Nucleoside Analogues. Part 10.[1] Synthesis of Three Unusual 5-Fluorouracil Seco-nucleosides Incorporating *N*-(2-Chloroethyl)-*N*-nitrosourea Residues

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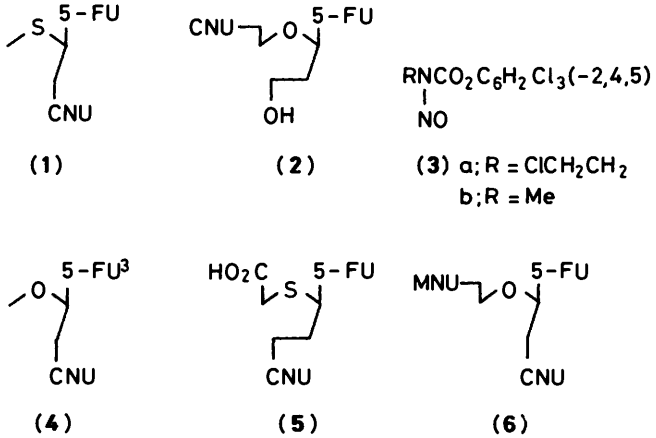
Seco-nucleosides in which 5-fluorouracil (5-FU) is attached at N^3 cannot be synthesised when the heteroatom is O by the methods effective when it is S. An *N*-phthaloyl representative of this class has now been made from a suitably protected pyrimidine and converted into the corresponding *N*-(2-chloroethyl)-*N*-nitrosourea (CNU), a molecular combination of anti-tumour drugs of great interest for comparison with other closely related structures. Further, the successful manipulation of the carboxy group in the standard synthetic scheme has led to the preparation of the first molecular combination incorporating this function. Thirdly, hydrazinolysis of phthalimido-CNU's has made possible the construction of complex drugs with both CNU and MNU (*N*-methyl-*N*-nitrosourea) moieties, thus achieving regiospecific location of two *N*-nitroso groups in molecules with four dissimilar urea NH's. All these drugs are undergoing anti-tumour evaluation, the effect of the CNU-MNU combinations on a repair enzyme of DNA metabolism being of additional significance.

N-(2-Chloroethyl)-*N*-nitrosoureas (CNU's) are used extensively in clinical cancer chemotherapy, from the established drug Carmustine (BCNU; $ClCH_2CH_2CNU$)[2] to the phosphonate ester Fotemustine [S10036; $(EtO)_2POCH(Me)CNU$] which is currently showing promise against malignant melanoma.[3] In recent years we have prepared molecular combinations, such as B.3839 (**1**) and B.3971 (**2**), of CNU's and the antimetabolite 5-fluorouracil (5-FU).[4–6] A number of these drugs have shown very good activity against colon and mammary tumours in mice.[5,6]



(**1**) (**2**) (**3**) a; R = $ClCH_2CH_2$, b; R = Me

(**4**) (**5**) (**6**)

5-FU = 5-fluorouracil-1-yl, 5-FU[3] = 5-fluorouracil-3-yl, CNU = $NHCON(NO)CH_2CH_2Cl$, MNU = NHCON(NO)Me

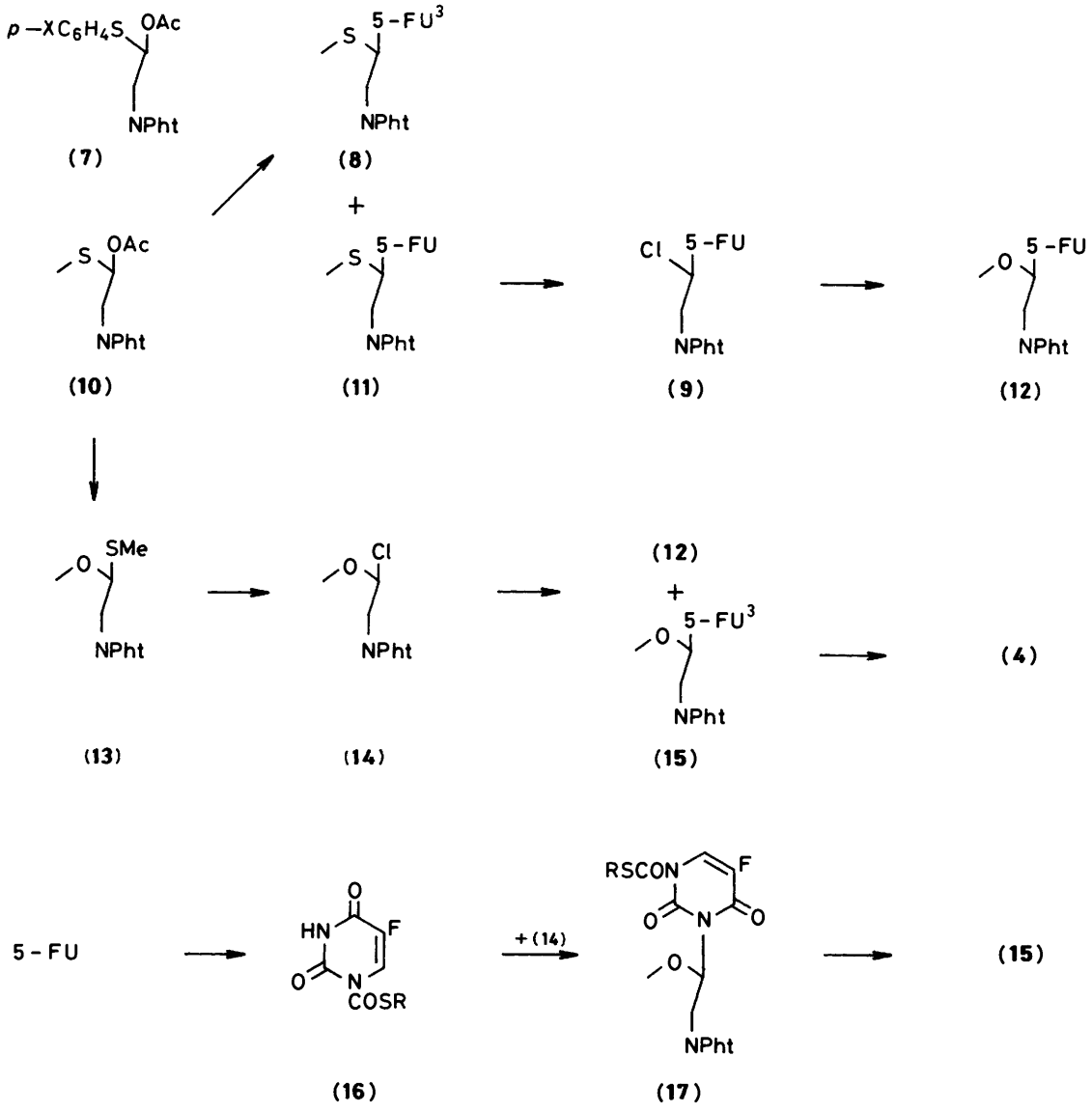
The synthesis of such seco-nucleoside CNU's from the corresponding phthalimides has recently[6] been simplified to an efficient 2-stage process: low-temperature dephthaloylation followed by condensation with the aryl *N*-nitrosocarbamate (**3a**). However, the preparation of the three compounds (**4**)–(**6**) involved some novel features either in obtaining the starting phthalimide or in the chemistry of the CNU grouping, and these are described in the present paper.

The phthalimide (**15**) precursor of compound (**4**) had proved elusive.[4] The N^1-isomer (**12**) was readily obtained (Scheme 1) from the methylthio analogue (**11**) *via* the chloride (**9**), but the N^3-phthalimide (**8**) [derived as a co-product of (**11**) from the Pummerer acetate (**10**)] was inert to sulphuryl chloride and to bromine. Aryl sulphides such as (**7**; X = Me or Cl) yielded only inseparable gummy mixtures of N^1- and N^3-substituted products from silylated 5-FU; this was disappointing since the sulphide (**7**; X = Me) was converted into the 5-unsubstituted uracil analogue of (**15**) without any difficulty.

Introduction of the methoxy group before 5-FU thus seemed necessary. *O*-Glycosides of thiosugars were readily formed from 1-*O*-acetates and alcohols, with toluene-*p*-sulphonic acid as catalyst.[7] This reaction worked smoothly with the linear acetate (**10**), yielding the *O*,*S*-acetal (**13**), and sulphuryl chloride in turn gave the chloroether (**14**). However, although silylated 5-FU reacted efficiently with this chloride, the N^1:N^3 product ratio [compounds (**12**) and (**15**)] was about 35:3 (% isolated yields) in contrast to the 45 : 20 ratio of the sulphides (**11**) and (**8**) from the acetate (**10**). Even the small fraction of N^3-isomer (**15**) was difficult to purify, but the third product (overall, 35:3:30) of the reaction, the N^1,N^3-bis(substituted)-5-FU, proved readily separable, and moreover was resolved into roughly equal proportions of diastereoisomers, by fractional crystallisation.

References to uracils bearing two sugar fragments are infrequent in the literature. Both 1,5-diribosyluracil[8] and 1,3-diribosyl-6-methyluracil[9] are of the β,β′-type with the sugars attached at the anomeric carbon in the β-configuration, and no α,β-isomers were observed. No details are available for 1,3-diribosyl-5-FU.[10] Reaction[11] of silylated 5-FU with 2-acetoxytetrahydrofuran was similar to that described above with compound (**14**). The yields of the principal products, the N^1-isomer (Ftorafur) and the N^1,N^3-bis(substituted) of unspecified configuration, varied according to the experimental conditions and only very small amounts of the N^3-isomer were formed. The bis-compound was readily and cleanly hydrolysed to Ftorafur, but our bis-compounds (corresponding to *e.g.* α,α′ and α,β′) could be recovered from hot aqueous ethanol. The stability imparted by 2-phthalimido substituents in these seco-nucleosides was noted earlier.[12]

While the reactivities of N^3-compounds cannot be measured by the UV method since (unlike N^1-) they exhibit the same shift in alkali as the free 5-FU formed by hydrolysis, an indirect estimate is possible using the bis-compounds. In the UV spectra of these the maximum intensity does not decrease in alkaline solution while that of the N^1-isomer (**12**) does, and it



Scheme 1. PhtN = Phthalimido, R = C_8H_{17}.

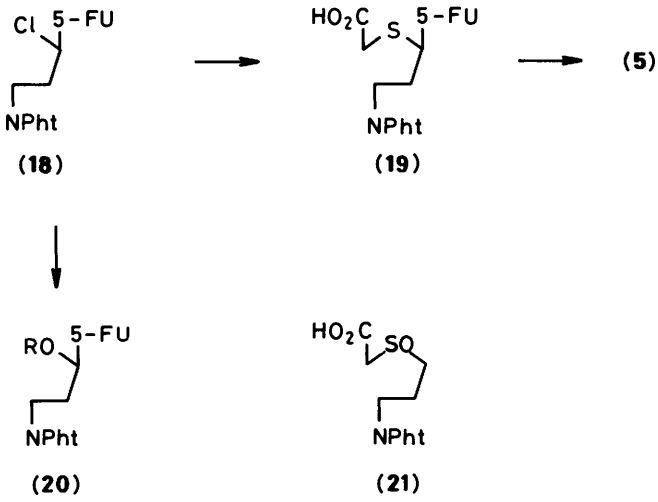
transpired that in 7 h under the standard conditions (2M HCl at 100 °C) about two-thirds of the bis-compounds are hydrolysed to the isomer (**12**), whereas (**12**) itself[12] gives < 5% free 5-FU.

To obtain the N^3-isomer (**15**), we evidently required a protected form of 5-FU. The 1-benzhydryl derivative,[13] obtained in 40% yield, has been used for making the N^3-isomer of Ftorafur. Tada[14] prepared (43% yield) N^1-benzoyl-5-FU, m.p. 170–172 °C, using benzoyl chloride and triethylamine in dioxane, while Kametani *et al.*[15] describe N^3-benzoyl-5-FU of m.p. 170–172 °C, made (85% yield) in pyridine. Using Tada's conditions[14] we obtained only starting 5-FU while the other procedure[15] in our hands yielded a derivative of m.p. 165–167 °C. Pyridine in acetonitrile was reported[16] to give the N^1-benzoyl derivatives of uracil and thymine, and in this way we obtained from 5-FU material of m.p. 174–176 °C, with UV spectrum different to that of the compound of m.p. 165–167 °C. The latter was less reactive towards alkali and is evidently the N^3-benzoyl compound as stated.[15] Attempts to silylate the N^1-benzoyl derivative (m.p. 174–176 °C) for reaction with the acetate (**10**) gave eventually only impure N^1-isomer (**11**), implying loss of the benzoyl group prior to condensation. This bears out the earlier impression[16] that unlike 3-acyluracils the 1-acyl derivatives would prove to be of limited use in synthesis.

Thiocarbamates were reported to be more effective *N*-protected forms of 5-FU, particularly with the *N*-(octylthio)carbonyl group,[17] and we have now confirmed this for the reaction with the chloroether (**14**). The readily prepared N^1-derivative (**16**) afforded, without prior silylation, the seconucleoside (**17**) as an oil. This was smoothly de-protected by isopropylamine, leaving the phthalimide group intact, and compound (**15**) was obtained in 85% yield based on the chloride (**14**). Dephthaloylation could be carried out in refluxing methanol since in N^3-derivatives the liberated amino group cannot readily attack the 5,6-double bond,[5] and reaction with the standard nitrosocarbamate (**3a**) then yielded the desired molecular combination (**4**) (B.4083). This completes a quartet of which the other 3 members have very high anti-tumour activity: B.3839 (**1**), its N^3-substituted analogue (B.3996), and the N^1-substituted analogue (B.3995) of compound (**4**).[6] These drugs release 5-FU at different rates and pharmacokinetic studies are in progress. Compound (**4**) proved significantly more water-soluble (4 mg ml^{-1} at 20 °C) than the other three (all about 1 mg ml^{-1}).

Compound (**5**) is the first combination we have prepared which carries a carboxy function. It is derived from a 5-FU-substituted isomer (6-amino-3-thiahexanoic acid) of methionine (2-amino-5-thiahexanoic acid). Tang and Eisenbrand[18] have prepared carboxy-substituted CNU's from simple amino-acids, using as reagent the azide $ClCH_2CH_2N(NO)CON_3$.[19] Derivatives of aminocyclohexanecarboxylic acids were obtained by nitrosation of the corresponding ureas.[20]

Preparation of the precursor phthalimide (**19**) from the sulphoxide (**21**) (Scheme 2) by the route often used for similar



Scheme 2.

compounds would present difficulties. The behaviour of the free acid in the strongly acylating conditions of the Pummerer rearrangement would have to be determined, but more importantly preferential migration towards the side of the sulphoxide carrying the α-carboxy would probably ensure that very little of the necessary rearrangement isomer would be obtained for conversion into the phthalimide (**19**).

We had actually prepared compound (**19**) earlier[12] from the readily available chloride (**18**). Although this reacts with alcohols to give the ethers (**20**) in good yield, it was preferable to attempt the reaction with thiols in the form of their sodio-derivatives. All experiments failed and reverting to neat mercaptoacetic acid we eventually obtained a little (29%) of the sulphide (**19**). This has now been increased to a more satisfactory 58%.

Attempts to dephthaloylate this acid as the sodium salt using hydrazine hydrate in dimethylformamide at −15 °C gave no useful result, but hydrazine (3 equiv.) without alkali was effective. After acidification, treatment of the resulting carboxy-substituted amine hydrochloride with NaOMe (2 equiv.) followed by the nitrosocarbamate (**3a**) afforded the CNU (**5**) (B.4084). This crystallised as a mono-ethanolate, the solvated structure being confirmed by the NMR spectrum. It proved readily water-soluble (12 mg ml^{-1} at 20 °C).

Compound (**6**) presented a considerable challenge, essentially that of preparing an amino-substituted CNU. Nitrosoureas are readily attacked by nucleophiles and reaction of CNU's with cyclohexylamine is a standard method of confirming the position of the nitroso group.

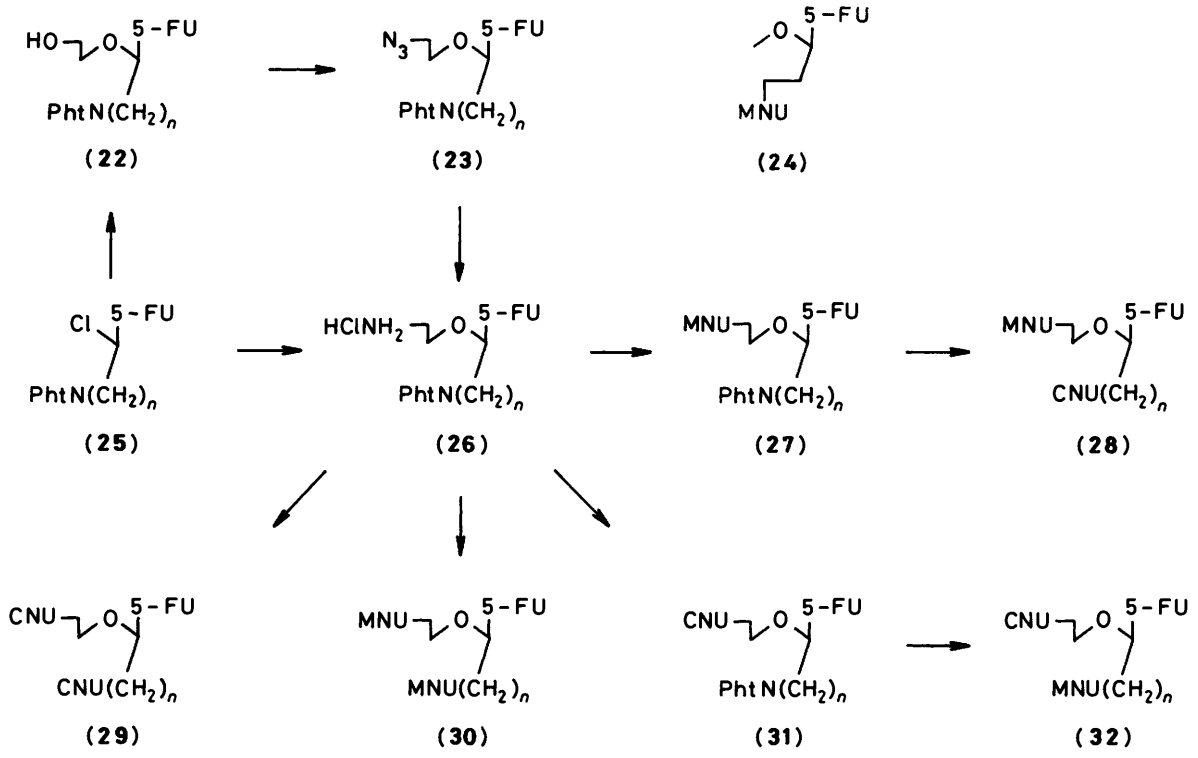
Although a variety of amine-protecting groups could be considered for removal in the presence of a CNU, we decided to test the phthaloyl since the phthalimide (**31b**) was available[21] (Scheme 3) and hydrazine at −15 °C might prove sufficiently selective. We were encouraged to find that the drug Lomustine [*N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea] could be recovered (85%) under the standard dephthaloylation conditions, and when we applied the reaction to compound (**31b**) and treated the product with the reagent (**3b**) an oil was obtained with satisfactory UV and TLC properties. This proved particularly difficult to crystallise, but compound (**32b**) was eventually obtained as a solvate from acetonitrile in a yield (38%) based on phthalimide (**31b**) comparable with those of most CNU's. The isomer (**28b**) of (**32b**) was also prepared, from the MNU (**27b**). Regiospecific location of two *N*-nitroso groups in molecules with four dissimilar urea NH's has thus proved possible.

The precursor of compounds (**27b**) and (**31b**), the hydrochloride (**26b**), can be conveniently synthesised (62% yield) directly from the chloride (**25b**) by fusion with ethanolamine hydrochloride, although it was also made from the alcohol (**22b**) *via* the mesylate and azide (**23b**).[21] It is a relatively simple phthalimido-amine salt, a class of compound not easily available otherwise. The location of the two nitrogen functions in these molecular systems has further significance, referred to below. The less reactive chloride (**25a**) requires the presence of Ag^+ for condensation with alcohols, and we had to proceed by the longer azide route in order to obtain the hydrochloride (**26a**).

The salt (**26a**) was readily converted into the MNU (**27a**), which in turn yielded compound (**28a**) [≡ (**6**)], and into the CNU (**31a**) and thence the isomer (**32a**) of (**6**). Further, dephthaloylation of the salts (**26a, b**) and reaction of each in turn with the nitrosocarbamates (**3a, b**) (2 equiv.) gave the bis(CNU's) (**29a, b**) and the bis(MNU's) (**30a, b**). Compound (**30b**) was also isolated as a solvate from acetonitrile, but the bis(CNU's) (**29**) have not so far crystallised. For biological comparison, the simple MNU (**24**) was prepared from the methoxyphthalimide (**20**; R = Me).[12]

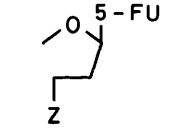
The location of the CNU grouping in 5-FU seco-nucleosides of general structure (**33**), (**34**) influences the anti-tumour activity. The figures in parenthesis in Scheme 4 (*e.g.* 4+/1+) indicate the effect of each drug (active intraperitoneal doses in the range 50–150 mg/kg body weight) on, respectively, the Bradford colon tumours MAC 13 (solid) and MAC 15A (ascitic) in mice.[6] Compound (**33a**), with CNU in the 2′ position (pentofuranose seco-nucleoside numbering), is particularly active against the solid tumour, whereas the isomer (**33b**), with CNU in the 5′ position is quite inactive. The difference in the 3′ and 5′ positions in the isomers (**34a**) and (**34b**) is less pronounced but still significant. Compounds (**33**) are hydrolysed (slowly under physiological conditions) to liberate free 5-FU and alcohol and aldehyde fragments (Scheme 4), isomer (**33b**) somewhat faster than (**33a**). In the analogous breakdown of compounds (**34**) to the aldehyde YCH_2CH_2CHO, the rates for the two isomers [both faster than (**33b**)] are similar perhaps because the group Y is somewhat more remote. Even if these hydrolysis rates may not be relevant to the observed activity against the MAC tumours, they demonstrate that CNU location is significant and may influence the biological properties of the pairs of CNU-MNU isomers (**28**) and (**32**). A number of active sugar derivatives with the CNU in various positions have been studied, and the recently developed Acomustine (NSC 609224; a hexopyranose with 3-CNU derived from acosamine) appears to have superior properties.[22] As is evident from the data for compounds (**35**), CNU's are in general more active than MNU's.

CNU's exert their cytotoxic activity by a two-stage cross-linking of DNA *via* a β-chloroethylcarbonium ion or its equivalent.[2,23] A guanine residue is rapidly O^6-alkylated, and an ethylene bridge with cytosine on the complementary strand is then formed more slowly by displacement of the β-Cl. In resistant cells the repair enzyme O^6-alkylguanine alkyltransferase (ATase) removes (suicidally) the β-chloroethyl group from guanine before cross-linking can take place. It is



Scheme 3.

(33a) : B. 3958 (4+/1+) (34a) : B. 4024 (3+/2+)
(33b) : B. 3970 (0/0) (2) ≡ (34b) : B. 3971 (2+/±)



(35a) : B. 4015 (4+/2+)
(24) ≡ (35b) : B. 4036 (2+/±)

(35) a; Z = CNU
b; Z = MNU

(33) + H_2O ⟶ XCH_2CH_2OH + 5-FU + YCH_2CHO

Scheme 4.

possible to saturate or inactivate the enzyme system in such cells by prior treatment with *e.g.* an MNU, thus leaving them vulnerable to a CNU.[24]

The transport and distribution *in vivo* of the CNU-MNU molecular combinations (**28**) and (**32**) – in addition to the location in the molecules of the nitrosourea groups as discussed above – may influence their effect on ATase and hence on tumour cells and the compounds are undergoing investigation in appropriate biological systems.

Experimental

IR spectra were run as KBr discs on a Unicam SP1000 spectrophotometer, UV spectra in methanol on a Unicam SP-800 instrument, and NMR spectra (80 MHz) in $(CD_3)_2SO$ (except otherwise stated) on a Bruker WP-80. M.p.s, uncorrected, were determined in capillaries. Light petroleum had b.p. 40–60 °C except otherwise stated. Column chromatography was on Merck silica gel 60 (35–70 mesh ASTM, Art.7733).

N-(2-*Methoxy*-2-*methylthioethyl*)*phthalimide* (**13**).—A solution of the acetate (**10**) (8.37 g, 30 mmol) and toluene-*p*-sulphonic acid hydrate (2.1 g) in methanol (300 ml) was refluxed for 2 h, cooled, and poured into water (75 ml). Methanol was evaporated and the product taken up in dichloromethane. Washing with saturated aqueous $NaHCO_3$, drying ($MgSO_4$), and evaporation gave an oil which readily crystallised. Methanol (15 ml) was added, and the *mixed O,S-acetal* (**13**) (6.50 g, 86%) filtered off; m.p. 86–88 °C (from methanol) (Found: C, 57.4; H, 5.2; N, 5.5; S, 12.5. $C_{12}H_{13}NO_3S$ requires C, 57.35; H, 5.2; N, 5.55; S, 12.75%); δ($CDCl_3$) 4.75 (t, *J* 6.9 Hz, OCHS), 4.02–3.92 (m, CH_2), 3.40 (s, OMe), and 2.07 (s, SMe).

Reaction of 5-Fluorouracil with Benzoyl Chloride.—(*a*) A solution of 5-FU (260 mg, 2 mmol) in dry pyridine (5 ml) was added over 10 min with stirring to freshly-distilled benzoyl chloride (0.7 ml, 6 mmol) in pyridine (1.2 ml), cooling in ice-water. The mixture was stirred for 1 h at room temperature, poured into water (30 ml), and extracted with benzene (4 × 15 ml). The solution was dried ($MgSO_4$) and evaporated

and the oil extracted with light petroleum, leaving a solid (370 mg, 79%), m.p. 143–146 °C, λ_{max} 253 and 277(sh) nm (248 and 295 in presence of NaOH). Recrystallisation from ethyl acetate raised the m.p. to 165–167 °C, with unchanged UV spectrum. The shifted alkaline spectrum was restored to the original on adding excess of acid. This product is N^3-benzoyl-5-FU (lit.,[15] m.p. 170–172 °C) and is slower-running on TLC ($CHCl_3$–MeOH, 19:1) than the N^1-isomer described under (*b*).

(*b*) Benzoyl chloride (0.28 ml, 2.4 mmol) was added in one portion to a stirred mixture of 5-FU (260 mg) in acetonitrile (2 ml) and pyridine (0.4 ml). Almost all the solid dissolved, but after 3 min product began to separate. After 1 h, filtration and washing with light petroleum yielded a solid (311 mg). This was triturated with water (5 ml) and N^1-benzoyl-5-FU (228 mg, 49%), m.p. 172–175 °C, was filtered off. After recrystallisation from benzene, the m.p. was 174–176 °C (lit.,[14] 170–172 °C). The UV spectrum (λ_{max} 260 and 270 nm) was shifted in presence of NaOH to that characteristic of 5-FU (λ_{max} 297 nm). On adding excess of acid it was shifted back, showing the single peak of 5-FU (λ_{max} 267 nm).

N-[2-(5-*Fluorouracil*-3-*yl*)-2-*methoxyethyl*]*phthalimide* (**15**). —A solution of the sulphide (**13**) (5.53 g, 22 mmol) in dichloromethane (300 ml) was treated with sulphuryl chloride (1.94 ml, 24 mmol), stirred for 2 h, and evaporated (finally at 0.5 mm/40 °C). To the crystalline chloroether (**14**) in dimethylformamide (30 ml) was added N^1-(octylthio)carbonyl-5-FU (**16**) [6.04 g, 20 mmol; made (88%) with m.p. 109–111 °C from 5-FU and *S*-octyl chlorothioformate as described[17]] and triethylamine (3.05 ml, 22 mmol) in dimethylformamide (30 ml) and the mixture stirred overnight at room temperature. Evaporation of solvent and addition of aqueous acetic acid (5%; 200 ml) caused separation of the oily condensation product (**17**) which was taken up in dichloromethane and dried ($MgSO_4$). After evaporation, the oil (11.96 g) in ether (200 ml) was treated dropwise, stirring briskly, with isopropylamine (2.0 ml, 21 mmol). A gum separated which had crystallised 30 min after the addition was complete. Filtration gave the *phthalimide* (**15**) [6.02 g, 90% based on (**16**)], m.p. 220–222 °C (from methanol) (Found: C, 53.9; H, 3.7; N, 12.5. $C_{15}H_{12}FN_3O_5$ requires C, 54.05; H, 3.65; N, 12.6%); λ_{max} 273 nm (304 in presence of NaOH; $E_{max}^{NaOH}/E_{max}^{MeOH}$, 1.35); single spot on TLC ($CHCl_3$–MeOH, 49:1), faster-moving than the N^1-isomer (**12**).

Reaction of Chloroether (**14**) *with Silylated* 5-*Fluorouracil*.—The chloroether prepared as above from the sulphide (**13**) (5.53 g) was dissolved in dichloromethane (140 ml) and added to the silylated product of 5-FU (2.6 g, 20 mmol). The mixture was stirred and treated, cooling in ice-salt, with tin(IV) chloride (2 ml). The resulting solution was left overnight at room temperature and poured into M HCl (80 ml). The organic layer was isolated, washed with saturated aqueous $NaHCO_3$ (50 ml), dried ($MgSO_4$), and evaporated, leaving a golden foam (7.16 g) which contained very little N^3-substituted product from its UV spectrum. Addition of methanol (35 ml) caused crystallisation, and the product (5.43 g) was filtered off and recrystallised from methanol. The mother liquor from the recrystallisation was evaporated and the residue crystallised again from methanol (10 ml), yielding mainly the N^3-isomer (**15**) (305 mg, 4.6%), m.p. 199–202 °C; λ_{max} 271 nm (303 in presence of NaOH; $E_{max}^{NaOH}/E_{max}^{MeOH}$, 0.94). This material contains N^3- and N^1-isomers in the ratio 2:1, and further recrystallisation did not increase the proportion of N^3.

The recrystallised product (4.50 g, m.p. 185–220 °C) from the crude N^1-isomer (5.43 g) was free from N^3-isomer but the UV maximum did not show the characteristic decrease in intensity in alkaline solution. The absence of N^3-isomer was confirmed by TLC, but two faster-moving spots were observed. Fractional crystallisation from acetonitrile yielded N^1-isomer (**12**) (total 2.11 g, 32%), m.p. 238–243 °C (lit.,[12] 238–240 °C); λ_{max} 268 nm (unchanged in presence of NaOH; $E_{max}^{NaOH}/E_{max}^{MeOH}$, 0.78). From the evaporated acetonitrile mother liquor were obtained by crystallisation from methanol further fractions consisting of the N^1, N^3-bis(substituted)-5-FU (total 1.67 g, 31%) responsible for the two faster-moving spots. Recrystallisation of the earlier of these final fractions from methanol yielded one *diastereoisomer* (**A**) (0.54 g), m.p. 236–239 °C (Found: C, 58.2; H, 3.9; N, 10.6. $C_{26}H_{21}FN_4O_8$ requires C, 58.2; H, 3.9; N, 10.45%); λ_{max} 273 nm (unchanged in position or intensity in presence of NaOH); ν_{max} 1 192, 999, and 970 cm^{-1}; $\delta(CDCl_3)$ 7.41 (d, *J* 5.3 Hz, pyrimidine 6-H), 7.83–7.71 (m, 2 × C_6H_4), 5.87–5.78 (m, 2 × OCHN), 4.46–4.25 (2 H) and 4.01–3.93 (2 H) (both m, 2 × CH_2), 3.29 (s, OMe), and 3.16 (s, OMe).

Recrystallisation of the later fractions from acetonitrile yielded the other *diastereoisomer* (**B**) (0.44 g), m.p. 210–211.5 °C (Found: C, 58.3; H, 3.9; N, 10.6%); λ_{max} 277 nm (unchanged in position or intensity in presence of NaOH); ν_{max} 989 cm^{-1}; $\delta(CDCl_3)$ 7.43 (d, *J* 5.4 Hz, pyrimidine 6-H), 7.9–7.6 (m, 2 × C_6H_4), 6.08–5.91 (m, 2 × OCHN), 4.82–4.53 (1 H) and 4.18–3.90 (3 H) (both m, 2 × CH_2), 3.58 (s, OMe), and 3.12 (s, OMe).

Apart from the small but characteristic differences in the UV maxima and in the methylene and methoxy proton signals of the NMR spectra, isomers (**A**) and (**B**) are also readily distinguishable on TLC. For $CHCl_3$–MeOH (49:1) using Merck aluminium plates (Art. 5554) pre-coated with silica gel 60 F_{254}, R_F values for compounds (**15**), (**12**), (**A**), and (**B**) are respectively 0.06, 0.14, 0.33, and 0.36.

When a solution of isomer (**A**) (134 mg, 0.25 mmol) in ethanol (25 ml) and water (5 ml) was heated at 80 °C for 2 h, unchanged material was quantitatively recovered. However, in 2M HCl (50% aqueous dioxane) at 100 °C after 7 h 65% of N^1-isomer (**12**) was formed (estimated from $E_{max}^{NaOH}/E_{max}^{MeOH}$; the hydrolysis of isomer (**B**) was marginally faster.

N-(2-*Chloroethyl*)-N′-[2-(5-*fluorouracil*-3-*yl*)-2-*methoxyethyl*]-N-*nitrosourea* (**4**).—The phthalimide (**15**) (6.66 g, 20 mmol) was refluxed for 1 h in methanol (160 ml) containing 0.5M NaOMe (40 ml) and hydrazine hydrate (2.0 ml, 41 mmol). After cooling, 2M HCl (32 ml) was added and the solvents evaporated. Addition of water (100 ml), refrigeration overnight, and filtration yielded phthalohydrazide (2.86 g, 88%). The filtrate (pH 4) was concentrated to 80 ml and treated with benzaldehyde (4.4 ml, 43 mmol) in methanol (80 ml). Benzalazine (3.28 g, 75%) was filtered off after 1 h, methanol evaporated, and the residual aqueous solution containing a little solid extracted with ether. The pH was adjusted from 1 to 7 with 2M NaOH (9 ml), and the solution concentrated to 40 ml. It was treated with methanol (460 ml), 0.5M NaOMe (40 ml), and the nitrosocarbamate (**3a**) (6.64 g, 20 mmol), and stirred for 2 h at 2–3 °C in the dark. Water (50 ml) was added and methanol evaporated. Aqueous acetic acid (1%; 300 ml) was added and the mixture extracted with ethyl acetate (4 × 100 ml). Drying ($MgSO_4$) and evaporation yielded a gum (10.78 g) which was dissolved in dichloromethane (70 ml) and chromatographed on a column of silica gel (320 g). Dichloromethane eluted 2,4,5-trichlorophenol, then dichloromethane–methanol (9:1) the product (4.44 g). Crystallisation from methanol (12 ml; 20 °C → −20 °C) yielded the *nitrosourea* (**4**) (2.17 g, 32%), m.p. 121–122 °C (with effervescence) (Found: C, 36.1; H, 4.0; N, 20.9. $C_{10}H_{13}ClFN_5O_5$ requires C, 35.6; H, 3.85; N, 20.7%); λ_{max} 265 nm (305 in presence of NaOH); ν_{max} 1 535 and 1 491 cm^{-1}; δ 10.95 (d, *J* 5.8 Hz, ring 1-H), 8.98 (t, *J* 6.0 Hz, CH_2NHCO), 7.81 (t, *J* 5.9 Hz, ring 6-H), 5.97 (t, *J* 6.0 Hz, OCHN), and 3.26 (s, OMe). On addition of

D_2O, the signal at δ 10.95 vanishes and at δ 7.81 becomes a doublet; after 1.5 h, the signal at δ 8.98 has also vanished.

A sample of crude amine hydrochloride, isolated following reaction of the phthalimide (**15**) (167 mg, 0.5 mmol) as above, was treated successively with 0.2M NaOMe (2.5 ml) and 2-chloroethyl isocyanate (0.047 ml, 0.55 mmol). Evaporation and addition of aqueous acetic acid (1%; 2 ml) gave the *urea* [(**4**), lacking the *N*-nitroso] (110 mg, 71%), m.p. 179 °C (decomp.) (from methanol) (Found: C, 38.7; H, 4.6; N, 18.0. $C_{10}H_{14}ClFN_4O_4$ requires C, 38.9; H, 4.55; N, 18.15%); λ_{max} 271 nm (306 in presence of NaOH); ν_{max} 1 564 cm^{-1}.

4-(5-*Fluorouracil*-1-*yl*)-6-*phthalimido*-3-*thiahexanoic Acid* (**19**).—The chloride (**18**)[12] (7.03 g, 20 mmol) dissolved in mercaptoacetic acid (13.2 ml) after 5 min at 100 °C. Heating was continued 15 min more and the solution cooled and treated with water (132 ml). An oil separated which was freed from supernatant water and rubbed with fresh water. This was repeated twice and next day the completely solid product (6.91 g) filtered off. Recrystallisation from acetic acid (25 ml) gave the acid (**19**) (3.30 g), m.p. 223–227 °C (lit.,[12] 225–227 °C), then further fractions; in all 4.73 g (58%).

N′-[3-(*Carboxymethylthio*-3-(5-*Fluorouracil*-1-*yl*)*propyl*]-N-(2-*chloroethyl*)-N-*nitrosourea* (**5**).—A solution of the phthalimide (**19**) (6.11 g, 15 mmol) in dimethylformamide (30 ml) was treated with hydrazone hydrate (2.24 ml, 45 mmol) while the internal temperature rose from −16 °C to −4 °C and left overnight in the freezer. 2M HCl (22.5 ml) was added and solvent evaporated at 0.5 mmHg/40 °C. Water (75 ml) was added and next day phthalohydrazide (1.73 g, 71%) filtered off. The filtrate was concentrated (60 ml) and treated with benzaldehyde (6.2 ml, 61 mmol) and methanol (60 ml). Benzalazine (5.86 g, 94%) was removed and the solution worked up as for the preparation of (**4**) above, using 2M NaOH (15 ml). The solution (30 ml; pH 4) was stirred with methanol (300 ml), 0.2M NaOMe (150 ml), and the nitrosocarbamate (**3a**) (4.98 g, 15 mmol) for 2 h at 2–5 °C, then ice-water (38 ml) was added. Evaporation of methanol and dilution with water (135 ml) gave an oil (6.43 g, containing most of the 2,4,5-trichlorophenol) which was taken up in dichloromethane (3 × 45 ml). The cloudy aqueous layer was treated gradually with 2M HCl (9 ml), causing separation of another oil. Extraction of this with ethyl acetate (3 × 45 ml), drying ($MgSO_4$), and evaporation yielded a foam (3.39 g) which crystallised from ethanol (17 ml) at room temperature. The *nitrosourea* (**5**) (2.76 g, 40%) had m.p. 100–102.5 °C (with effervescence) (from methyl acetate–ethanol) (Found: C, 36.5; H, 4.55; N, 15.6; S, 7.3. $C_{12}H_{15}ClFN_5O_6S$·EtOH requires C, 36.7; H, 4.6; N, 15.3; S, 7.0%); λ_{max} 270 nm (269 in presence of excess of NaOH); ν_{max} 1 529 and 1 499 cm^{-1}; δ 12.5 (br s, CO_2H), 11.74 (d, *J* 5.0 Hz, ring 3-H), 8.75 (m, CH_2NHCO), 8.13 (d, *J* 7.0 Hz, ring 6-H), 5.7–5.9 (m, SCHN), and 1.06 (t, CH_3CH_2OH; 1 mole solvent per mole compound).

Treatment of Lomustine with Hydrazine at −15 °C.—The nitrosourea (234 mg, 1 mmol) in dimethylformamide (2 ml) was treated at −15 °C with hydrazine hydrate (0.055 ml, 1.1 mmol) and left overnight in the freezer. 2M HCl (0.55 ml) was added and the solvents evaporated at 40 °C. Addition of water (5 ml) and filtration gave starting-material (200 mg, 85%), m.p. 86–87.5 °C (with effervescence) (lit.,[21] 90 °C); IR spectrum unchanged. The filtrate was concentrated (2 ml) and treated with benzaldehyde (0.27 ml, 2.6 mmol) and methanol (2 ml). Benzalazine (153 mg, 74%), m.p. 86–89 °C, was filtered off after 1 h.

N-[2-(2-*Azidoethoxy*)-2-(5-*fluorouracil*-1-*yl*)*ethyl*]*phthalimide* (**23a**).—The alcohol (**22a**)[4] (5.45 g, 15 mmol) in dry pyridine (15 ml) was stirred and treated over 3 min with methanesulphonyl chloride (1.28 ml, 16.5 mmol) while the internal temperature rose from −10 °C to 0 °C. The ice-salt bath was removed and after 1 h the solution (now steady at 25 °C) was poured into ice-cold 1.25M HCl (150 ml). The separated gum rapidly crystallised and the mesylate (6.17 g, 93%) was filtered off. It was dissolved in dimethylformamide (28 ml) and stirred with sodium azide (2.73 g, 42 mmol) for 2 h at 80 °C. After cooling, ethyl acetate (225 ml) was added and the mixture extracted with water (2 × 225 ml). The aqueous solution was extracted with ethyl acetate (225 ml), and the combined organic layers dried ($MgSO_4$) and evaporated. The residual foam (6.2 g) was triturated with acetonitrile (7 ml) and the solid product (2.67 g) filtered off. Two further fractions (total 3.97 g, 68% based on alcohol) were obtained from the mother liquor at −15 °C, and the *azide* (**23a**) had m.p. 166.5–168 °C (from acetonitrile) (Found: C, 49.3; H, 3.35; N, 21.6. $C_{16}H_{13}FN_6O_5$ requires C, 49.5; H, 3.35; N, 21.65%); ν_{max} 2 113 cm^{-1} (N_3).

Hydrochlorides (**26**).—(*a*) The azide (**23a**) (3.10 g, 8 mmol) in acetic acid (120 ml) containing 2M HCl (4.8 ml) was hydrogenated (30 lb in^{-2}, 4 h, room temperature) in the presence of palladised charcoal (10%; 0.8 g). The catalyst was filtered off through Celite and evaporation left a gum which was triturated with ethyl acetate (40 ml). The resulting solid was isolated and boiled briefly in ethanol (40 ml), filtration yielding the *salt* (**26a**) (2.80 g, 79%), m.p. 159 °C (with effervescence) (from ethanol) (Found: C, 48.3; H, 4.95; N, 12.7. $C_{16}H_{15}FN_4O_5$·HCl·EtOH requires C, 48.6; H, 4.95; N, 12.6%).

(*b*) To molten 2-hydroxyethylamine hydrochloride (14.6 g, 0.15 mol) in an oil bath at 110 °C was added the chloride (**25b**)[12] (2.64 g, 7.5 mmol) and the mixture stirred vigorously (excluding moisture), first with a glass rod (5 min) and then magnetically (25 min). The syrup was cooled slightly, diluted with hot ethanol (300 ml), and allowed to cool by leaving at room temperature for 3–4 h. The hydrochloride (**26b**) (1.91 g, 62%), m.p. 223–225 °C (decomp.) (lit.,[21] 214–216.5 °C) was filtered off.

N-(2-*Chloroethyl*)-N′-{2-[1-(5-*fluorouracil*-1-*yl*)-2-*phthalimidoethoxy*]*ethyl*}-N-*nitrosourea* (**31a**).—The salt (**26a**) (1.11 g, 2.5 mmol) suspended in dimethylformamide (2 ml) was cooled in ice-water and treated with triethylamine (0.35 ml, 2.5 mmol), then the nitrosocarbamate (**3a**) (0.83 g, 2.5 mmol). Stirring in the bath was continued for 2 h. Dilution with ice-water (90 ml) gave a gum which was treated with dichloromethane (75 ml). Part (375 mg) of the product crystallised, and the filtrate was dried ($MgSO_4$) and evaporated. Addition of ether (25 ml) caused separation of the bulk of the *nitrosourea* (**31a**) (in all 1.13 g, 91%), m.p. 153.5 °C (with effervescence) (from ethanol) (Found: C, 46.0; H, 3.6; N, 16.7. $C_{19}H_{18}ClFN_6O_7$ requires C, 45.9; H, 3.65; N, 16.9%); λ_{max} 263 nm (267 in presence of NaOH); ν_{max} 1 537 and 1 498 cm^{-1}.

Bis(*nitrosoureas*) (**32**).—A solution of the nitrosourea (**31b**)[21] (2.04 g, 4 mmol) in dimethylformamide (8 ml) at −15 °C was treated with hydrazine hydrate (0.39 ml, 8 mmol) and kept overnight at this temperature. 2M HCl (4 ml) was added and the solution evaporated (oil pump, 40 °C). After addition of water (20 ml) the pH was adjusted from 3 to 4 by a few drops of 2M NaOH. The mixture was kept at 0 °C and next day phthalohydrazide (327 mg, 50%) was filtered off. The filtrate was concentrated to 16 ml and treated with benzaldehyde (1.31 ml, 12 mmol) and methanol (16 ml), cooling under the tap. After 5 min, benzalazine (877 mg, 4.06 mmol; m.p. 79–86 °C) was filtered off and the now strongly acid filtrate brought back to pH 6 using 2M NaOH (1.6 ml).

Methanol was evaporated and the pH readjusted to 6–7 with a little more alkali (1.8 ml in all). Ether (10 + 5 ml) was added to remove traces of benzaldehyde and the mixture decanted from further, less pure, phthalohydrazide. The isolated aqueous solution of CNU-substituted amine hydrochloride was concentrated to 8 ml, diluted with methanol (80 ml), and treated with the nitrosocarbamate (**3b**) (1.13 g, 4 mmol) followed by 0.2M NaOMe (20 ml). After the usual stirring at 0–5 °C for 2 h in the dark, ice-water (10 ml) was added and methanol evaporated. The oily mixture was diluted with aqueous acetic acid (1%; 60 ml) and extracted with dichloromethane (3 × 40 ml). Drying ($MgSO_4$) and evaporation left a gum (2.9 g) which did not crystallise in contact with ether. It was taken up in dichloromethane (15 ml) and chromatographed on a column of silica gel (88 g). After rapid elution of the phenol with dichloromethane, fractions (1.65g) were obtained with dichloromethane–methanol (9:1) showing principally a single spot on TLC [benzene–methanol (4:1)]. Chromatography was repeated and elution with dichloromethane–methanol (19:1) gave material showing a single spot which did not crystallise from a wide variety of solvents. However, acetonitrile readily yielded a solvate of the *bis(nitrosourea)* (**32b**) (0.77 g, 38%), m.p. 92–96 °C (with effervescence) (Found: C, 38.0; H, 4.55; N, 24.9. $C_{14}H_{20}ClFN_8O_7$·MeCN requires C, 37.85; H, 4.55; N, 24.85%); λ_{max} 259 nm (258sh in presence of NaOH); ν_{max} 2250w (CN), 1 534 and 1 476 cm^{-1} (both vs, N–NO); δ 11.78 (d, *J* 5.0 Hz, ring 3-H), 8.7 (m, 2 × CH_2NHCO), 7.88 (d, *J* 6.8 Hz, ring 6-H), 5.75 (m, OCHN), 3.07 (s, MeN), and 2.07 (s, MeCN; 1 mole solvent per mole compound).

Similar treatment of the nitrosourea (**31a**) (1.24 g, 2.5 mmol) yielded a phenol-containing gum (1.70 g) which after chromatography gave material (572 mg) showing mainly a single spot on TLC. The *bis(nitrosourea)* (**32a**) (246 mg, 22%) crystallised very slowly from ethanol, m.p. 132.5 °C (with effervescence) (from ethanol) (Found: C, 34.9; H, 4.1; N, 24.7. $C_{13}H_{18}ClFN_8O_7$ requires C, 34.45; H, 4.0; N, 24.75%); λ_{max} 258 nm (262sh in presence of NaOH); ν_{max} 1 538 and 1 484 cm^{-1}; δ 11.70 (d, *J* 5.0 Hz, ring 3-H), 8.8 (m, 2 × CH_2NHCO), 7.87 (d, *J* 6.9 Hz, ring 6-H), 5.8 (m, OCHN), and 3.04 (s, MeN).

Phthalimidonitrosoureas (**27**).—These were prepared as described for the corresponding CNU's (**31**). The salt (**26a**) (1.11 g, 2.5 mmol) yielded 2 crystalline fractions (700 + 385 mg, total 96%) of the *nitrosourea* (**27a**), m.p. 161–161.5 °C (with effervescence) (from acetonitrile) (Found: C, 48.6; H, 3.8; N, 19.4. $C_{18}H_{17}FN_6O_7$·0.5MeCN requires C, 48.6; H, 3.95; N, 19.4%); λ_{max} 263 nm (261sh in presence of NaOH); ν_{max} 2 260w (CN), 1 535 and 1 465 cm^{-1}.

From the hydrochloride (**26b**) (1.86 g, 4.5 mmol) was obtained the *nitrosourea* (**27b**) (1.67 g, 80%), m.p. 154 °C (with effervescence) (from acetonitrile) (Found: C, 49.1; H, 4.1; N, 18.3. $C_{19}H_{19}FN_6O_7$ requires C, 49.35; H, 4.1; N, 18.2%); λ_{max} 264 nm (261sh in presence of NaOH); ν_{max} 1 536 and 1 465 cm^{-1}.

Bis(nitrosoureas) (**28**).—As described for the preparation of the isomers (**32**) from the phthalimides (**31**), the phthalimide (**27a**) (1.21 g, 2.7 mmol) gave a phenol-containing oil which on chromatography yielded a gum (625 mg) consisting mainly of product. Seed crystals were obtained by taking this up in methyl formate, diluting with ether, and cooling to −18 °C. Solvents were evaporated and the *bis(nitrosourea)* (**28a**) (176 mg, 14%) crystallised from ethanol (1–2 ml). The analysis sample had m.p. 116–116.5 °C (with effervescence) (from ethanol) (Found: C, 34.9; H, 4.05; N, 24.2. $C_{13}H_{18}ClFN_8O_7$·0.25EtOH requires C, 34.9; H, 4.2; N, 24.15%); λ_{max} 259 nm (263sh in presence of NaOH); ν_{max} 1 536 and 1 489 cm^{-1}; δ 11.71 (d, *J* 5.3 Hz, ring 3-H), 8.9 (m, 2 × CH_2NHCO), 7.86 (d, *J* 6.7 Hz, ring 6-H), 5.8 (m, OCHN), 3.05 (s, MeN), and 1.06 (t, CH_3CH_2OH).

From phthalimide (**27b**) (1.62 g, 3.5 mmol) was obtained after chromatography fractions of product (809 mg) which were crystallised as for the homologue, yielding the *bis(nitrosourea)* (**28b**) (431 mg, 26%), m.p. 123–123.5 °C (with effervescence) (from ethanol) (Found: C, 36.7; H, 4.5; N, 23.9. $C_{14}H_{20}ClFN_8O_7$·0.125EtOH requires C, 36.2; H, 4.4; N, 23.7%); λ_{max} 258 nm (261sh in presence of NaOH); ν_{max} 1 533 and 1 482 cm^{-1}; δ 11.79 (d, *J* 4.9 Hz, ring 3-H), 8.7 (m, 2 × CH_2NHCO), 7.89 (d, *J* 6.6 Hz, ring 6-H), 5.7 (m, OCHN), 3.07 (s, MeN), and 1.06 (t, CH_3CH_2OH).

Bis(nitrosoureas) (**30**).—The hydrochloride (**26a**) (0.56 g, 1.25 mmol) in dimethylformamide (5.6 ml) and water (0.56 ml) was dephthaloylated using hydrazine hydrate (0.14 ml, 2.8 mmol) as described for compound (**31b**). Half (1.4 ml) of the resulting concentrated aqueous solution of bis(hydrochloride) was diluted with methanol (14 ml) containing 0.2M NaOMe (7 ml) and allowed to react in the usual way with the nitrosocarbamate (**3b**) (397 mg, 1.4 mmol). Chromatography of the crude, phenol-containing product (548 mg) yielded a fraction (187 mg) which crystallised from ethanol to give the *bis(nitrosourea)* (**30a**) (67 mg, 27%), m.p. 126.5–127 °C (with effervescence) (from ethanol) (Found: C, 36.0; H, 4.2; N, 27.6. $C_{12}H_{17}FN_8O_7$ requires C, 35.65; H, 4.2; N, 27.7%); λ_{max} 258 nm (261sh in presence of NaOH); ν_{max} 1 540 and 1 493 cm^{-1}.

Similar reaction of the salt (**26b**) afforded a phenol-containing gum (402 mg). Extraction with ether (2.5 ml) left material (154 mg) which yielded crystalline *bis(nitrosourea)* (**30b**) (32 mg, 14%), m.p. 60–66 °C (from acetonitrile) (Found: C, 39.2; H, 4.8; N, 27.2. $C_{13}H_{19}FN_8O_7$·MeCN requires C, 39.2; H, 4.8; N, 27.45%); λ_{max} 259 nm (258sh in presence of NaOH); ν_{max} 2 230w (CN), 1 537, and 1 473 cm^{-1}; δ 11.75 (br s, ring 3-H), 8.7 (m, 2 × CH_2NHCO), 7.88 (d, *J* 6.3 Hz, ring 6-H), 5.7 (m, OCHN), 3.07 (s, 2MeN), and 2.07 (s, MeCN).

The other halves of the aqueous solution of each bis(hydrochloride) were treated similarly with the reagent (**3a**), but in neither case could the gummy products (**29**) be induced to crystallise from any solvent, even after chromatography.

N′-[3-(5-*Fluorouracil*-1-*yl*)-3-*methoxypropyl*]-N-*methyl*-N-*nitrosourea* (**24**).—Dephthaloylation of the phthalimide (**20**; R = Me)[12] at −15 °C yielded the crystalline amine hydrochloride.[25] This (0.25 g, 1 mmol) in water (2 ml), methanol (20 ml), and 0.2M NaOMe (5 ml) reacted with the nitrosocarbamate (**3b**) (284 mg, 1 mmol) to yield a product (394 mg) containing the phenol. The *nitrosourea* (**24**) (109 mg, 36%) solidified following trituration with ether and was recrystallised from ethanol. It had m.p. 150–150.5 °C (with effervescence) (Found: C, 39.3; H, 4.65; N, 23.2. $C_{10}H_{14}FN_5O_5$ requires C, 39.6; H, 4.6; N, 23.1%); λ_{max} 264 nm (260sh in presence of NaOH); ν_{max} 1 528 and 1 467 cm^{-1}; δ 11.86 (br s, ring 3-H), 8.80 (t, *J* 6.0 Hz, CH_2NHCO), 7.91 (d, *J* 6.7 Hz, ring 6-H), 5.61 (dt, *J* 6.6, 1.2 Hz, OCHN), 3.25 (s, MeO), and 3.09 (s, MeN).

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