Synthesis and Reactions of α-Ketoaldehyde Adducts of some Heterocyclic Ureas

T. L. Hough* and, in part, I. R. Hough and R. W. Pannell

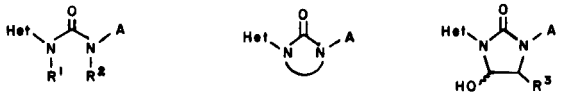
Chemical Synthesis Group, FBC Limited, Chesterford Park Research Station, Saffron Walden, Essex, CB10 1XL, England

Received December 3, 1985

Pyruvaldehyde reacts with heterocyclic ureas **4a-d** giving dihydroxyimidazolidin-2-ones **5a-d**. Phenyl glyoxal reacts with **4a** giving an analogous adduct **5e**. These 1,2-diols are smoothly dehydrated to hydantoins **9a-e** which on mild reduction provide monohydroxyimidazolidin-2-ones **10a-e**. *Cis* and *trans* isomers of **10d** have been isolated and observed to epimerise under suitable conditions. An unusual halogenation converts **5a** to the bromomethyl derivative **14b** which is a convenient starting material for the synthesis of 4-substituted imidazolin-2-ones such as **15**, **16**, **17**, **18** and **19**.

J. Heterocyclic Chem., **23**, 1125 (1986).

Members of the urea class of compounds have been used in weed control for some time [1]. In recent years, heterocyclic analogues **1** have been commercialised [2] and a considerable number of patents have appeared on related cyclic compounds **2**. Examples of the latter include the diols **3a** which are prepared from *N,N'*-disubstituted ureas **1a** by 1,3-addition of glyoxal [3a,b], and various hydroxyimidazolidinones **3b** which are produced in acid-catalysed cyclisations of ureidoactals **1b** [4a-e]. As part of an objective to discover new herbicides, we investigated the reactions of α-ketoaldehydes with ureas **1a** and devised routes to hydroxyimidazolidinones analogous to **3a** and **3b**. Further, a useful synthetic transformation allowing access to other cyclic ureas has been found. We now wish to describe this work.



1 **2** **3**

a, $R^1 = R^2 = H$

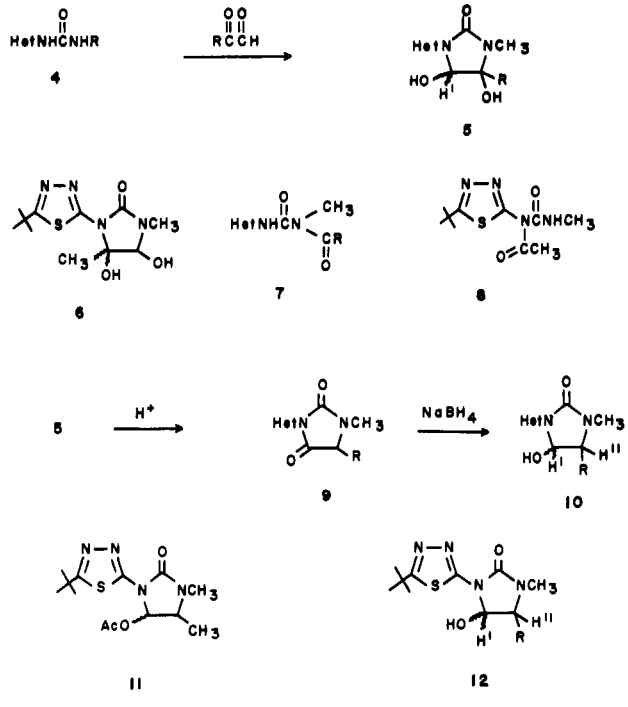
b, $R^1 = H$, $R^2 = -CHCH(Oalkyl)_2$

a, $R^3 = OH$

b, $R^3 = H$, alkyl

Het = heterocycle, A = alkyl

Previous workers have shown that α-ketoaldehydes [5a,b] and α-diketones [6a-c] can give rise to a variety of structures in reactions with urea and simple substituted ureas. In the present study, 1-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-3-methylurea (**4a**) reacted with pyruvaldehyde under alkaline conditions to give a crystalline product. The ^1H nmr spectrum (deuteriochloroform) was consistent with a 1:1 mixture of *cis* and *trans* components of the 1,2-diol **5a** or its regio isomer **6**. Evidence for **5a** resulted from treatment of the diastereomeric mixture with sodium metaperiodate. Cleavage of the diol system occurred with loss of a carbon fragment [7] and the formation of the acetyl urea **7a** and not the alternative degradation product **8** [8]. Confirmation was provided by converting the material from the pyruvaldehyde reaction to the known [4a] acetoxyimidazolidinone **11** in a series of transformations involving dehydration to the hydantoin **9a**, reduction to the hydroxyimidazolidinone **10a** [9] and finally acetylation [10]. The heterocyclic ureas **4b,c,d** also reacted with pyruvaldehyde and gave addition products which were spectroscopically similar to **5a** and are assigned the appropriate configurations **5b,c,d**. Additionally, the oxadiazolyl isomers **5b** on



4 **5** **6** **7** **8** **9** **10** **11** **12**

a, Het = 5-t-Butyl-1,3,4-thiadiazol-2-yl, R = CH_3

b, Het = 5-t-Butyl-1,3,4-oxadiazol-2-yl, R = CH_3

c, Het = Thiazol-2-yl, R = CH_3

d, Het = 3-Methylmercaptoisothiazol-5-yl, R = CH_3

e Het = 5-t-Butyl-1,3,4-thiadiazol-2-yl, R = C_6H_5

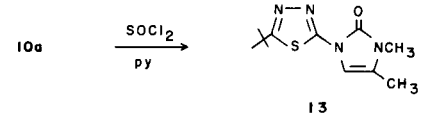
f, R = OH

g, R = H

oxidation with metaperiodate gave the open chain derivative **7b** [8]. Isomeric diols formed from phenyl glyoxal and **4a** underwent oxidative cleavage to the benzoyl urea **7e** [8] and are therefore accorded structure **5e**. No reaction took place between **4a** and diacetyl in alkaline solution.

Dehydration of **5a-e** to the corresponding hydantoins **9a-e** occurred under reflux in an appropriate solvent using catalytic quantities of *p*-toluenesulphonic acid or oxalic acid. The low yield (29%) of **9b** may be related to the thermal instability of **5b** which partially dissociated (approximately 50% estimated by ^{1}H nmr) to the open chain form **4b** when boiled in a solution of acetonitrile for 1 hour.

Whilst the reduction of hydantoins with lithium aluminium hydride can involve more than one functionality [11], we found that sodium borohydride affects only the 4-oxo group of **9a-e** to provide the hydroxyimidazolidinones **10a-e**. The phenyl derivative **10e** consisted entirely of the *trans* isomer whilst the methyl analogues **10a-d** each contained *cis* and *trans* forms in a ratio of approximately 1:4 as estimated by ^{1}H nmr spectroscopy. The same ratio was also observed in attempts to prepare exclusively *cis*-**10a** by reducing **9a** with lithium tri-secondary-butyl borohydride [12] and *trans*-**10a** in the hydroboration [13] of the imidazolinone **13** which was obtained by dehydrating the diastereomers **10a** with thionyl chloride in pyridine. Hplc was applied successively to the separation, and subsequent isolation, of the isomers of **10d**, only. Both of these compounds epimerised [14] in deuterated dimethyl suphoxide and equilibrated to the diastereomeric mixture after a few hours. In deuteriochloroform, however, interconversion was barely detected in either case. Epimerisation in these isomers is perhaps facilitated by hydrogen bonding between the hydroxylic hydrogen atom and a suitably polar molecule. The apparently facile interconversion of the isomers of **10a,b,c** may be due to intramolecular hydrogen bonding between the same hydrogen atom and the α-nitrogen atom in each heteroaromatic ring. Epimerisation of diols **5a-e** has not been explored, but the rapid and good-yielding oxidations of **5a,b,e** to **7a,b,e** suggest conversion of *trans* isomers to *cis* because reactions of this nature usually occur readily with *cis* 1,2-diols only [15].



13

The Table summarises the ^{1}H nmr characteristics of the mono- and dihydroxyimidazolidinones described above. Data on the glyoxal addition product **12f** [3a] and the homologue **12g** [4b] are included for comparison. As would be expected, chemical shifts associated with H′ in *cis*-**10a**, *cis*-**12f** and **12g** are similar. Also, the signals at δ 5.70 and δ 6.10 in the spectrum (deuteriochloroform + deuterium oxide) of the isomers of **5a** are assigned to *cis*-H′ and *trans*-H′ since their positions correspond closely to those observed for H′ in the spectra of *trans*-**10a** and *trans*-**12f**, respectively.

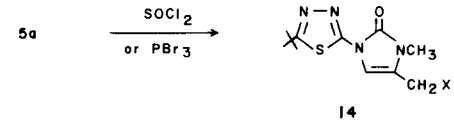
Table

Selected ^{1}H NMR Properties of **5**, **10**, **11**, **12** [a]

	H′	H″
5a [b]	5.50 (bs)	
5a [c]	5.70 (s), 6.10 (s)	
5b [b]	5.27 (bs)	
5c [b]	5.47 (s [d])	
5d [b]	5.16 (s, [d])	
5e [b]	5.48 (s), 5.59 (s)	
cis-**10a** [c]	6.00 (d, J = 6.8)	3.84 (qd, J = 6.8, 6.8)
trans-**10a** [c]	5.65 (d, J = 2.8)	3.59 (qd, J = 6.6, 2.8)
cis-**10b** [c]	5.73 (d, J ≈ 7)	3.39 - 3.90 (m)
trans-**10b** [c]	5.37 (d, J ≈ 3	3.39 - 3.90 (m)
cis-**10c** [c]	5.90 (d, J ≈ 7)	3.35 - 3.85 (m)
trans-**10c** [c]	5.53 (d, J ≈ 3)	3.35 - 3.85 (m)
cis-**10d** [c]	5.42 (d, J ≈ 7)	3.74 (qd, J ≈ 7,7)
trans-**10d** [c]	5.05 (d, J ≈ 3)	3.58 (qd, J ≈ 6,3)
trans-**10e** [c]	5.82 (d, J ≈ 3)	4.52 (d, J ≈ 3)
cis-**11** [e]	7.05 (d, J ≈ 7)	4.00 (qd, J ≈ 7,7)
trans-**11** [e]	6.55 (s)	3.63 (q, J ≈ 8)
cis-**12f** [c]	5.95 (d, J ≈ 7)	5.17 (d, J ≈ 7)
trans-**12f** [c]	6.01 (s)	4.95 (s)
12g [c]	5.98 (dd, J ≈ 8,3)	3.33 (dd, J ≈ 12,3) 3.67 (dd, J ≈ 12,8)

[a] More data is given in the experimental section. [b] Determined in DMSO-d_6 + deuterium oxide. [c] Determined in deuteriochlorofom + deuterium oxide. [d] Contains shoulder. [e] Determined in deuteriochloroform.

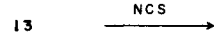
The action of thionyl chloride on **12f** results in replacement of the hydroxyl groups by chlorine [3a]. An attempt at a similar transformation of **5a** gave a monochlorinated product which was characterised as the chloromethyl derivative **14a** and authenticated by halogenation of **13** with *N*-chlorosuccimide. Phosphorous tribromide converted **5a** to the bromomethyl analogue **14b** from which the halogen atom was readily displaced in nucleophilic reactions with dimethylamine and potassium acetate to give **15** and **16**, respectively. *N*-Bromosuccinimide oxidised **16** to the aldehyde **17** which was further oxidised by silver oxide to the carboxylic acid **18**. Borohydride reduction of **17** provided the alcohol **19**.

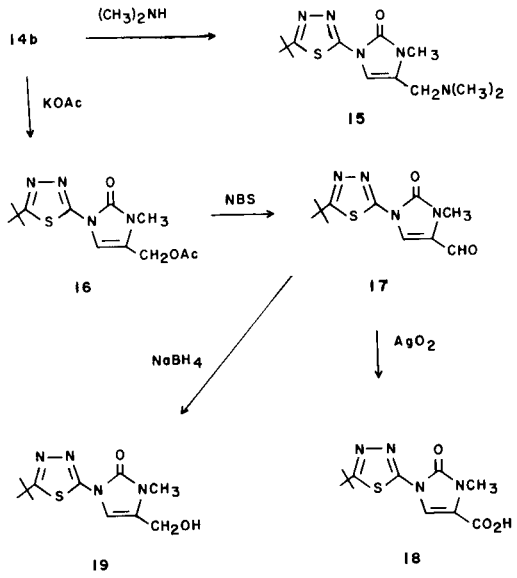


14

a, X = Cl

b, X = Br





EXPERIMENTAL

Melting points are uncorrected. Infrared spectra (ir) were run on a Pye Unicam SP1100 spectrophotometer using potassium chloride discs. The symbol b is used to indicate a broad absorption. The ^{1}H nmr spectra were recorded on a Perkin-Elmer R-32 or a Bruker WM 300. Chemical shifts are in parts per million (δ) relative to TMS, and coupling constants (J values) are in hertz. Spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectral data were obtained on AEI MS-30 and Varian MAT 44 spectrophotometers. Elemental analyses were performed on a Carlo Erba Elemental Analyser Model 1102.

1-(5-*t*-Butyl-1,3,4-oxadiazol-2-yl)-3-methylurea (**4b**).

A stirred suspension of 6.06 g (0.043 mole) of 2-amino-5-*t*-butyl-1,3,4-oxadiazole [16] in 50 ml of dry pyridine was treated with 2.68 g (0.047 mole) of methyl isocyanate. The starting material dissolved and the product soon separated. The reaction mixture was stirred at room temperature for 24 hours. The product was filtered, washed thoroughly with ethyl acetate and dried, yield 6.3 g (74%), mp 204-207°; ir: ν NH 3220-3290, C=O 1720 cm^{-1}; ^{1}H nmr (TFA): δ 1.51 (s, 9H), 3.05 (bs, 3H).

Anal. Calcd. for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.27. Found: C, 48.31; H, 7.22; N, 28.42.

1-Methyl-3-(3-methylmercaptoisothiazol-5-yl)urea (**4d**).

A solution of 9.93 g (0.068 mole) of 5-amino-3-methylmercaptoisothiazole [17], 4.30 g (0.075 mole) of methyl isocyanate and a few drops of di-*n*-butyltin diacetate in 80 ml of ethyl acetate was boiled under reflux for 10 hours. After cooling to room temperature, the product was filtered and washed with ethyl acetate, yield 10.0 g (79%); ir: ν NH 3200-3400, C=O 1675 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.45 (s, 3H), 2.63 (d, 3H, collapses to a singlet on addition of deuterium oxide), 6.46 (s, 1H), 6.58 (q, 1H, exchanges with deuterium oxide), 10.27 (bs, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_6H_9N_3OS_2$: C, 35.45; H, 4.46; N, 20.67. Found: C, 35.80; H, 4.40; N, 20.63.

General Procedure for the Synthesis of *cis/trans*-4,5-Dihydroxyimidazolidin-2-ones **5a-d**.

To a stirred suspension of 0.1 mole of the urea **4a-d** [18a,b] in 50-100 ml of ethanol was added 20 ml of pyruvaldehyde (40% aqueous solution). The reaction mixture was treated with aqueous sodium hydroxide until the solution had reached *p*H 8-9. The starting material dissolved and the reaction mixture was stirred overnight. The products **5a** and **5c-e** separated from solution and were filtered, washed with a suitable solvent and dried. No further purification was required. The oxadiazolyl derivative **5b** was isolated by concentrating the reaction mixture under vacuum to a small volume before filtering and recrystallising from water.

The thiadiazole **5a** was washed with ethanol after filtration from the reaction mixture and obtained as fine white needles, yield 88%, mp 172-175°; ir: ν OH 3100 (b), 3320, C=O 1720 cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 1.43 (s with shoulder, 12H), 2.79 (s, 3H), 5.50 (bs, 1H), 6.00-7.00 (b, 2H, exchange with deuterium oxide); ^{1}H nmr (deuteriochloroform): δ 1.35 (s, 9H), 1.41 (s, 9H), 1.52 (s, 3H), 1.59 (s, 3H), 2.90 (s, 3H), 2.95 (s, 3H), 5.30-6.10 (b, 4H, exchange on addition of deuterium oxide), 5.70 (s, 1H), 6.10 (s, 1H).

Anal. Calcd. for $C_{11}H_{18}N_4O_3S$: C, 46.14; H, 6.34; N, 19.57. Found: C, 46.26; H, 6.50; N, 19.15.

The oxadiazole **5b** was obtained in 42% yield, mp 131-134° dec; ir: ν OH 3100-3400, C=O 1765 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.39 (s with shoulder, 12H), 2.75 (s, 3H), 5.27 (bs, 1H), 6.20-7.10 (b, 2H, exchange with deuterium oxide).

Anal. Calcd. for $C_{11}H_{18}N_4O_4$: C, 48.88; H, 6.71; N, 20.73. Found: C, 48.62; H, 7.06; N, 20.40.

The thiazole **5c** was washed with a small quantity of ethanol after filtration from the reaction mixture, yield 74%, mp 158-160°; ir: ν OH 3320 (b), C=O 1735 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.38 (s, 3H), 2.74 (s, 3H), 5.47 (s with shoulder, 1H), 6.20 (b, 1H, exchanges with deuterium oxide), 6.85 (b, 1H, exchanges with deuterium oxide), 7.13 (d, J ≈ 3, 1H), 7.40 (d, J ≈ 3, 1H).

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.50; H, 4.60; N, 18.00.

The isothiazole **5d** was washed with ethanol after filtration from the reaction mixture, yield 82%, mp 176-178° dec; ir: ν OH 3150-3400, C=O 1695 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.39 (s, 3H), 2.51 (s, 3H), 2.73 (s, 3H), 5.16 (s with shoulder, 1H), 6.00-7.20 (b, 2H, exchange with deuterium oxide), 6.69 (s, 1H).

Anal. Calcd. for $C_9H_{13}N_3O_3S$: C, 39.26; H, 4.76; N, 15.26. Found: C, 39.50; H, 4.80; N, 14.90.

cis/trans-1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-4,5-dihydroxy-3-methyl-4-phenylimidazolidin-2-one (**5e**).

To a suspension of 32.10 g (0.15 mole) of **4a** and 25.08 g (0.165 mole) of phenyl glyoxal monohydrate in 100 ml of ethanol was added aqueous sodium hydroxide until the reaction mixture became slightly alkaline (*p*H ≈ 9). The starting material quickly dissolved and was superceded by a white solid which was filtered, washed with a small quantity of ethanol and dried, yield 78%, mp 178-180° dec; ir: ν OH 3100-3300, C=O 1725 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.38 (s, 9H), 2.58 (s, 3H), 5.48 and 5.59 (s and d with combined integrals of 1H, the doublet collapses to a singlet on addition of deuterium oxide), 6.60-7.10 (b, 2H, exchange with deuterium oxide), 7.20-7.60 (m, 5H).

Anal. Calcd. for $C_{16}H_{20}N_4O_3S$: C, 55.15; H, 5.79; N, 16.08. Found: C, 55.43; H, 6.01; N, 15.73.

General Procedure for the Synthesis of the Ureas **7a,b,e**.

To a suspension of 0.02 mole of the dihydroxyimidazolidin-2-one **5a,b,e** in 30 ml water was added 0.022 mole of sodium metaperiodate. The mixture was gently warmed on a steam bath and sufficient methanol added to dissolve the starting material. A mildly exothermic reaction ensued. After it had ceased, the mixture was concentrated to a small volume under vacuum. The oily product was extracted into dichloromethane and the extracts dried. The solvent was removed *in vacuo* and the solid residue crystallised from di-isopropyl ether.

The thiadiazolyl derivative **7a** was produced in 74% yield as a colourless crystalline material, mp 98-100°; ir: ν NH 3050-3200; C=O 1720, 1680 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.40 (s, 9H), 2.42 (s, 3H), 3.27 (s, 3H), 9.80-10.50 (bs, 1H, exchanges with deuterium oxide); ms: m/e 256 (M$^+$).

Anal. Calcd. for $C_{10}H_{16}N_4O_2S$: C, 46.86; H, 6.29; N, 21.86. Found: C, 47.20; H, 6.33; N, 22.21.

The oxadiazolyl urea **7b** was obtained in 73% yield, mp 108-110°; ir: ν NH 3350 (b), C=O 1690, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.32 (s, 9H), 2.41 (s, 3H), 3.22 (s, 3H), 9.50-10.30 (bs, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 50.35; H, 6.55; N, 23.65.

The benzoyl urea **7e** was obtained as colourless crystals in 70% yield, mp 102-104°; ir: ν 3100-3400, C=O 1705, 1675 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.35 (s, 9H), 3.29 (s, 3H), 7.30-7.60 (m, 5H), 12.60-13.20 (bs, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 57.03; H, 6.01; N, 17.85.

Synthesis of Hydantoins **9a,d,e.**

To a suspension of 0.025 mole of the dihydroxyimidazolidin-2-one **5a,d,e** in 100 ml of acetonitrile was added 0.15 g of either *p*-toluenesulphonic acid monohydrate (**5a,e**) or oxalic acid dihydrate (**5d**). The reaction mixture was stirred under reflux until no starting material was detected on tlc. Reaction was usually complete after 12 hours. The solvent was removed under vacuum and the residual solid dissolved in dichloromethane. The solution was washed with water, dried and evaporated to dryness *in vacuo*. Recrystallisation of the residue gave pure material.

The thiadiazolyl hydantoin **9a** recrystallised from 2-propanol/hexane as white flakes, yield 75%, mp 98-100°; ir: ν C=O 1785, 1735 cm^{-1}, ^1H nmr (deuteriochloroform): δ 1.46 (s, 9H), 1.53 (d, J ≈ 7 Hz, 3H), 3.04 (s, 3H), 4.19 (q, J ≈ 7 Hz, 1H).

Anal. Calcd. for $C_{11}H_{16}N_4O_2S$: C, 49.23; H, 6.01; N, 20.88. Found: C, 49.34; H, 6.37; N, 21.00.

The isothiazole **9d** recrystallised from a mixture of ethyl acetate and hexane as white needles, yield 95%, mp 118-119°; ir: ν C=O 1775, 1730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (d, J ≈ 7 Hz, 3H), 2.58 (s, 3H), 2.99 (s, 3H), 4.06 (q, J ≈ 7 Hz, 1H), 7.67 (s, 1H).

Anal. Calcd. for $C_9H_{11}N_3O_2S_2$: C, 42.01; H, 4.31; N, 16.33. Found: C, 42.30; H, 3.90; N, 16.20.

The 4-phenyl hydantoin **9e** recrystallised from a mixture of ethanol and hexane, yield 87%, mp 159-161°; ir: ν 1790, 1745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (s, 9H), 2.91 (s, 3H), 5.13 (s, 1H), 7.10-7.45 (m, 5H).

Anal. Calcd. for $C_{16}H_{18}N_4O_2S$: C, 58.16; H, 5.49; N, 16.96. Found: C, 58.50; H, 5.70; N, 17.00.

1-(5-*t*-Butyl-1,3,4-oxadiazol-2-yl)-3,4-dimethylhydantoin (**9b**).

A solution of 11.9 g (0.044 mole) of **5b** and 0.3 g of oxalic acid dihydrate in 200 ml of 1,2-dichloroethane was boiled under reflux for 3 hours. The water formed in the reaction was removed by azeotropic distillation. The solution was washed with water, dried and the solvent removed under vacuum. The residual solid recrystallised from a mixture of ethyl acetate and hexane as fine white needles, yield 3.2 g (29%), mp 90-92°; ir: ν C=O 1805, 1750 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.32 (s, 9H), 1.38 (d, J ≈ 7 Hz, 3H), 2.87 (s, 3H), 4.36 (q, J ≈ 7 Hz, 1H).

Anal. Calcd. for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.34; N, 22.21. Found: C, 52.40; H, 6.70; N, 22.40.

3,4-Dimethyl-1-(thiazol-2-yl)hydantoin (**9c**).

A solution of 32.1 g (0.14 mole) of **5c** and 2.0 g of *p*-toluenesulphonic acid monohydrate in 200 ml of acetonitrile was boiled under reflux for 8 hours. The solvent was removed under vacuum and the residual oil chromatographed on silica gel (particle size 32-63 μM). The product was eluted with ethyl acetate and was obtained as a pale yellow solid, yield 7.4 g (23%), mp 81-83° (after recrystallisation from a mixture of ethyl acetate and hexane); ir: ν C=O 1790, 1735 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (d, J ≈ 7 Hz, 3H), 2.96 (s, 3H), 4.07 (q, J ≈ 7 Hz, 1H), 7.19 (d, J ≈ 3 Hz, 1H), 7.65 (d, J ≈ 3 Hz, 1H).

Anal. Calcd. for $C_8H_9N_3O_3S$: C, 45.48; H, 4.29; N, 19.48. Found: C, 45.40; H, 4.40; N, 19.70.

Synthesis of *cis/trans*-4-Hydroxyimidazolidin-2-ones **10a-e.**

A solution or suspension of 0.025 mole of the appropriate hydantoin **9a-e** was stirred in 30 ml of ethanol and treated with 0.26 g (10% excess) of sodium borohydride. The course of the ensuing reduction was followed by tlc.

In the preparation of the thiadiazolyl derivative **10a** [9], solvent was removed under vacuum after 30 minutes. The residual solid was mixed with dichloromethane and the solution washed with water. The organic layer was dried and the solvent removed under vacuum. The product recrystallised from ethyl acetate as fine white needles, yield 86%, mp 165-167° [9]; ir: ν OH 3180 (b), C=O 1710 cm^{-1}; ^1H nmr (deuteriochloroform + deuterium oxide): δ 1.25-1.39 (m, 12H), 2.83 and 2.86 (s, and s with combined integrals equivalent to 3H), 3.59 and 3.84 (qd, J = 6.6, 2.8 and qd, J = 6.8, 6.8; combined integrals corresponded to 1H), 5.65 and 6.00 (d, J = 2.8, and d, J = 6.8; combined integrals were equivalent to 1H).

Anal. Calcd. for $C_{11}H_{18}N_4O_2S$: C, 48.87; H, 6.71; N, 20.73. Found: C, 49.12; H, 6.85; N, 21.02.

In the synthesis of the oxadiazolyl derivative **10b**, the reaction mixture was stirred for 30 minutes. The solvent was then removed under vacuum and the residual gum dissolved in 1,2-dichloroethane. The organic solution was washed with water, dried and distilled under vacuum leaving a viscous, colourless oil which solidified on trituration with ether. The solid recrystallised from a mixture of ethyl acetate and hexane as white needles, yield 44%, mp 101-102°; ir: ν OH 3320 (b), C=O 1715 cm^{-1}; ^1H nmr (deuteriochloroform + deuterium oxide): δ 1.21-1.33 (m, 12H), 2.77 and 2.81 (s and s with combined integrals of 3H), 3.39-3.90 (m, 1H), 5.37 and 5.73 (d, J ≈ 3 and d, J ≈ 7; combined integrals were equivalent to 1H).

Anal. Calcd. for $C_{11}H_{18}N_4O_3$: C, 51.95; H, 7.14; N, 22.04. Found: C, 52.20; H, 7.30; N, 22.00.

In the synthesis of the thiazole **10c**, a further 0.1 g of sodium borohydride was added to the reaction mixture after 30 minutes and stirring was continued for a further 30 minutes. The solvent was distilled under vacuum and the residual yellow oil taken up in dichloromethane. The organic solution was washed with water, dried and evaporated to dryness under vacuum. The residual solid recrystallised from a mixture of ethyl acetate and hexane as white crystals, yield 71%, mp 128-130°; ir: ν OH 3100, C=O 1720 cm^{-1}; ^1H nmr (deuteriochloroform + deuterium oxide): δ 1.27 and 1.32 (d, J ≈ 7 and d, J ≈ 7; combined integrals were equivalent to 3H), 2.80 and 2.84 (s and s with combined integrals equivalent to 3H), 3.35-3.85 (m, 1H), 5.53 and 5.90 (d, J ≈ 3 and d, J ≈ 7; combined integrals equivalent to 1H), 6.82 (d, J ≈ 5, 1H), 7.23 (d, J ≈ 5, 1H).

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.05; H, 5.20; N, 19.71. Found: C, 44.70; H, 5.41; N, 19.62.

In the preparation of the isothiazole **10d**, the reaction mixture was stirred for 1 hour and then concentrated under vacuum to a small volume. The product was filtered, washed with water and recrystallised as fine white needles from acetonitrile, yield 68%, mp 184-186°. The *cis* and *trans* isomers were separated on a Water's hplc system using a column packed with porasil and eluted with a 40% solution of ethyl acetate in hexane. *Cis*-**10d** had mp 182-183°; ir: ν OH 3260 (b), C=O 1690 cm^{-1}; ^1H nmr (deuteriochloroform + deuterium oxide): δ 1.39 (d, J ≈ 7, 3H), 2.59 (s, 3H), 2.61 (s, 3H), 3.74 (qd, J ≈ 7,7, 1H), 5.42 (d, J ≈ 7, 1H), 6.60 (s, 1H).

Anal. Calcd. for $C_9H_{13}N_3O_2S_2$: C, 41.68; H, 5.05; N, 16.20. Found: C, 42.00; H, 5.10; N, 16.23.

Trans-**10d** had mp 183-185°; ir: ν OH 3260 (b), C=O 1685 cm^{-1}; ^1H nmr (deuteriochloroform + deuterium oxide): δ 1.26 (d, J ≈ 6, 1H), 2.54 (s, 3H), 2.60 (s, 3H), 3.58 (qd, J ≈ 6,3, 1H), 5.05 (d, J ≈ 3, 1H), 6.63 (s, 1H).

Anal. Calcd. for $C_9H_{13}N_3O_2S_2$: C, 41.68; H, 5.05; N, 16.20. Found: C, 41.90; H, 5.20; N, 16.33.

In the preparation of *trans*-**10e**, the reaction mixture was stirred for 1½ hours. The product was filtered and dissolved in 1,2-dichloroethane. The organic solution was washed with water, dried and the solvent removed under vacuum. The residue recrystallised from ethanol affording the product as a colourless crystalline solid, yield 76%, mp 200-202°; ir: ν OH 3100 (b), C=O 1730 cm^{-1}; ^1H nmr (deuteriochloroform + deute-

rium oxide): δ 1.37 (s, 9H), 2.78 (s, 3H), 4.52 (d, J ≈ 3, 1H), 5.82 (d, J ≈ 3, 1H), 7.15-7.45 (m, 4H).

Anal. Calcd. for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.86. Found: C, 58.00; H, 6.30; N, 16.81.

cis/trans-5-Acetoxy-1-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-3,4-dimethylimidazolidin-2-one (**11**).

Prepared from *cis/trans*-**10a** by a previously described method [4a], mp 128-130°, lit mp 126-128°; ir: ν C=O 1745, 1725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30-1.50 (m, 12H), 2.04 (s, 3H), 2.90 and 2.93 (s and s with combined integrals of 3H), 3.63 and 4.00 (q, J ≈ 8 and q,d, J ≈ 7,7; combined integrals equivalent to 1H), 6.55 and 7.05 (s and d, J ≈ 7; combined integrals of 1H).

Anal. Calcd. for $C_{13}N_{20}N_4O_3S$: C, 49.98; H, 6.45; N, 17.94. Found: C, 50.30; H, 6.80; N, 17.60.

1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-3,4-dimethylimidazolin-2-one (**13**).

A solution of 13.50 g (0.05 mole) of *cis/trans*-**10a** and 8.70 g (0.11 mole) of pyridine in 150 ml of dichloromethane was stirred at 10° and treated dropwise with a solution of 6.54 g (0.055 mole) of thionyl chloride in 20 ml of dichloromethane. The reaction mixture was stirred at room temperature overnight and then washed with water, aqueous sodium carbonate and dilute hydrochloric acid. The organic solution was dried and the solvent removed under vacuum. The residual solid recrystallised from acetonitrile, yield 6.8 g (54%), mp 138-140°; ir: ν C=O 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (s, 9H), 2.11 (bs, 3H), 3.24 (s, 3H), 7.10 (bs, 1H).

Anal. Calcd. for $C_{11}H_{16}N_4OS$: C, 52.36; H, 6.39; N, 22.21. Found: C, 52.61; H, 6.60; N, 22.02.

1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-4-chloromethyl-3-methylimidazolin-2-one (**14a**).

Method A.

A suspension of 5.72 g (0.02 mole) of *cis/trans* **5a** and 5.22 g (0.066 mole) of pyridine in 80 ml of dichloromethane was stirred at 10° and treated dropwise with 5.24 g (0.044 mole) of thionyl chloride. The temperature of the reaction mixture was kept below 20° during the addition. The organic solution was stirred at room temperature for 16 hours and then washed successively with water, aqueous sodium carbonate, dilute hydrochloric acid and water. After drying, the solvent was removed under vacuum and the residual solid recrystallised from ethyl acetate, yield 3.0 g (52%), mp 163-165° dec: ir: ν C=O 1730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (s, 9H), 3.39 (s, 3H), 4.59 (bs, 2H), 7.60 (bs, 1H).

Anal. Calcd. for $C_{11}H_{15}ClN_4OS$: C, 46.07; H, 5.27; N, 19.54. Found: C, 45.70; H, 5.32; N, 19.22.

Method B.

A suspension of 1.01 g (0.004 mole) of **13** and 0.53 g (0.004 mole) of *N*-chlorosuccinnimide in 25 ml of carbon tetrachloride was boiled under reflux for 2½ hours. The solution was cooled to room temperature and filtered. The filtrate was distilled to dryness under vacuum and the residual material recrystallised from ethyl acetate, yield 0.8 g (70%), mp 163-165°; spectral properties identical to those described in Method A.

4-Bromomethyl-1-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-3-methylimidazolin-2-one (**14b**).

A suspension of 11.44 g (0.04 mole) of *cis/trans* **5a** and 3.16 g (0.04 mole) of pyridine in 100 ml of dichloromethane was stirred at 8° and treated dropwise with 7.32 g (0.027 mole) of phosphorous tribromide in 10 ml of dichloromethane. The temperature of the reaction mixture was kept below 20° during the addition. The solution was stirred at room temperature for 1 hour. It was decanted from some immiscible material and washed with water. After drying, the solvent was evaported under vacuum and the solid residue recrystallised from ethyl acetate as white needles, yield 7.5 g (57%), slowly decomposes at approximately 150°; ir: ν C=O 1725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (s, 9H), 3.38 (s, 3H), 4.42 (bs, 2H), 7.55 (bs, 1H).

Anal. Calcd. for $C_{11}H_{15}BrN_4OS$: C, 39.88; H, 4.56; N, 16.92. Found: C, 39.80; H, 5.01; N, 16.95.

1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-4-dimethylaminomethyl-3-methylimidazolin-2-one (**15**).

A solution of 4.96 g (0.015 mole) of **14b**, 2.13 g (0.0165 mole) of *N,N*-diisopropylethylamine and 0.74 g (0.0165 mole) of dimethylamine in 20 ml of dichloromethane was kept at room temperature overnight and then gently refluxed for 20 minutes. The solution was washed with water, dried and the solvent removed under vacuum. The residual solid was washed with hexane and recrystallised from ethyl acetate/hexane as white needles, yield 2.6 g (59%), mp 171-172°; ir: ν C=O 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (s, 9H), 2.22 (s, 6H), 3.23 (bs, 2H), 3.35 (s, 3H), 7.13 (bs, 1H).

Anal. Calcd. for $C_{13}N_{21}N_5OS$: C, 52.85; H, 7.17; N, 23.71. Found: C, 53.22; H, 7.43; N, 23.86.

4-Acetoxymethyl-1-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-3-methylimidazolin-2-one (**16**).

A suspension of 1.47 g (0.015 mole) of potassium acetate in 45 ml of acetonitrile was treated with 0.4 g of 18-crown-6 and the mixture stirred at room temperature. After 20 minutes, 4.95 g (0.015 mole) of **14b** was added and stirring was continued overnight. The mixture was filtered and the filtrate distilled to dryness under vacuum. The residual solid was dissolved in dichloromethane and the solution washed with water, dried and the solvent removed *in vacuo*. The product crystallised from ethyl acetate/hexane, yield 3.4 g (73%), mp 141-142°; ir: ν C=O 1740, 1725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (s, 9H), 2.06 (s, 3H), 3.32 (s, 3H), 4.97 (bs, 2H), 7.38 (bs, 1H).

Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.31; H, 5.85; N, 18.05. Found: C, 50.50; H, 6.22; N, 18.25.

1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-4-formyl-3-methylimidazolin-2-one (**17**).

A suspension of 21.7 g (0.07 mole) of **16** and 12.5 g (0.07 mole) of *N*-bromosuccinimide in 300 ml of carbon tetrachloride was boiled under reflux for 18 hours. The solvent was removed under vacuum and the residual solid triturated with water and filtered. The solid was dissolved in dichloromethane and the solution washed with water and dried. The solvent was removed under vacuum and the residual solid mixed with 100 ml of hot ethyl acetate and filtered. The solid was washed with ether affording 15.8 g (85%) of pure product. Recrystallisation from toluene gave mp 196-198°; ms: m/e 266 (M^+); ir: ν NC=O 1725, CH=O 1665 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (s, 9H), 3.62 (s, 3H), 8.18 (s, 1H), 9.57 (s, 1H).

Anal. Calcd. for $C_{11}H_{14}N_4O_2S$: C, 49.61; H, 5.30; N, 21.04. Found: C, 49.95; H, 5.55; N, 21.40.

1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-4-carboxy-3-methylimidazolin-2-one (**18**).

Silver oxide was prepared by adding a solution of 7.5 g of silver nitrate in 20 ml of water to a solution of 3.5 g of sodium hydroxide in 20 ml of water. A brown semi-solid mixture was formed to which was added 5.64 g (0.0212 mole) of **17**. The mixture was warmed gently on a steam bath until none of the aldehyde remained in suspension (approx. 1 hour). The solution was filtered and acidified with concentrated hydrochloric acid. A white precipitate formed and was extracted into dichloromethane. The extracts were dried and the solvent removed *in vacuo*. The residual solid recrystallised from acetonitrile affording fine white needles, yield 3.1 g (52%), mp 213-215° dec; ms: m/e 282 (M^+); ir: ν OH 3150-3250, C=O 1730, 1715 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (s, 9H), 3.63 (s, 3H), 8.21 (s, 1H), 11.08 (s, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_{11}H_{14}N_4O_3S$: C, 46.80; H, 5.00; N, 19.85. Found: C, 46.52; H, 4.75; N, 19.63.

1-(5-*t*-Butyl-1,3,4-thiadiazol-2-yl)-4-hydroxymethyl-3-methylimidazolin-2-one (**19**).

To a suspension of 5.32 g (0.02 mole) of **17** in 50 ml of ethanol was added 0.21 g (0.0055 mole) of sodium borohydride. The reaction mixture was

stirred at room temperature for 2 hours. The solution was filtered from a small quantity of insoluble material and then the solvent removed *in vacuo*. The residual solid was dissolved in dichloromethane and the solution washed with water. After drying, the solution was evaporated to dryness under vacuum and the product recrystallised from ethyl acetate/-hexane as fine white needles, yield 4.5 g (84%), mp 136-137.5°; ir: ν OH 3370 (b), C=O 1685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.46 (s, 9H), 3.36 (s, 3H), 4.24 (bs, 1H, exchanges with deuterium oxide), 4.52 (bs, 2H), 7.27 (bs, 2H).

Anal. Calcd. for $C_{11}H_{16}N_4O_2S$: C, 49.23; H, 6.01; N, 20.88. Found: C, 48.90; H, 6.22; N, 21.13.

Acknowledgements.

We wish to thank Dr. A. A. S. Bright, Dr. D. A. Evans and Dr. P. McCloskey for helpful suggestions and FBC Ltd. for permission to publish this work.

REFERENCES AND NOTES

[1] A. S. Crafts, "Chemstry and Mode of Action of Herbicides" Interscience Publishers, Inc., New York, NY, 1961, p 84.

[2] G. Jager in "Chemistry of Pesticides", K. H. Buchel, ed, John Wiley and Sons, Inc., New York, 1983, p 356.

[3a] German Patent Application 2,123,450 (1970); *Chem. Abstr.*, **78**, 43485q (1973); [b] German Patent Application 1,817,119 (1970); *Chem. Abstr.*, **73**, 77248b (1970).

[4a] United States Patent 4,063,924 (1977); *Chem. Abstr.*, **88**, 105355q (1978); [b] Unites States Patent 3,904,640 (1975); *Chem. Abstr.*, **83**, 193342h (1975); [c] German Patent Application 2,724,614 (1977); *Chem. Abstr.*, **88**, 105336j (1978); [d] United States Patent 4,268,697 (1981); *Chem. Abstr.*, **95**, 43121u (1981); [e] German Patent Application 3,007,556 (1980); *Chem. Abstr.*, **94**, 139805a (1981).

[5a] H. J. Fisher, J. B. Ekeley and A. R. Ronzio, *J. Am. Chem. Soc.*, **64**, 1434 (1942); [b] L. Seekles, *Rec. Trav. Chim.*, **46**, 77 (1927).

[6a] A. R. Butler and I. Hussain, *J. Chem. Soc., Perkin Trans.* 2, 310 (1981); [b] A. R. Butler, I. Hussain and K. M. Peet, *J. Chem. Soc., Perkin Trans.* 2, 320 (1981); [c] A. R. Butler, I. Hussain and E. Leitch, *J. Chem. Soc., Perkin Trans.* 2, 106 (1980).

[7] This observation agrees with earlier studies on the action of sodium metaperiodate on a pyruvaldehyde: guanine adduct reported by R. Shapiro, B. I. Cohen, S.-J. Shiuey and H. Maurer, *Biochemistry*, **8**, 238 (1969).

[8] The ^1H nmr spectrum of the degradation product showed a singlet corresponding to the NCH_3 group.

[9] Reference [4a] describes a synthesis of **10a** but no physical properties are recorded for this compound.

[10] The final product **11** consisted of *cis* and *trans* isomers in a ratio of 1:4 as estimated from the ^1H nmr spectrum.

[11] S. Cortes and H. Kohn, *J. Org. Chem.*, **48**, 2246 (1983).

[12] H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).

[13] C. F. Lane, *J. Org. Chem.*, **39**, 1437 (1974).

[14] The epimerisation of other 4-hydroxyimidazolidin-2-ones is reported in reference [11].

[15] H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Inc., Menlo Park, California, 1972, pp 355, 361.

[16] D. F. Hayman, V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **16**, 538 (1964).

[17] E. C. Taylor and E. Wacksen, *J. Org. Chem.*, **43**, 4154 (1978).

[18a] Compound **4a** was prepared by the method of H. Kubo, R. Sato, I. Hamura and T. Ohi, *J. Agric. Food Chem.*, **18**, 60 (1970); [b] **4c** was prepared by the method described in German Patent Application 2,456,822 (1973); *Chem. Abstr.*, **83**, 114831u (1975).