R=CH_2CH_2OH

16 R=Pr
17 R=CH_2Ph



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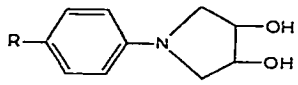


19 R=H
20 R=Cl
21 R=MeO

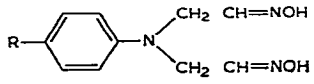
of 40–80% Like the other singly-bonded compounds **12** and **1**, these morpholines showed maximal absorption at 242 ±4 nm They could be converted readily into the bis(thiosemicarbazones), *e g* , compound **9**, by treatment with a second equivalent of the same thiosemicarbazide Treatment with a different thiosemicarbazide led to disproportionation, we were thus unable to obtain "mixed" compounds similar to those having high anti-tumour activity derived from pyruvaldehyde[7]

The benzyloxy dialdehyde obtained from benzyl β-L-arabinopyranoside gave only cyclic products (**1**) whether one or two equivalents of thiosemicarbazide were used[1] Fresh attempts to obtain a bis(thiosemicarbazone) from this dialdehyde, under the conditions used to prepare compounds **9-11**, gave intractable products Whether this difference in behaviour of the benzyloxy dialdehyde from the simple analogue **4** is due to steric or electronic effects is not yet clear In the case of the sulphur compound **5**, we have so far been able to prepare only bis-derivatives analogous to compound **9**, even with equimolecular amounts of dialdehyde and thiosemicarbazide[3]

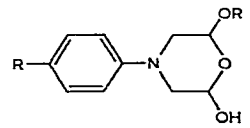
Iminodiacetaldehyde has been known as the hydrate (**18**) for many years[8] The bis-acetals of the *N*-methyl and *N*-benzyl compounds were prepared later[9], but no attempt to make *N*-aryl compounds was recorded until recently[3] Since anilinoacetal-

dehyde is much less stable than its alkylamino counterparts[10], some trouble was anticipated in attempts to oxidise the glycols **19–21**. However, when compound **19** was oxidised and treated with 2 equivalents of 4-methylthiosemicarbazide in the presence of acetic acid, the analysis figures for the product, although difficult to reproduce, were always approximately correct, and the yield of product was good, indicating that the reaction was, on the whole, proceeding as desired[3] The situation required clarification, and the first step was to study, in greater detail, the oxidation of pyrrolidine glycols

A *cis*-[12] and a *trans*-series[13] of these has been prepared, but the method of Roberts and Ross[14] is more convenient, and we used it to make the three *cis*-glycols **19–21** We found that milder conditions (10 min at 0–3°) than hitherto[3] used were quite adequate for the oxidation, although even then the reaction between compound **6** and 4-methylthiosemicarbazide led to inconsistent analytical results However, on changing the reagent from 4-methylthiosemicarbazide to hydroxylamine, we were able to isolate the dioximes **22–24** in 69, 93, and 46% yields, respectively, without



22 R = H
23 R = Cl
24 R = MeO



25 R = Cl , R' = Me
26 R = R = H

any difficulty From these results, it appears that the oxidation of the *p*-chloro compound proceeds as desired under these conditions, whereas, as the aromatic substituent becomes more electron-repelling in character, other centres in the pyrrolidine **3** are vulnerable to attack, giving rise to increasing proportions of by-products Since the pure dioximes are readily obtained, the contaminating hydroxylamine derivatives of those by-products are evidently more easily eliminated by fractional crystallisation than are the corresponding thiosemicarbazide derivatives

As well as at the glycol grouping, periodate could attack compound **3** in two ways Like other oxidants, it converts arylamines into highly-coloured products of the quinoneimine type[11a] In the special case where the amine is a 3-arylamino-1,2-glycol and excess periodate is present, cleavage readily proceeds beyond breaking of the glycol linkage, and the intermediate α-arylaminoaldehyde is further oxidised[11b] The presence of electron-attracting substituents retards the first type of oxidation, but not the second[11] It now appears that, when one equivalent of periodate is used, an electron-attracting substituent will inhibit the second type of oxidation, but that with other or no substituents this can still proceed to varying degrees We assume that, with this limited amount of periodate at the temperature employed, non-specific oxidation of the arylamine function does not take place to any significant extent, since no dark colours were observed Co-products arising from the second type of oxidation were identified in the case of compounds **19** and **21** and are discussed below.

The oxidation product from the *p*-chloro compound crystallised readily from methanol and proved to have a methyl glycoside type of structure (**25**) It could be

isolated in 63% yield When a methanolic solution of the unsubstituted compound **19** was treated with aqueous periodate in the usual way, a syrupy product always resulted However, the inverse mode of addition permitted the use of a smaller proportion of methanol in the reaction mixture, and the product was crystalline It proved to be compound **26**, but the yield, after recrystallisation, was poor Although, in general, we prefer to add the periodate solution to these glycols, the yield of dioxime **22** was independent of the mode of addition

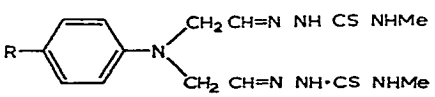
Having established that the periodate oxidation took the desired course, within limits, we returned to the study of thiosemicarbazone formation U v -monitoring provided a key to the problem of isolating pure compounds The most readily accessible dialdehyde, **7**, reacted with 4-methylthiosemicarbazide more satisfactorily in the absence of acetic acid, even though several days were required for separation of the product Successive fractions were examined spectroscopically and, since all had an absorption maximum at 270 nm, characteristic of thiosemicarbazones, they were combined and recrystallised to give compound **28** without any difficulty

TABLE I

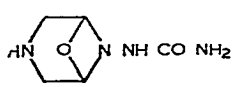
ULTRAVIOLET SPECTRAL DATA

Compound	λ_{max} (*nm*)	*log* ε_{max}
13	238[a]	4 13
14	241[b]	4 15
15	238[a]	4 13
16	243[b]	4 13
17	244[b]	4 14
12	246–247[b]	4 38
27	270[c]	4 64
28	270–271[c]	4 64
29	269–270[c]	4 59
31	244–245[c]	4 52
32	242[c]	4 54

[a]In water [b]In 95% ethanol [c]The compound (*ca* 30 mg) was dissolved in 2-methoxyethanol (20–30 ml) and diluted with 95% ethanol



27 R=H
28 R=Cl
29 R=MeO



30

The reaction with the oxidation products from the other two pyrrolidine glycols was more complex Under the same conditions as used above, a series of fractions was obtained from the unsubstituted compound **19**, these all melted in the same region, but differed spectroscopically. Only the first fraction, which had an absorption maximum at 270 nm, proved to be compound **27** Successive, further fractions had

increasing proportions of material with maximal absorption at 243–247 nm, as shown in Fig 1 This is discussed later

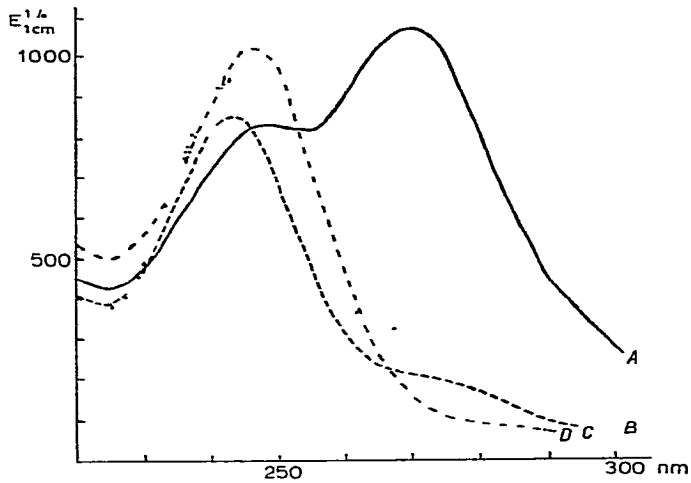


Fig 1 Ultraviolet spectra of the first four fractions (*A–D*) of product arising from the reaction of 4-methylthiosemicarbazide with periodate-oxidised **19** (————, *A*, , *B*, – – – – –, *C*, and – – – –·– , *D*)

Treatment of the *p*-anisyl derivative **21** with periodate, followed by 4-methylthiosemicarbazide, as before gave a product which showed no significant absorption at 270 nm, but had a peak at 242 nm However, when the reaction with the thiosemicarbazide was carried out in the presence of water, the small amount of thiosemicarbazone (**29**) formed, with appropriate absorption at 270 nm, separated together with the principal product The less-soluble thiosemicarbazone was isolated readily by fractional crystallisation

The yields of bis(4-methylthiosemicarbazones) obtained from the oxidation products of the three glycols paralleled the yields of the dioximes This provided further evidence that the *p*-chlorophenyl compound (**20**) was attacked by one equivalent of periodate at the glycol grouping, with a high degree of specificity. The hemiacetal (**25**) was next treated with one equivalent of 4-methylthiosemicarbazide under the conditions used to prepare the cyclic derivative **14** in the oxygen series The only isolated product, however, was the bis(4-methylthiosemicarbazone) (**28**) The dialdehyde (**7**) thus differs from the oxygen compound (**4**) and its benzyloxy derivative Wolff and Marburg[8] obtained a cyclic derivative formulated as structure **30** from the *N*-unsubstituted iminodialdehyde hydrate (**18**) and semicarbazide, although phenylhydrazine gave the normal bis-compound

Some confirmation of the course of periodate oxidation of the pyrrolidine glycols was provided by the secondary products which sometimes crystallised following treatment with thiosemicarbazides These had u v. maxima characteristic of thiosemicarbazide (C–N) as distinct from thiosemicarbazone (C=N). Fig 2 shows the spectra of the purified co-product from oxidised **19** and 4-propylthiosemicarbazide

and of the bis(thiosemicarbazone) **27**. Analysis figures obtained from several samples of two co-products were very consistent and fitted best a structure comprising one arylamine and two thiosemicarbazide residues, together with two carbon atoms Some indication of a similar loss of two carbons of the original pyrrolidine ring had also been obtained earlier[3] Molecular-weight determination precluded a dimeric formula, and of the possible structures accommodating these features, **31** and **32** seemed the most reasonable A similar ortho-derivative (**33**) has been described previously[15]

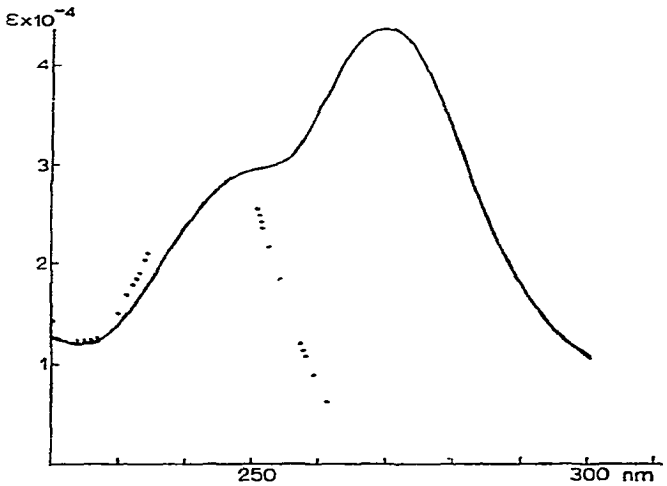
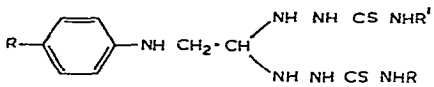
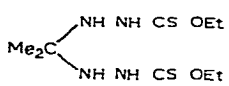


Fig 2 Ultraviolet spectra of **27** (————) and **31** ( )



31 R=H, R'=Pr
32 R=MeO, R'=Me



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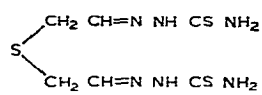

34

Glyoxal bis(2,4-dinitrophenylhydrazone) was formed readily on treatment of compounds **31** and **32** with 2,4-dinitrophenylhydrazine sulphate, in yields of the same order as afforded by the α-arylaminoaldehyde derivative **27** The appropriate glyoxal bis(thiosemicarbazone) was obtained by acid hydrolysis of compounds **31** and **32**, although in neither case could the intermediate arylaminoacetaldehyde thiosemicarbazone be isolated

It is thus evident that the 1,2-bond in the pyrrolidines **3** may be at least as susceptible to attack by periodate as the 3,4-bond, even with *cis*-hydroxyl groups The degree of specificity is determined by the substituent in the benzene ring

The ethers **12–14** and **1** all afforded glyoxal bis(2,4-dinitrophenylhydrazone) in better yields than the amines **27**, **31**, and **32**, as is shown in Table IV The sulphide **34**, in which the hetero atom is less electronegative, leading to almost completely covalent bonds with the flanking carbon atoms, behaved quite differently Here the product was thiodiacetaldehyde bis(2,4-dinitrophenylhydrazone) The reaction of 2,4-di-

nitrophenylhydrazine with several α-functionally-substituted aldehydes has been described in the literature[16], but no comparative data on the oxidation of derivatives of these compounds could be found

Further investigation of the chemistry of the dialdehydes referred to in this paper is in progress

EXPERIMENTAL

Melting points are corrected. Solutions were concentrated under diminished pressure below 40° For recrystallisation, solutions of compounds were not heated above 70°

Preparation of aqueous oxydiacetaldehyde (**4**) — 1,4-Anhydroerythritol[17] (2 08 g, 20 mmoles), dissolved in water (30 ml), was added with stirring to a solution of sodium metaperiodate (4 28 g, 20 mmoles) in water (150 ml), and the mixture was kept (24 h) in the dark at room temperature The consumption of periodate was shown[18] to be 0 98 mole/mole Iodate and excess periodate were precipitated from the resulting solution of oxydiacetaldehyde by the addition of barium chloride dihydrate (2 96 g) in water (48 ml) The mixture was neutralised ($BaCO_3$) and filtered through Celite, the insoluble material being washed with water (3 × 6 ml) Barium ions were removed by using potassium sulphate (1 86 g) in water (60 ml), and the resulting precipitate was separated and washed with water (3 × 6 ml) The solution of oxydiacetaldehyde was deionised by treatment (3 h) with Amberlite MB-1 (50 g). The resin was removed by filtration through Celite and washed with water (3 × 100 ml) This deionisation was unnecessary in the preparation of water-insoluble derivatives

Water-soluble 3,5-dihydroxy-4-thioureidomorpholines (See Table II) — Aqueous oxydiacetaldehyde, after deionisation with Amberlite MB-1, was treated with an equimolecular amount of the appropriate thiosemicarbazide (in solution), and the resulting mixture was evaporated to dryness The addition and evaporation of several portions of methanol left a solid residue which, on recrystallisation, afforded the colourless, water-soluble 3,5-dihydroxy-4-thioureidomorpholine

4-(3-Benzylthioureido)-3,5-dihydroxymorpholine (**17**) — A solution of 4-benzylthiosemicarbazide (543 mg, 3 mmoles) in ethanol (48 ml) was added to aqueous oxydiacetaldehyde, from 1,4-anhydroerythritol (3 mmoles), and the resulting mixture was concentrated to *ca* 10 ml Compound **17** (622 mg, 73%), m p 119–120°, separated initially as an oil The analytical results are given in Table II

Oxidiacetaldehyde bis(4-methylthiosemicarbazone) (**9**) — Aqueous oxydiacetaldehyde, from 1,4-anhydroerythritol (12 mmoles), was added to a solution of 4-methylthiosemicarbazide (2 52 g, 24 mmoles) in water (42 ml) containing acetic acid (0 48 ml) After 2 days at room temperature, the opaque mixture deposited crystals which were collected Further crops were obtained during the next 5 days (in all 1 82 g, 55%, after drying at room temperature/18 mm), m p 151 5–155° Crystallisation from *N,N*-dimethylformamide–water (3 4) gave colourless plates, m p 153–154°, which absorbed water (6 6%) in a hygrostat (saturated sodium nitrite)

TABLE II

3,5-DIHYDROXY-4-THIOUREIDOMORPHOLINES[a]

Compound	M p [b] (degrees)	Yield (%)	Analysis	C	H	N	S	Crystallised from
13	Decomposed gradually > 150[c]	79	Found	31 2	5 9	22 0	16 4	*N,N*-Dimethylformamide–ether (2 3)
			Calc	31 1	5 7	21 8	16 6	
14	152–153 5	44	Found	35 1	6 3	20 1	15 3	Methanol
			Calc	34 8	6 3	20 3	15 5	
15	131–131 5	38	Found	35 7	6 4	17 2	13 5	Methanol–chloroform (1 12)
			Calc ·	35 45	6 3	17 7	13 5	
16	140–141 5	45	Found	41 3	7 1	18 2	14 0	Methanol-ether (1 4)
			Calc	40 85	7 2	17 9	13 6	
17	130–132	73	Found	50 9	6 1	14 9	11 5	Chloroform–light petroleum (b p 40–60°) (1 1)
			Calc	50 9	6 0	14 8	11 3	

[a]These compounds are sensitive to heat [b]All melting points were with decomposition [c]Recrystallised **13**, dried at room temp /18 mm, has m p 99–100° (dec), and contains 39 6% of *N,N*-dimethylformamide which is removed at 78°/0 01 mm

to yield 3,5-bis(4-methylthiosemicarbazido)-*p*-dioxane (**12**), m p 150–153° (Found C, 32 9; H, 6 1, N, 28 5, S, 21 7 $C_8H_{18}N_6O_2S_2$ calc C, 32 7, H, 6 1; N, 28 6, S, 21 8%) The *p*-dioxane derivative **12** lost 6 3% by weight (≡ 1 mole of H_2O/mole) at room temperature/18 mm over phosphorus pentaoxide to give compound **9**

Oxydiacetaldehyde bis(4-propylthiosemicarbazone) (**10**) — Compound **10** was prepared by the dropwise addition with stirring, at 13–14°, of aqueous oxydiacetaldehyde, from 1,4-anhydroerythritol (3 mmoles), to a solution of 4-propylthiosemicarbazide (798 mg, 6 mmoles) in methanol (25 ml) containing acetic acid (1 2 ml) The product (784 mg, 79%) m p 138 5–140°, was collected after 18 hours and crystallised from *N,N*-dimethylformamide–water (2 3) to give colourless crystals, m p 138–139° (Found C, 43 7, H, 7 2, N, 25 4, S, 19 6 $C_{12}H_{24}N_6OS_2$ calc C, 43 4, H, 7 2, N, 25.3; S, 19 3%)

Oxydiacetaldehyde bis(4-benzylthiosemicarbazone) (**11**) — Oxydiacetaldehyde solution, from 1,4-anhydroerythritol (2 mmoles), was added dropwise with stirring to a solution of 4-benzylthiosemicarbazide (724 mg, 4 mmoles) in a mixture of ethanol (32 ml) and water (20 ml) containing acetic acid (1 6 ml) The initially, oily product **11** (810 mg, 95%) had m p 147–148° Crystallisation from *N,N*-dimethylformamide–water (2 1) raised the m p to 155 5–156.5° (Found C, 56 0, H, 5 8, N, 19 6, S, 15.1. $C_{20}H_{24}N_6OS_2$ calc C, 56 1, H, 5 6, N, 19 6, S, 15 0%)

Conversion of compound **14** *into compound* **12** — The morpholine **14** (207 mg, 1 mmole) and 4-methylthiosemicarbazide (105 mg, 1 mmole) were mixed in water (10 ml) containing acetic acid (0 02 ml) During 7 days, the *p*-dioxane derivative **12** (61%) was deposited

cis-*4*-p-*Chlorophenyl-3,4-dihydroxypyrrolidine* (**20**) — *meso*-1,4-Dichloro-

butane-2,3-diol[19] (2 862 g, 18 mmoles) and *p*-chloroaniline (8.04 g, 63 mmoles) were heated at 150° (1 5 h) The product (3.16 g, 82%), m p 146–148°, was collected after addition of water. Recrystallisation from benzene yielded colourless needles, m p 148 5–150° (Found C, 56.7, H, 5 8; Cl, 17.1; N, 6 5 $C_{10}H_{12}ClNO_2$ calc C, 56 2; H, 5 6, Cl, 16 6, N, 6 6%). The corresponding *trans* compound[13] has m p 182°.

Preparation of phenyliminodiacetaldehydes (**6–8**) — To the appropriate 1-aryl-3,4-dihydroxypyrrolidine (6 mmoles) in methanol (100 ml) was added dropwise, at 0–2° (7–9° in the case of **21**), 0 1M sodium metaperiodate (60 ml) Precipitated inorganic salts were dissolved by the addition of water (100 ml), and the resulting phenyliminodiacetaldehyde was extracted immediately with ether (100 ml and 3 × 50 ml) The extract was washed with saturated brine (40 ml) and dried ($MgSO_4$), and the solvent was removed

The crude dialdehyde **7** was crystalline When heated (10 min, 70°) in concentrated methanolic solution, it yielded colourless needles of the cyclic hemiacetal **25** (63%), m p 98–103 5° Recrystallisation from benzene–light petroleum (b p 40–60°) (5 2) raised the m p to 103 5–106° (Found C, 54 3, H, 5 8, Cl, 15 0, N, 5 7, OMe, 12 8 $C_{11}H_{14}ClNO_3$ calc · C, 54 2, H, 5 75, Cl, 14 6, N, 5 75, OMe, 12 7%). The infrared spectrum of compound **25** had a strong band at 3330 cm^{-1} (OH) and no absorption in the 1700 cm^{-1} region (C=O) Recrystallisation from aqueous acetone did not convert compound **25** into the corresponding hemialdal (*cf* Ref 20)

Dioximes (**22–24**) *of phenyliminodiacetaldehydes* (*See Table III*) — The derivatives were prepared by the procedure here given for the dioxime (**23**) of *p*-chlorophenyliminodiacetaldehyde The crude dialdehyde, prepared as above from compound **20** (2 mmoles), was dissolved in methanol (8 ml) and treated with a mixture of hydroxylamine hydrochloride (278 mg, 4 mmoles) and sodium acetate trihydrate (545 mg, 4 mmoles) in water (5 ml) The mixture, after 30 min at room temperature, was concentrated, and the dioxime which separated was recrystallised from aqueous methanol

TABLE III

DIOXIMES OF PHENYLIMINODIACETALDEHYDES

Dioxime	*Yield* (%)	*M p* [a] (*degrees*)		*Analysis*			
				C	*H*	*Cl*	*N*
22	69[b]	137 5	Found	58 1	6 7		20 2
			Calc	58 0	6 3		20 3
23	93	144–145	Found	50 1	5 2	14 9	17 5
			Calc	49 7	5 0	14 7	17 4
24	46	130–130 5	Found	55 5	6 4		17 9
			Calc	55 7	6 3		17 7

[a] All melting points were with decomposition [b] When the dialdehyde was prepared by the addition of glycol to periodate (*cf* **26**), the yield of compound **22** was 68 5%

Phenyliminodiacetaldehyde bis(4-methylthiosemicarbazone) (**27**) — The crude dialdehyde, from compound **19** (6 mmoles), was treated with a solution of 4-methylthiosemicarbazide (1 26 g, 12 mmoles) in methanol (30 ml). The resulting, almost colourless solution deposited (overnight) colourless crystals of compound **27** (918 mg, 44%), m p. 154–155° (dec) More crystalline material separated on subsequent days, but this showed no ultraviolet absorption maximum in the region (270 nm) characteristic of thiosemicarbazones Recrystallisation of the first fraction from *N,N*-dimethylformamide–methanol–water (1 5 1) raised the m p to 159.5–160° (dec) (Found C, 47 9, H, 6 3, N, 27 4, S, 17 7 $C_{14}H_{21}N_7S_2$ calc C, 47 9, H, 6 0, N, 27 9, S, 18 2%)

p-*Chlorophenyliminodiacetaldehyde bis(4-methylthiosemicarbazone)* (**28**) — 4-Methylthiosemicarbazide (630 mg, 6 mmoles), dissolved in methanol (16 ml), was added to a solution of the crude dialdehyde, from compound **20** (3 mmoles), in methanol (10 ml) During the next 5 days, 4 crops of colourless crystals of compound **28** (totalling 816 mg, 70%), m p 163 5–171°, each showing an ultraviolet absorption peak at 269–270 nm, were collected, the mother liquor gradually became yellow The combined fractions, on recrystallisation from *N,N*-dimethylformamide–methanol–water (1 4 1), had m p 170 5° (dec) (Found· C, 43 6, H, 5 5, Cl, 9 2, N, 24 8, S, 16 3 $C_{14}H_{20}ClN_7S_2$ calc C, 43 6, H, 5 2; Cl, 9 2; N, 25 4, S, 16 6%)

p-*Anisyliminodiacetaldehyde bis(4-methylthiosemicarbazone)* (**29**) — A solution of the crude dialdehyde, from compound **21** (4 mmoles), in methanol (24 ml) was treated with 4-methylthiosemicarbazide (840 mg, 8 mmoles), dissolved in water (24 ml) The mixture, after 2 h at room temperature, was concentrated The solid (863 mg) which separated had λ_{max} at 243 nm, in addition to significant absorption at 270 nm Crystallisation first from *N,N*-dimethylformamide–methanol–water (1 7 5) and then from the same solvents (2 10 1) eliminated the material with an absorption peak at 243 nm and afforded colourless crystals of compound **29** (206 mg, 14%), m p 157° (dec) The analytical sample had m p 158–159° (dec) (Found C, 47 1, H, 6 3, N, 25 6, S, 17 1 $C_{15}H_{23}N_7OS_2$ calc C, 47 35, H, 6 0, N, 25 7, S, 16 8%)

Treatment of compound **25** *with 1 equivalent of 4-methylthiosemicarbazide* — The cyclic hemiacetal **25** (243 mg, 1 mmole) and 4-methylthiosemicarbazide (105 mg, 1 mmole) were mixed in methanol (6 8 ml) The solution became dark-red overnight and deposited colourless crystals of the bis(4-methylthiosemicarbazone) (**28**) (58 mg, 30%), m p 171° (dec) No further material separated from the mother liquor

Phenyliminodiacetaldehyde hemialdal (**26**) — The pyrrolidine **19** (537 mg, 3 mmoles), in methanol (15 ml), was added dropwise with stirring, at 2–4°, to an equimolecular amount of 0 1M aqueous sodium metaperiodate The product was extracted immediately with ether From the washed (saturated brine) and dried ($MgSO_4$) extract, after removal of solvent, was obtained a pink, semi-solid residue which, on trituration with benzene (8 5 ml), yielded colourless crystals of compound **26** (190 mg, 32 5%), m p 96 5–98°. Recrystallisation from benzene–light petroleum (b p 40–60°) (2 1) raised the m.p to 100 5–102 5° (Found C, 61 3, H, 6 6, N, 7.3

$C_{10}H_{13}NO_3$ calc C, 61 5, H, 6 7, N, 7 2%) The infrared spectrum of compound **26** had a very strong band at 3330 cm^{-1} (OH) and no absorption in the 1700 cm^{-1} region (C=O)

Secondary products from the reaction of thiosemicarbazides with periodate-oxidised pyrrolidine glycols — The pyrrolidine (**19**) (716 mg, 4 mmoles) was oxidised as described for the preparation of compound **26** The crude product was treated with 4-propylthiosemicarbazide (1 064 g, 8 mmoles), dissolved in methanol (6 ml) From the resulting solution, colourless crystals (485 mg), m p 142–143 5° (dec), separated overnight Two recrystallisations, from (*a*) *N,N*-dimethylformamide–methanol–water (2 10 1) and (*b*) *N,N*-dimethylformamide–methanol (1 5), afforded compound **31** (339 mg, 22%), m p 147–148° (dec) [Found (for different samples) C, 49 2, 49 6, 50 3, H, 7 5, 7 5, 7 4, N, 25 6, 25 1, 25 7, S, 17 4, 17 5, 17 4 $C_{16}H_{29}N_7S_2$ calc C, 50 1, H, 7 6, N, 25 55, S, 16 7%]

When compound **31** (153 mg, 0 4 mmole) was stirred (18 h) in ethanol (6 1 ml) containing 2N HCl (0 61 ml), it yielded glyoxal bis(4-propylthiosemicarbazone) (11 7 mg, 10%), m p 203 5–208° (dec), undepressed by an authentic sample. The latter was made in the usual way and crystallised from aqueous pyridine as yellow crystals, m p 220–221° (dec) (Found C, 42 1, H, 7 0, N, 29 6, S. 22 8 $C_{10}H_{20}N_6S_2$ calc C, 41 7, H, 6 9, N, 29 2, S. 22 2%)

The pyrrolidine **21** (1 672 g, 8 mmoles) was oxidised as usual, *i e* , by addition of periodate to the glycol, and the resulting product was treated with a solution of 4-methylthiosemicarbazide (1 68 g, 16 mmoles) in methanol (30 ml) Fractions [406 mg, m p 128–130° (dec)] and [1 3 g, m p 135–136 5° (dec)] separated after 17 and 41 h, respectively These, having λ_{max} at *ca* 242 nm and no significant absorption at 270 nm, were combined and recrystallised twice from *N,N*-dimethylformamide–methanol–water (2 10 1) to give colourless crystals (1 08 g, 38%), m p 132 5–134 5° (dec), tentatively assigned the structure **32** [Found (for different samples) C, 41 8, 41 7, H, 6 7, 6 8, N, 26.7, 26 9, S, 18 4, 18 5; OMe, 11 7%, Mol wt , <450 $C_{13}H_{23}N_7OS_2$ calc C, 43 65, H, 6 5, N, 27 45, S, 17 95, OMe, 8 7%, Mol wt , 357 5] Hydrolysis as above afforded glyoxal bis(4-methylthiosemicarbazone) (15%), m p 240–241° (dec), undepressed by an authentic sample, m p 243° (dec)

Treatment of thiosemicarbazide derivatives with 2,4-dinitrophenylhydrazine sulphate (DNP) — The derivatives were refluxed (1 5 h) with DNP in methanol In each case, orange crystals of glyoxal bis(2,4-dinitrophenylhydrazone), m p 312–313° (dec), undepressed by an authentic sample, m p 315–316° (dec), separated

TABLE IV

YIELDS OF GLYOXAL BIS(2 4-DINITROPHENYLHYDRAZONE) FROM THIOSEMICARBAZIDE DERIVATIVES

Derivative	**31**[a]	**32**[a]	**27**[b]	**13**[b]	**14**[b]	**12**[b]	**1**[b c]
Yield (%)	18	9 5	14	50	45	36	77

[a]Treated with 2 equivalents of reagent [b]Treated with 4 equivalents of reagent [c]R=CSNHPr

Yields are given in Table IV. When the solution of compound **12** was refluxed for 15 min, the yield of derivative was 9 5%. Similar treatment of the sulphide[3] **34** for 15 min with 4 equivalents of DNP gave thiodiacetaldehyde bis(2,4-dinitrophenylhydrazone), m p 220–222°, undepressed by an authentic sample (lit.[4], m p 219–221°), in 46% yield In this case, refluxing for 1 5 h also gave largely the thiodiacetaldehyde derivative (40% yield, m p 216–223°)

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