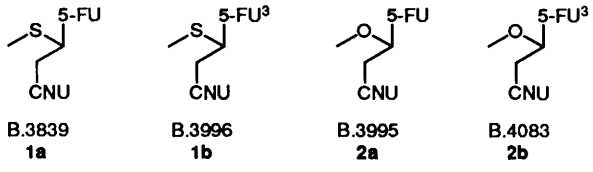
Nucleoside Analogues. Part 12.[1] The Anomalous ^{19}F NMR Spectrum of B.3996, a Molecular Combination of 5-Fluorouracil and *N*-(2-Chloroethyl)-*N*-nitrosourea and Synthesis of its *N'*-Nitroso Isomer and Related Compounds

Joan E. McCormick,[a] R. Stanley McElhinney,*[,a] T. Brian H. McMurry[b] and Ross J. Maxwell[c]

[a] *Laboratories of the Medical Research Council of Ireland, Trinity College, Dublin 2, Ireland*
[b] *University Chemical Laboratory, Trinity College, Dublin 2, Ireland*
[c] *CRC-Biomedical Magnetic Resonance Research Group, Department of Cellular and Molecular Sciences, St. George's Hospital Medical School, London SW17 0RE, UK*

In an attempt to explain the two signals in the ^{19}F NMR spectrum of the 5-fluorouracil (5-FU)/*N*-(2-chloroethyl)-*N*-nitrosourea (CNU) molecular combination B.3996, we synthesised the isomeric *N*-(2-chloroethyl)-*N'*-nitrosourea (isoCNU) by an unequivocal route involving *N*-nitrosation of an aryl carbamate bearing the appropriate pyrimidine-containing *N*-substituent. In the event, this isoCNU was not responsible for the second peak in the ^{19}F NMR spectrum, but itself showed two peaks. The ^1H NMR spectra at 300 MHz of these sulphides and the two corresponding N^1-isomers and the two methoxy CNU analogues confirmed that a combination of methylthio/N^3-substitution is necessary for the duplication pattern. In the compounds which show this behaviour, it is suggested that the *Z* and *E* isomers (around the N–N=O system) equilibrate at a rate slower than the NMR time scale. This may have implications for the mechanism of biological action of B.3996.

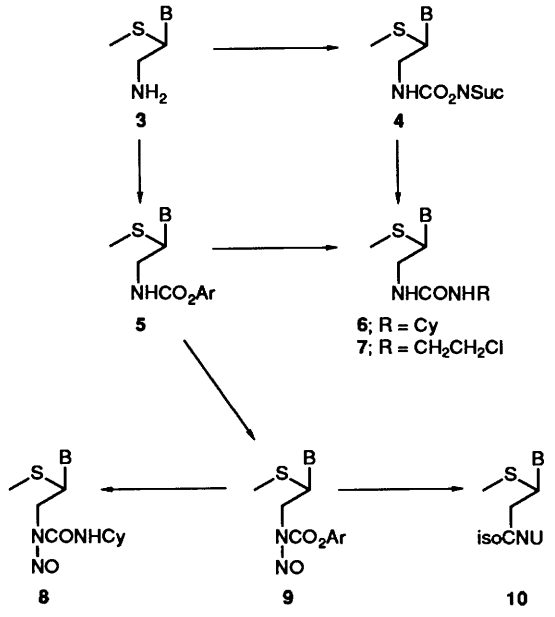
In our investigation[2,3] of seco-nucleoside *N*-nitrosoureas as molecular combinations of anti-tumour agents, four closely related compounds C.3839 **1a**,[4] B.3996 **1b**,[3] B.3995 **2a**,[5] and B.4083 **2b**[6] are emerging as candidates for more detailed



5-FU = 5-fluorouracil-1-yl, 5-FU^3 = 5-fluorouracil-3-yl, CNU = NHCON(NO)CH_2CH_2Cl

comparative study. This group has shown high activity against various solid tumours in mice, but individual drugs sometimes behave quite differently with particular tumours. The considerable variations in *in vivo* activity may be due to drug transport and bioavailability, dependent on physicochemical properties, or perhaps to chemical factors (ease of release of free 5-FU). With the goal of correlating (physico)chemical and biological properties we have embarked on both a classical pharmacokinetic study[7] and an examination of the fate of these *N*-(2-chloroethyl)-*N*-nitrosoureas (CNUs) in mice using *in vivo* ^{19}F NMR spectroscopy.[8]

At the outset it transpired that while three of the compounds, in water, showed the expected single peak in the ^{19}F NMR spectra at 376.3 MHz, the methylthio isomer B.3996 **1b** in which the pyrimidine is attached by N^3 showed two peaks. One explanation for this was the possibility that migration of the nitroso group from urea *N* to *N'* was somehow facilitated in this molecule, so we decided to prepare, for comparison, the further isomeric pair of methyl sulphides **10a** and **10b** (Scheme 1), designated isoCNUs and bearing the nitroso group on the alternative urea nitrogen. Compound **10b** was actually mentioned some time ago[9] as part of an apparent 50:50 mixture with **1b**, the result of an attempt to prepare the latter by nitrosation of the urea **7b**. (The N^1-substituted compound **1a** was the sole nitrosation product from **7a** in a similar



Suc = succinyl, Cy = cyclohexyl, Ar = 2,4,5-trichlorophenyl, isoCNU = N(NO)$CONHCH_2CH_2Cl$

Scheme 1 a, B = 5-FU(N^1-substituted); b, B = 5-FU^3(N^3-substituted)

experiment.[4]) The unequivocal preparation of compounds **10** and their 300 MHz ^1H NMR spectra are now described, and the significance of the type of acetal structure (*N,S*- or *N,O*-) and of the points of attachment of the uracil ring (by N^1 or N^3) and of the nitroso group (at *N* or *N'*) in molecules of this nature is discussed.

The regiospecific synthesis of *N*-nitrosoureas has become routine in recent years through the device of introducing the nitroso group before the urea is formed. Thus CNUs are now readily prepared free from isoCNUs by treating amines with the reagent $Cl(CH_2)_2N(NO)CO_2Ar$ (Ar = 2,4,5-$C_6H_2Cl_3$).[10] This activated carbamate is a relatively stable crystalline com-

pound, and analogues have been used for synthesising certain isoCNUs.[11] In contrast to these aryl esters, *N*- succinimido esters [10,12] have the potential advantage that the liberated by-product (*N*-hydroxysuccinimide) is water-soluble. The *N*-nitrosocarbamates are prepared by addition of phenol or *N*-hydroxysuccinimide to isocyanate followed by nitrosation using nitrosyl chloride.

Such a route to the isoCNUs **10** would require the precursors **9** and **5**, or alternatively **4**. The isocyanate approach to the carbamates **5** and **4** was not attractive, but we have been able to obtain compounds **5a** and **5b** in good yield from the amines **3** and the diaryl carbonate.[1] In similar fashion the esters **4a** and **4b** were prepared from *N*,*N*′-disuccinimido carbonate, also known [12] to undergo selective aminolysis. While the N^3-isomer **4b** was a gum it gave the crystalline urea **6b** with cyclohexylamine. Compound **6a** was similarly prepared from the aryl carbamate **5a**; it had been used earlier [4] to characterise the original molecular combination B.3839 **1a** in which *N*-nitrosoalkyl acted as the leaving group in reaction with cyclohexylamine.

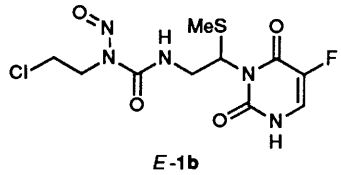
The carbamates **5** were nitrosated using nitrosyl chloride [13] in pyridine. The product **9a** and the derived *N*-cyclohexyl-*N*′-nitrosourea **8a** were crystalline, unlike the corresponding N^3-isomers **9b** and **8b**. Nitrosation of the succinimido ester **4a** gave, in low yield, an oily product which had to be extracted from water and was not further investigated. Each of the aryl carbamates **9** when treated with 2-chloroethylamine afforded, after careful work-up, the desired isoCNUs **10**.

The availability of the authentic isomer **10b**, m.p. 146.5 °C, led us to look again at the original [9] nitrosation product, m.p. 144.5–145 °C, from the urea **7b**. Repetition of the reaction of the urea **7b**, now prepared in the improved manner described earlier,[1] with nitrosyl formate gave a foamy product (*ca.* 100% yield). The 80 MHz ^{1}H NMR spectrum showed two sets of broad multiplets (ratio 1:1) at δ 5.85 and 5.55, characteristic of the SCHN proton in the CNU **1b**, m.p. 115.5–116.5 °C, and the isoCNU **10b** respectively. Crystallisation of the mixture from ethanol afforded (25% yield) almost pure isoCNU **10b**.

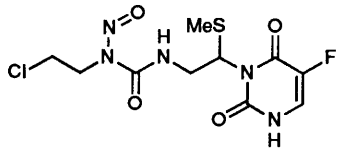
The original nitrosation product, m.p. 144.5–145 °C, was believed [9] to be a 50:50 mixture of the two possible *N*-nitroso isomers **1b** and **10b** on the basis that the ^{1}H NMR spectrum (200 MHz) shows two double doublets in the set of peaks due to the SCHN proton at δ 5.4–5.65. It is now clear to us that no CNU **1b** was present in the original product, as this would have shown up in the NMR spectrum as peaks at δ 5.85. No signal was shown in this region.

The ^{19}F NMR spectrum of compound **10b** did not show the two peaks observed in the case of the CNU **1b**. Rather it consisted of two new peaks, with similar separation to those of compound **1b**. Accordingly, the second peak in the original spectrum cannot be due to migration of the nitroso group. In a renewed effort to explain the effect, we measured the ^{1}H NMR spectra of all four sulphide isomers **1** and **10** and of the methoxy analogues **2** at 300 MHz, and the results are summarised in Table 1. Again the spectrum of compound **1b** is atypical; the SCHN signal is duplicated as was evident in the 200 MHz spectrum. The separation in Hz of the two sets of peaks is field dependent, showing that this was not caused by coupling. Furthermore, the signal due to 6-H in the pyrimidine ring is also visibly duplicated at 300 MHz, albeit with less separation. The same pattern is shown in the spectrum of the other N^3-substituted isomer **10b**, but not in the N^1 isomers **1a** and **10a**, nor in the methoxy compounds **2a** and **2b**. A combination of sulphur and N^3-substitution is evidently necessary for duplication of peaks to be observed.

We can explain these results if we assume that the CNU **1b** and the isoCNU **10b** are equilibrating mixtures (ratio *ca.* 7:5) of the *Z*- and *E*-isomers arising from the non-linearity of the N–N=O system. We cannot predict which isomer predominates. This equilibrium is slow compared with the NMR time scale at 300 MHz. For N^1-substituted and methoxy compounds such as **1a** or **2b**, either the same pair of isomers exists but the equilibrium rate is faster than the NMR time scale, or one of the isomers (probably *E* [14]) is much more stable than the other. With either explanation a single set of signals would be expected. The origin of the behaviour of compounds **1b** and **10b** is not clear.



E-**1b**



Z-**1b**

Such a phenomenon has not to our knowledge been observed hitherto for *N*-nitroso amides at room temperature, although it has been demonstrated at −40 °C for *N*-aryl-*N*-nitrosoureas by ^{13}C NMR spectroscopy.[15] Typical CNUs like Semustine (MeCCNU) are *E*-isomers in the solid state; X-ray diffraction shows that the N=O bond is aligned towards the chloroethyl group.[14] The configuration and mobility of the nitroso group in B.3996 **1b** may prove significant in the mechanism of its biological action, as the products of solvolysis of nitrosoureas are dependent on the orientation of the nitroso group.[16]

Experimental

UV spectra were measured in methanol on a Unicam SP-800 spectrophotometer, and IR spectra using KBr discs on a Unicam SP1000 instrument. ^{1}H NMR spectra in $(CD_3)_2SO$ were run at 80 MHz on a Bruker WP-80, or at 300 MHz on a Bruker MSL-300 and ^{19}F NMR spectra at 376.3 MHz on a Bruker AM-400 machine. *J* Values are given in Hz. M.p.s, uncorrected, were determined in capillaries. Light petroleum had b.p. 40–60 °C except where otherwise stated. Column chromatography was on Merck silica gel 60 (35–70 mesh ASTM, Art.7733).

Succinimido N-[2-(5-*Fluorouracil*-1 (*and* 3)-*yl*)-2-(*methylthio*)*ethyl*]-N-*carbamates* **4**.—A solution of the amine **3a** (1.31 g, 6 mmol) and disuccinimido carbonate (1.54 g, 6 mmol) in dimethylformamide (DMF) (72 cm^3) was evaporated (below 40 °C) after 2 h. Addition of aqueous acetic acid (1%; 60 cm^3) and filtration afforded the *carbamate* **4a** (1.72 g, 80%), m.p. 209–212 °C (from ethyl acetate) (Found: C, 40.1; H, 3.7; N, 15.6; S, 9.0. $C_{12}H_{13}FN_4O_6S$ requires C, 40.0; H, 3.6; N, 15.55; S, 8.9%); λ_{max}/nm 272 (265 in presence of NaOH); ν_{max}/cm^{-1} 1773, 1742, 1711, 1685 and 1665.

A solution of the hydrochloride (1 mmol) of the amine **3b**, purified [1] *via* the picrate, in NaOMe (0.5 mol dm^{-3}; 2 cm^3) was evaporated. The base in DMF (12 cm^3) reacted with the carbonate (256 mg) as above. After evaporation, the residual syrup dissolved in aqueous acetic acid (1%; 10 cm^3) and the products were extracted into ethyl acetate. Drying ($MgSO_4$), evaporation, trituration with ether (in all, 10 cm^3) and decantation left the carbamate **4b** (266 mg, 74%) as a gum.

Table 1 ^1H and ^{19}F NMR signals[a] of seco-nucleoside nitrosoureas

Compound	M.p. °C	δ 3-H	1-H	urea NH	6-H	XCHN[b]	NCH_2CH	NCH_2CH_2	$ClCH_2$	MeX[b]	^{19}F
2a	145.5–146	11.73 (d, *J* 4.9)	—	8.95 (t, *J* 6.8)	7.89 (d, *J* 6.8)	5.68 (m)	3.65 (m)	4.07 (t, *J* 6.3)	3.57 (t, *J* 6.3)	3.29 (s)	3.94
2b	121–122	—	10.94 (d, *J* 5.6)	8.97 (t, *J* 5.4)	7.81 (t, *J* 5.9)	5.97 (t, *J* 5.7)	3.91 (m) 4.05 (m)	4.07 (t, *J* 6.2)	3.58 (t, *J* 6.2)	3.26 (s)	1.84
1a	127.5–128.5	11.77 (d, *J* 5.0)	—	9.12 (t, *J* 5.9)	8.18 (d, *J* 7.1)	5.78 (m)	3.71 (m)	4.07 (t, *J* 6.2)	3.57 (t, *J* 6.4)	2.09 (s)	5.01
10a	127–127.5	11.81 (d, *J* 4.6)	—	8.93 (t, *J* 5.4)	8.22 (d, *J* 7.1)	5.53 (dd, *J* 4.3 and 9.8)	4.35 (dd, *J* 9.8 and 14.2) 4.04 (dd, *J* 4.3 and 14.2)	3.6 (m)		2.05 (s)	—
1b	115.5–116.5	—	11.09 (d, *J* 5.4)	9.06 (br s)	7.83 (m)	5.78 (m) 5.82 (m)	3.82 (m) 4.07 (m)	4.07 (t, *J* 6.4)	3.57 (t, *J* 6.5)	2.20 (s)	2.18 1.71
10b	145	—	11.21 (br s)	8.88 (br s)	7.86 (m)	5.45 (m) 5.58 (m)	4.60 (m) 4.25 (m)	3.5 (m)		2.18 (s)	2.06 1.52

[a] δ values given, *J* in Hz; ^1H NMR spectra measured in $(CD_3)_2SO$ at 300 MHz, ^{19}F NMR spectra measured in H_2O (pH 7.0; phosphate buffer) at 376.3 MHz; references samples $SiMe_4$ (H) and 5-FU (F). [b] X = O or S as in formulae.

N-[2-(5-*Fluorouracil*-1 (*and* 3)-*yl*)-2-(*methylthio*)*ethyl*]-N′-*cyclohexylureas* **6**.—Reaction of the carbamate **5a** (58 mg, 0.13 mmol) in DMF (0.1 cm^3) with cyclohexylamine (0.015 cm^3, 0.14 mmol) for 3 h and addition of aqueous acetic acid (1%; 2 cm^3) gave a gum, taken up in ethyl acetate. Evaporation and treatment with ether caused separation of the *N*-cyclohexylurea **6a** (29 mg, 64%), m.p. and mixed m.p. 196–197 °C (from methanol) (lit.,[4] m.p. 189–190.5 °C); IR spectrum identical with authentic.

The gummy carbamate **4b** (266 mg) was dissolved in DMF (0.2 cm^3) and treated with cyclohexylamine (0.085 cm^3, 0.75 mmol). After 1 h, addition of aqueous acetic acid (1%; 3 cm^3) caused separation of the N-*cyclohexylurea* **6b** (103 mg, 40%) which gradually solidified. The analysis sample had m.p. 205–205.5 °C (from ethanol) (Found: C, 48.8; H, 6.2; N, 16.4. $C_{14}H_{21}FN_4O_3S$ requires C, 48.85; H, 6.1; N, 16.3%); λ_{max}/nm 270 (304 in presence of NaOH).

2,4,5-*Trichlorophenyl* N-[2-(5-*Fluorouracil*-1-*yl*)-2-(*methylthio*)*ethyl*]-N-*nitrosocarbamate* **9a**.—A slurry of the carbamate **5a** (2.66 g, 6 mmol) in dry pyridine (6 cm^3) was treated at −18 °C with, in one portion, liquid nitrosyl chloride (1.5 cm^3, *ca.* 33 mmol; generated[13] from sodium nitrite and conc. HCl). After thorough mixing, the flask contents were kept for 2 h at −12 °C. Ice–water (22 cm^3) and HCl (2 mol dm^{-3}; 38 cm^3) were then added and the golden coloured product (2.58 g) was filtered off. Recrystallisation of an aliquot (1.48 g), containing insoluble impurity (36 mg), from acetonitrile (5 cm^3; 15 °C to −15 °C) yielded the *nitrosocarbamate* **9a** (863 mg, corresponding to 53% yield), m.p. 143–145 °C (with effervescence). The analysis sample had m.p. 156 °C (from acetonitrile) (Found: C, 35.6; H, 2.2; N, 12.1; S, 6.8. $C_{14}H_{10}Cl_3FN_4O_5S$ requires C, 35.65; H, 2.1; N, 11.85; S, 6.8%); λ_{max}/nm 267 and 287sh (248 and 314, 272sh in presence of NaOH); ν_{max}/cm^{-1} 1768, 1731, 1712, 1666, 1530 and 1460; δ_H(80 MHz) 11.92 (d, *J* 5.3, ring 3-H), 8.33 (d, *J* 7.0, ring 6-H), 8.17 and 8.00 (both s, Ar-H), 5.66–5.49 (m, SCHN), 4.42–4.06 (m, CH_2) and 2.10 (s, MeS).

Treatment of the nitrosocarbamate **9a** (141 mg, 0.3 mmol) in DMF (0.3 cm^3) cooled in ice–water with cyclohexylamine (0.07 cm^3, 0.6 mmol), stirring for 1 h without the bath, and quenching with aqueous acetic acid (1%; 4.5 cm^3) gave a gum (165 mg) which was washed with water by decantation, taken up in ethyl acetate (6 cm^3) and dried ($MgSO_4$). The phenol was removed by dissolution in ether (0.3 cm^3) and addition of light petroleum (3 + 1 cm^3). Decantation left a gum (126 mg) which crystallised from ethanol (0.6 cm^3), yielding the cyclohexylurea **8a** (54 mg, 43%) as a *monoethanolate*, m.p. 104–105 °C (with effervescence) (from ethanol) (Found: C, 45.5; H, 6.0; N, 17.0; S, 7.8. $C_{14}H_{20}FN_5O_4S$·EtOH requires C, 45.8; H, 6.2; N, 16.7; S, 7.65%); λ_{max}/nm 268 (unchanged in presence of NaOH); ν_{max}/cm^{-1} 1716, 1667, 1530 and 1492 cm^{-1}.

The succinimido carbamate **4a** (1.69 g, 4.7 mmol) in pyridine (2.35 cm^3) was treated with nitrosyl chloride (2 cm^3, *ca.* 43 mmol) as above, followed by HCl (2 mol dm^{-3}; 15 ml) and ice–water (33 cm^3). Only a trace of solid separated. From the filtrate, some yellow oil (164, in all 368 mg; λ_{max}/nm 268) was extracted into dichloromethane (3 × 50 cm^3) followed by ethyl acetate (3 × 50 cm^3)

2,4,5-*Trichlorophenyl* N-[2-(5-*Fluorouracil*-3-*yl*)-2-(*methylthio*)*ethyl*]-N-*nitrosocarbamate* **9b**.—Nitrosation of the N^3-isomer **5b** (3.32 g, 7.5 mmol) in pyridine (3.75 cm^3) with nitrosyl chloride (2.5 cm^3, *ca.* 54 mmol), followed by addition of HCl (2 mol dm^{-3}; 24 cm^3) and ice–water (51 cm^3) and filtration, afforded a brown amorphous solid (3.59 g) which showed mainly a single spot in TLC [CH_2Cl_2–EtOAc (3:7)]. It could not be induced to crystallise from a variety of solvents. Chromatography of a portion (0.16 g) in dichloromethane (2 cm^3) on a column of silica gel (8 g) gave in poor recovery, eluting with MeCN–CH_2Cl_2(1:9), material showing two principal spots in TLC. Another portion (2.17 g) was stirred with dichloromethane (68 cm^3) and charcoal (1.5 g). Filtration and evaporation gave the crude nitrosocarbamate **9b** as a foam (1.71 g), used for subsequent reaction.

Reaction of an aliquot (47 mg) of the original product with cyclohexylamine as for the N^1-isomer above gave a product showing two spots in TLC and yielding no crystalline material.

N-(2-*Chloroethyl*)-N′-[2-(5-*fluorouracil*-1-*yl*)-2-(*methylthio*)*ethyl*]-N′-*nitrosourea* **10a** *and the* (5-*Fluorouracil*-3-*yl*) *Isomer* **10b**.—2-Chloroethylamine hydrochloride (387 mg, 3.34 mmol) was stirred in DMF (1.67 cm^3) at 0 °C and treated

successively with triethylamine (0.46 cm^3, 3.34 mmol) and the nitrosocarbamate **9a** (787 mg, 1.67 mmol). Stirring was continued 30 min at room temperature and aqueous acetic acid (1%; 25 cm^3) added. The gum (747 mg) was isolated by decantation, taken up in ethyl acetate (33 cm^3) and dried ($MgSO_4$). Treatment with ether (1.7 cm^3) left a crystalline product (375 mg), and a further fraction (119 mg) with virtually the same UV spectrum and single spot in TLC separated from the decanted aqueous solution. Recrystallisation of the total from ethanol gave the *urea* **10a** (352 mg, 60%), m.p. 127–127.5 °C (with effervescence) (Found: C, 33.9; H, 3.7; N, 20.0; S, 9.1. $C_{10}H_{13}ClFN_5O_4S$ requires C, 33.95; H, 3.7; N, 19.8; S, 9.05%; λ_{max}/nm 267 (270 in presence of NaOH); ν_{max}/cm^{-1} 1534, 1502 and 1472.

A solution of 2-chloroethylamine hydrochloride (835 mg, 7.2 mmol) in methanol (72 cm^3) was treated at 5 °C with NaOMe (0.5 mol dm^{-3}; 14.4 cm^3) and the cold solution added all at once to the crude nitrosocarbamate **9b** (1.71 g, obtained as described above). After 1 h at room temperature, water (16 cm^3) was added, methanol evaporated and aqueous acetic acid (1%; 60 cm^3) added. The oil was taken up in dichloromethane and a little more extracted using ethyl acetate. After drying ($MgSO_4$), the crude product (1.75 g) in dichloromethane (6 cm^3) was chromatographed on a column of silica gel (75 g). The fractions (581 mg) eluted by CH_2Cl_2–MeOH (19:1) showed mainly a single spot in TLC [C_6H_6–MeOH (4:1)] and were crystallised from ethanol (0.6 cm^3) to give the isomeric *urea* **10b** (111 mg, 7% based on the carbamate **5b**), m.p. 145 °C (with effervescence) (Found: C, 34.1; H, 3.75; N, 19.8%); λ_{max}/nm 265 (304 in presence of NaOH); ν_{max}/cm^{-1} 1539, 1503 and 1430.

The isomers **10a** and **10b** were also prepared, in somewhat lower yields, by reversing the triethylamine–DMF and NaOMe–methanol reaction conditions.

Nitrosation of the Urea **7b** *by Nitrosyl Formate.*—A solution of the urea **7b** (325 mg, 1 mmol) in formic acid (3 cm^3) was treated at 2–5 °C with sodium nitrite (207 mg, 3 mmol) in regular portions over 30 min. Stirring and cooling were continued (4 h) and then the solvent was evaporated and replaced by water (3 cm^3). The gum was taken up in ethyl acetate (40 cm^3), washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The brittle foam (354 mg, 100%) after evaporation showed a single spot in TLC [C_6H_6–MeOH (4:1)] with only a trace corresponding to starting urea; δ 5.85 and 5.55 (both m, SCHN of **1b** and **10b** respectively, present in the ratio 1:1) and 2.20 and 2.18 (both s, MeS of **1b** and **10b**). Crystallisation from ethanol (2 cm^3) gave the isoCNU **10b** (86 mg, 25%), m.p. 145–145.5 °C (with effervescence) (from ethanol), with the same NMR spectrum as the sample prepared unequivocally above.

Acknowledgements

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References

1 Part 11, J. E. McCormick, R. S. McElhinney and T. B. H. McMurry, *J. Chem. Res.*, 1991, in press.
2 R. S. McElhinney, J. E. McCormick and C. M. Lucey, *Cancer Treat. Rev.*, 1988, **15**, 73; J. E. McCormick and R. S. McElhinney, *Eur. J. Cancer*, 1990, **26**, 207.
3 R. S. McElhinney, J. E. McCormick, M. C. Bibby, J. A. Double, G. Atassi, P. Dumont, G. Pratesi and M. Radacic, *Anti-Cancer Drug Design*, 1989, **4**, 1.
4 J. E. McCormick and R. S. McElhinney, *J. Chem. Res.*, 1981, (*S*), 310; (*M*), 3601.
5 R. S. McElhinney, J. E. McCormick, M. C. Bibby, J. A. Double, G. Atassi, P. Dumont, G. Pratesi and M. Radacic, *Anti-Cancer Drug Design*, 1989, **3**, 255.
6 N. M. Lucey, J. E. McCormick and R. S. McElhinney, *J. Chem. Soc., Perkin Trans. 1*, 1990, 795.
7 P. M. Loadman, M. C. Bibby, J. A. Double and R. S. McElhinney, *Brit. J. Cancer*, 1990, **62**, 515.
8 M. J. W. Prior, R. J. Maxwell and J. R. Griffiths, *Biochem. Pharmacol.*, 1990, **39**, 857.
9 J. E. McCormick and R. S. McElhinney, *J. Chem. Soc., Perkin Trans. 1*, 1985, 93.
10 J. Martinez, J. Oiry, J. L. Imbach and F. Winternitz, *J. Med. Chem.*, 1982, **25**, 178; J. E. McCormick and R. S. McElhinney, *Anti-Cancer Drug Design*, 1986, **1**, 111.
11 J. Oiry, A. Pompon, J. C. Madelmont and J. L. Imbach, *Eur. J. Med. Chem.*, 1984, **19**, 311; J. C. Madelmont, D. Godeneche, D. Parry, J. Duprat, J. L. Chabard, R. Plagne, J. Mathe and G. Meyniel, *J. Med. Chem.*, 1985, **28**, 1346.
12 K. Takeda, Y. Akagi, A. Saiki, T. Tsukahara and H. Ogura, *Tetrahedron Lett.*, 1983, **24**, 4569.
13 J. R. Morton and H. W. Wilcox, *Inorg. Synth.*, 1953, **4**, 48.
14 H. W. Smith, A. Camerman and N. Camerman, *J. Med. Chem.*, 1978, **21**, 468; J. W. Lown and S. M. S. Chauhan, *J. Org. Chem.*, 1981, **46**, 5309.
15 M. Tanno and S. Sueyoshi, *Chem. Pharm. Bull.*, 1987, **35**, 1353.
16 N. Buckley, *J. Org. Chem.*, 1987, **52**, 484; N. Buckley and T. P. Brent, *J. Am. Chem. Soc.*, 1988, **110**, 7520.

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