Nucleoside Analogues. Part 2.[1] Further Molecular Combinations of (5-Substituted) Uracil and *N*-(2-Chloroethyl)-*N*-nitrosourea Residues as Anticancer Agents

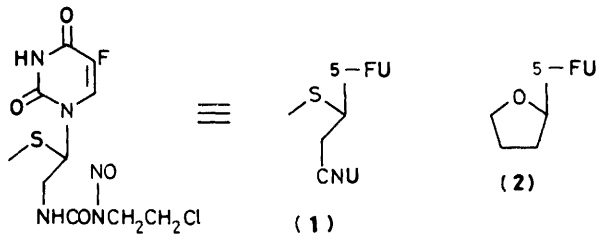
Joan E. McCormick and R. Stanley McElhinney*
Laboratories of the Medical Research Council of Ireland, Trinity College, Dublin 2, Ireland

To assess the contribution of 5-fluorouracil (5-FU) to the antitumour activity observed in B.3839 (**1**), the original molecular combination of 5-FU and *N*-(2-chloroethyl)-*N*-nitrosourea residues, the antimetabolite has been replaced by thymine and by uracil. The pyrimidine 5-substituent influenced the ratio of N^1:N^3 seco-nucleosides formed at the outset of the synthesis, and later the production of bicyclic bases by intramolecular addition across the 5,6-double bond. To provide drugs from which 5-FU would be cleaved more readily than from B.3839, first the antimetabolite has been attached at a different point (N^3 instead of N^1) although the intermediates proved more difficult to crystallise; and secondly, the methylthio group attached to the 'anomeric' carbon has been replaced by methylsulphinyl and by alkoxy. Investigation of alternative synthetic sequences confirmed that alkoxy groups had to be incorporated at an early stage, and, since they were sensitive to HBr, base-catalysed isomerisation of the bicyclic bases was necessary, best yields being obtained with the trifluoroacetyl derivatives. N^3-Substituted uracil derivatives with alkoxy groups could be prepared, but not the 5-fluoro analogues.

The compound B.3839 (**1**) was the first in which the antimetabolite 5-fluorouracil (5-FU) and the alkylating group *N*-(2-chloroethyl)-*N*-nitrosourea (CNU) were incorporated.[2] It was highly active against leukaemia P.388 in mice, giving 5/6 long-term survivors at doses of 25 and 50 mg/kg.† Replacement of 5-FU in compound (**1**) by naturally occurring bases such as thymine (Thy) and uracil (U) should give some indication of the significance of the antimetabolite moiety for anticancer activity. Replacement of the methylthio group in compound (**1**) by functions which would lead to easier cleavage[1] of the C–N bond linking the 5-FU moiety, or attachment of this moiety at a different point (N^3 instead of N^1), might be expected to enhance the activity; the linking of certain alkoxy groups to the 'anomeric' carbon would have the further advantage of providing carriers for 5-FU with a much greater resemblance to 2-deoxyribose than is conferred by the methylthio group. The successful synthesis of these variations on compound (**1**) showed some differences from the original route, and these are described in the present paper.

In order to obtain compound (**15a**), bis(trimethylsilyl)-thymine was condensed in the usual manner with the Pummerer rearrangement product (**11**)[2] (Scheme 1). The principal product was the N^1-isomer (**12a**), although the yield (31%) was lower than from the corresponding reaction with 5-FU (Table 1). However, dephthaloylation with hydrazine afforded an amine, isolated (90%) as the hydrochloride (**13a**), which showed no evidence in its u.v. spectrum of any intramolecular interaction[2] between the amino group and the 5,6-double bond. This facilitated the remainder of the synthesis, and chloroethylurea formation in methanol followed by nitrosation gave compound (**15a**) (76% yield over the 2 stages from the amine hydrochloride). As expected, the n.m.r. spectrum closely resembles that of B.3839 (**1**) of which the structure was confirmed by cyclohexylurea formation.

The uracil analogue (**15b**) was prepared similarly. The hydrochloride (**13b**) had been obtained[2] by catalytic hydrogenation of the corresponding azide (**8b**); the necessary alcohol (**10b**) was the deiodination product of the 5-iodouracil seco-nucleoside (**10**; B = 5-iodouracil-1-yl). The reason for this was that direct condensation of silylated uracil with the diacetate $MeSCH(OAc)CH_2OAc$ gave a mixture from which the N^1-isomer could not be separated. We have now investigated the reaction of silylated uracil with the phthalimidoacetate (**11**), and in this case were able to isolate both the N^1- and N^3-isomers [(**12b**) and (**6b**) respectively].



Pyrimidines are N^1-substituted throughout except where indicated by, *e.g.* 5-FU[3]

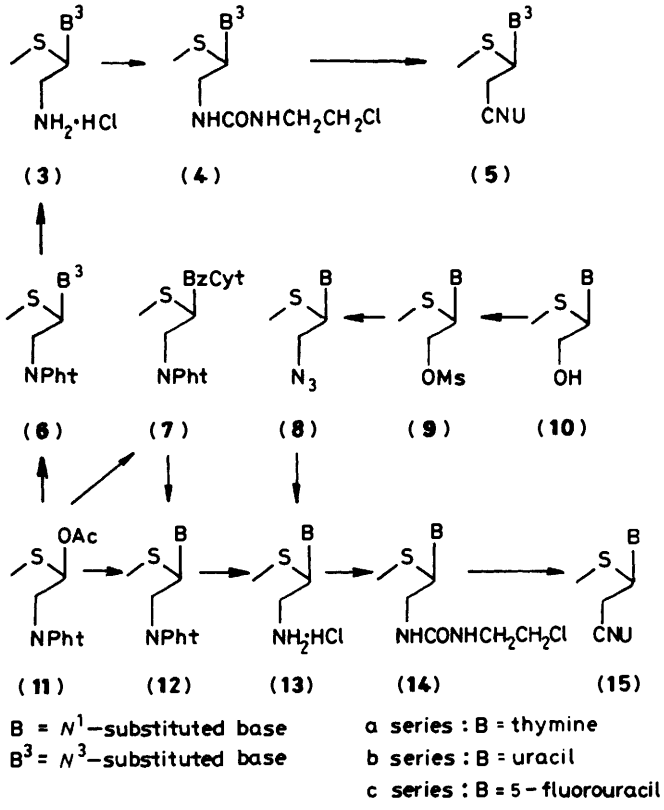
Table 1. Yields of seco-nucleosides from 5-R-uracil and acetate

R	% N^1-isomer	% N^3-isomer
I	84	—
F	58	22
CH_3	31	27
H	8.5	55

Typical yields of N^1- and N^3-isomers isolated from reaction of 5-substituted uracils and the acetate (**11**) under the standard conditions are given in Table 1. Data for the halogenated compounds were recorded previously.[2] It should be emphasised that the yields are variable, fractional crystallisation being difficult, but there is a significant trend as noted earlier.[3]

Dephthaloylation of compound (**12b**) yielded a salt identical with that (**13b**) obtained from the azide. The route from the phthalimide is preferable and became even more attractive when we found that N^4-benzoylcytosine (BzCyt) reacted with the acetate (**11**) to yield (35%) compound (**7**). This was converted (67%) into the uracil seco-nucleoside (**12b**) in boiling 80% acetic acid.[3]

† We thank Dr. J. A. Montgomery, Southern Research Institute, Birmingham, Alabama, for these results; see also J. E. McCormick, R. S. McElhinney, and S. Thompson, Proceedings of 13th International Congress of Chemotherapy, Vienna, August—September 1983, Part 262, p. 14.



Scheme 1. Pht = Phthalimido. Ms = CH_3SO_2

We then turned to the synthesis of analogues of compound (**1**) from which 5-FU could be split off[1] more readily. Before attempting replacement of methylthio by other groups, we considered the isomer (**5c**) in which the 5-FU moiety is attached to N^3, amounting to a rotation of the pyrimidine ring in structure (**1**). 3-(β-D-Ribofuranosyl)uracil[4] (isouridine) is hydrolysed to uracil (43%) in 3 h by M-HCl at 100 °C, while uridine is substantially unchanged under these conditions.[5] It may also be relevant that the bond linking the 5-FU moiety in Ftorafur (**2**) is broken in animals by enzymic hydrolysis, whereas the corresponding hydrolysis in the N^3-isomer is apparently non-enzymic.[6]

The necessary precursors for the N^3-isomers (**5**) would be the phthalimides (**6**), and since the uracil derivative (**6b**) was readily available (Table 1) it was examined first. The salt (**3b**) resulting from dephthaloylation was difficult to purify, but reaction of the liberated amine with 2-chloroethyl isocyanate (1 equiv. in methanol) gave the urea (**4b**) [41% yield based on the phthalimide (**6b**)], converted in turn into the CNU (**5b**).

Urea formation in dimethylformamide (DMF) was complicated by secondary reactions. Excess of the isocyanate (2 equiv.) in this solvent had proved advantageous[2] in the preparation of ureas containing a pyrimidine moiety linked through N^1. The base of (**3b**) afforded material with $\lambda_{max.}$ 252 nm, possibly implying the presence of a bicyclic product arising from interaction between the amino group and, in this N^3 case, the carbonyl group at position 4 of the pyrimidine. Treatment *with* alkali caused a shift to $\lambda_{max.}$ 291 nm, reverting to 261 nm on subsequent acidification. These are the normal values for N^3-substituted uracils, and the urea (**4b**) could be isolated in 21% yield based on the phthalimide (**6b**). When the isocyanate (1 equiv.) in DMF was added to the base of (**3b**), the reaction followed a similar course but in much lower yield.

Depthaloylation of the 5-FU derivative (**6c**) was best carried out using isobutylamine. Although the salt (**3c**) did not crystallise, we had earlier[2] obtained (32%) its *N*-benzoyl derivative, and this yield has now been increased to 66%. The purity of the phthalimide (**6c**) is critical for the success of the reaction of the amine with 2-chloroethyl isocyanate. Some batches contaminated with small amounts of unidentified compounds as well as traces of N^1-isomer (**12c**) gave only oily products which could not be purified. However, the urea (**4c**) was eventually obtained and converted into the CNU (**5c**).

Of analogues of compounds (**1**) in which the methylthio group is replaced by other groups, the first candidate for biological testing was the corresponding sulphoxide (**29**) (Scheme 2) since the group RSO is in general more reactive[1] than RS. We required more of the urea (**24a**) for *S*-oxidation experiments, and investigated some alternatives to the original[2] synthesis. This involved hydrazinolysis of the phthalimide (**21a**) at 100 °C, conditions which led to extensive isomerisation of the anticipated amine to the bicyclic compound (**18a**). Reaction of this with 2-chloroethyl isocyanate gave a urea (**17a**) which had to be converted into the monocycle (**24a**).

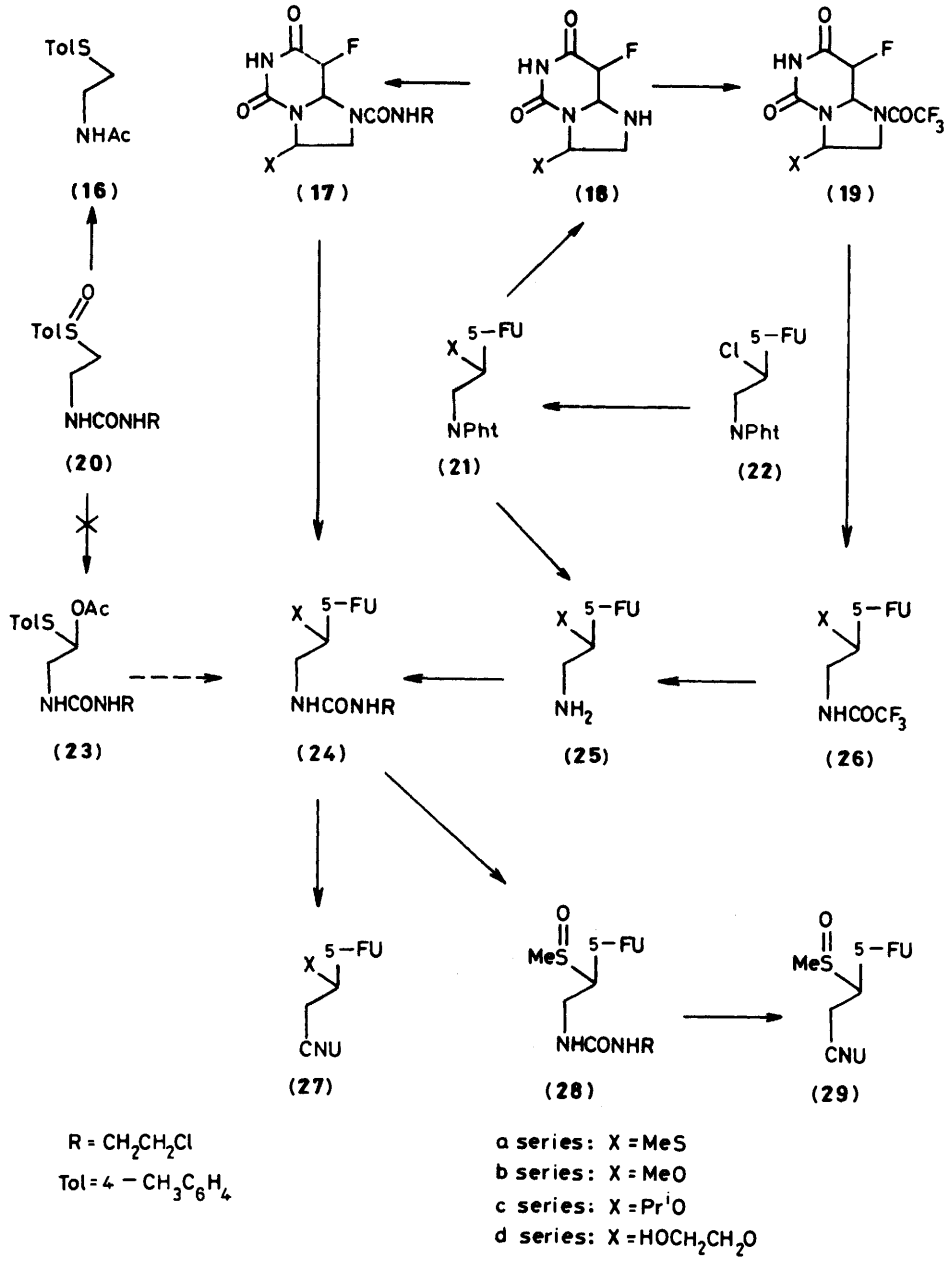
We prepared the ureidosulphoxide (**20**) in order to determine whether or not Pummerer rearrangement to (**23**) followed by condensation with silylated 5-FU would give the urea (**24**; X = TolS), thus avoiding the synthesis of bicyclic compounds. Even though aryl sulphoxides such as (**20**) can in principle give only one rearrangement product, in contrast to *e.g.* $MeS(O)CH_2CH_2NPht$,[2] the reaction with acetic anhydride was not simple and only the reduced product (**16**) could be isolated. It is recalled that no crystalline Pummerer product was obtained from the amide (**20**; CF_3 for NHR).[1]

Next the preparation of the hydrochloride of the amine (**25a**) was attempted. In contrast to our experience[2] with the uracil derivative (**9b**), the methanesulphonate (**9c**)[7] could not be converted into the corresponding azide, thus blocking one attractive route. However, vigorous acid hydrolysis of the phthalimide (**21a**) yielded the hydrochloride of (**25a**) (25—30%, not improved by varying the reaction conditions). When this salt was treated with sodium methoxide the liberated base was apparently stable, showing no change in the u.v. spectrum after 20 h, and forming the monocyclic urea (**24a**) (67%) with no evidence for the presence of the bicyclic isomer.

The original synthesis of compound (**24a**) is thus preferable. Oxidation with *m*-chloroperbenzoic acid yielded a mixture of sulphoxides (**28**) from which one was isolated. Nitrosation in formic acid afforded the CNU (**29**).

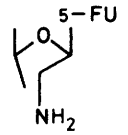
Synthesis of alkoxy CNUs (**27b—d**) seemed a more arduous task. The halogen in the pyrimidine 5-position would presumably ensure isomerisation to the bicyclic bases (**18**) during dephthaloylation of (**21**), and treatment of the alkoxy compounds (**21b** and **c**) with HBr in acetic acid caused considerable cleavage of 5-FU, confirming that this reagent, which had successfully yielded[2] the (methylthio)urea (**24a**) from its bicyclic isomer (**17a**), must now be avoided. Furthermore, attempts to replace MeS by RO *via* chlorinolysis[1] at any stage later than the phthalimide (**21**) in the synthesis were unsuccessful, since reaction of the ureas (**17a**), (**24a**), and (**27a**) with sulphuryl chloride gave intractable mixtures.

Of the alkoxyphthalimides (**21b—d**), only the methyl derivative (**21b**) had been prepared earlier,[1] from the chloride (**22**) and methanol in the presence of silver carbonate at room temperature. We now found that these reactions proceeded much more efficiently in boiling solvent, or at 80 °C for ethylene glycol. (Sodium thiolates did not react cleanly under any of the conditions tried.) Hydrazinolysis yielded the bicyclic amines (**18**), conveniently isolated as hydrochlorides. The key derivatives of these alkoxy compounds were the trifluoroacetamides (**19**) [an *O*,*N*-bis(trifluoroacetate) from the salt (**18d**)]. Isomerisation to the monocycle (**26**) was smoothly catalysed by sodium methoxide as before,[2] and the protecting group was

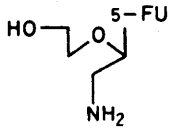


Scheme 2.

removed by sodium hydroxide in aqueous dioxane. It is perhaps worth noting that the base (**25c**) (2′-amino-2′,3′,5′-trideoxy-5-fluoro-2′,3′-secouridine) has the same carbon skeleton as 5-fluorouridine, while (**25d**) (2′-amino-2′,3′-dideoxy-5-fluoro-3′-nor-2′,3′-secouridine) has the 2-hydroxyethoxy fragment



(**25c**)



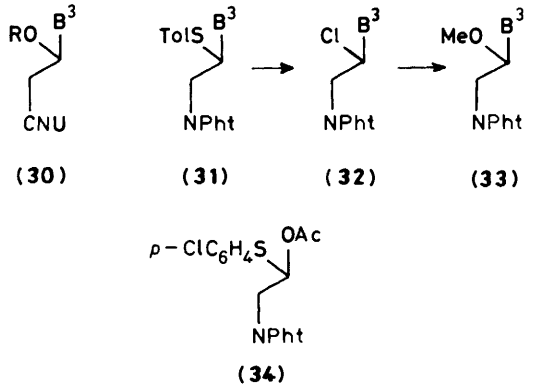
(**25d**)

characteristic of the powerful antiviral agent acyclovir.[8] Successive reaction with 2-chloroethyl isocyanate and nitrous acid yielded the required CNUs (**27**). Attempts to bring about reaction of isocyanate with the trifluoroacetamides (**26**) before *N*-deacylation were unsuccessful.

Milder dephthaloylation conditions[9] did not prove effective with compounds (**21**), and elimination of phthalohydrazide using HCl was greatly preferable to direct treatment of the reaction mixture with trifluoroacetic anhydride. Although the bicyclic urea (**17c**) was formed in good yield from the hydrochloride of (**18c**), it could be isomerised in only 15% yield using sodium methoxide.

Combination of the principles leading from the CNU (**1**) to (**5c**) and to (**27b—d**) would give structure (**30**) (Scheme 3), but such compounds have proved elusive. Although the methylthio group was readily displaced from the phthalimide (**12c**) by sulphuryl chloride to give the chloride (**22**),[1] the N^3-isomer (**6c**) was inert both to this reagent and to bromine.

We accordingly investigated the arylthio analogues (**31**). The uracil derivative (**31b**) was readily prepared, and chlorinolysis followed by treatment with silver carbonate in methanol yielded



Scheme 3. Abbreviations as in Scheme 1

(**32b**) and (**33b**) respectively. However, the yield of the 5-FU derivative (**31c**) was considerably lower than that of (**31b**) and it failed to crystallise.[1] Reaction of the *p*-chlorophenyl sulphide (**34**) with silylated 5-FU also gave a gummy mixture of N^1- and N^3-isomers in which the former predominated.

Experimental

U.v. spectra were run in methanol on a Unicam SP-800 spectrophotometer, and n.m.r. spectra in $(CD_3)_2SO$ on a Varian XL-200 instrument. M.p.s. were determined in capillaries and are uncorrected.

Phthalimides (*Table* 2).—*Methylthio derivatives.* These were prepared by condensation of the acetate (**11**) in methylene dichloride with the appropriate base, as the bistrimethylsilyl derivative, in presence of tin(IV) chloride as described earlier.[3] Hexamethyldisilazane (1.5 ml $mmol^{-1}$) was used for the silylation of N^4-acetylcytosine, while thymine required larger amounts of hexamethyldisilazane and ammonium sulphate (3 ml and 6 mg, respectively) and at least 6 h reflux for efficient silylation.

The crude products (foams) were isolated after the standard work-up procedure using saturated aqueous $NaHCO_3$, but the reaction mixture from N^4-benzoylcytosine was poured into M-HCl (4 ml $mmol^{-1}$). In this case a small amount of solid (m.p. > 300 °C) was removed before the organic layer was separated and washed with water. The u.v. spectrum of the crude product from thymine indicated the presence of much N^1- as well as N^3-substituted pyrimidine whereas that from uracil was shown to be mainly N^3-substituted.

In general, crystalline materials separated from solutions of crude products in hot benzene (1 ml $mmol^{-1}$; 2.5 ml in the case of the N^4-*acetylcytosine derivative*) but the N^4-*benzoylcytosine derivative* (**7**) crystallised from methanol (7.5 ml $mmol^{-1}$). The *thymin-1-yl derivative* (**12a**) crystallised preferentially (up to 31% yield) but in one large-scale (40 mmol) preparation the benzene mother liquors from filtration of this isomer (25%) subsequently deposited material which on recrystallisation afforded the *thymin-3-yl isomer* (**6a**) (27%). Similarly, in the case of the *uracil derivatives*, crystallisation of the predominant N^3-isomer (**6b**) was preceded by separation of a small amount of the N^1-isomer (**12b**).

Alkoxy derivatives. The *uracil derivative* (**33b**) was prepared from the chloride (**32b**) (see below) by the method described[1] for the methoxy derivative (**21b**).

The other ethers were prepared, similarly, from the chloride (**22**) except that less alcohol (preheated; 16—25 ml $mmol^{-1}$) was used and the reaction was carried out for 2 h under reflux [or at 80 °C in the case of the *2-hydroxyethoxy derivative* (**21d**)]. The hot reaction mixture was filtered twice, the second time through Celite. Low boiling alcohols were evaporated and the product isolated by trituration of the crystalline residue with a little of the same solvent. In the case of the ether (**21d**) the solution was concentrated at below 70 °C (to 2 ml $mmol^{-1}$). Addition of water (6 volumes) and refrigeration yielded solid material.

Dephthaloylation Procedures.—Amines were obtained from the corresponding phthalimides using one of the following reagents. It was important to evaporate last traces of water from solutions by co-distillation with methanol. Some crystalline hydrochlorides (Table 3) were isolated.

(a) *Hydrazine.* The phthalimide (10 mmol) in 2-methoxyethanol (30 ml) was heated (1 h; 100 °C) [1.5 h in the case of the uracil derivative (**6b**)] with hydrazine hydrate (0.58 ml, 12 mmol). The evaporated reaction mixture was acidified (dil. HCl) and insoluble material was removed by filtration. Evaporation of the filtrate left the crude hydrochloride as a foam which was treated with ethanol.

The N^1-*isomers* (**13a** and **b**) crystallised readily (from solutions 2 ml $mmol^{-1}$), the *uracil-3-yl derivative* (**3b**) much more slowly. The hydrochlorides from the 5-fluorouracil-1-yl compounds (**21b—d**) were used directly for further reactions. They were salts of mainly the bicyclic amines (**18**) but the u.v. spectra indicated[2] the presence of some monocyclic form (**25**). The salt of compound (**18d**) was nicely crystalline, that of (**18c**) was hygroscopic, and that of (**18b**) did not crystallise.

When, in the dephthaloylation of the thymine derivative (**12a**), acetic acid replaced HCl in the work-up, a crystalline *acetate* was isolated after trituration with ethanol. It had m.p. 161—163.5 °C (from acetonitrile) (Found: C, 43.6; H, 6.3; N, 15.4; S, 11.8. $C_8H_{13}N_3O_2S$·AcOH requires C, 43.6; H, 6.2; N, 15.3; S, 11.6%).

(b) *Isobutylamine.* The 5-fluorouracil-3-yl compound (**6c**) (1 mmol) was refluxed for 6 h in methanol (10 ml) containing isobutylamine (1.4 ml). Water (3 ml) was added to the evaporated reaction mixture. Insoluble material was removed by filtration and the filtrate was evaporated to yield the crude amine corresponding to the salt (**3c**) as a foam, which was used directly for further reactions. The efficiency of dephthaloylation was monitored by preparation of the *N*-benzoate,[2] the yield of which was now raised to 66%.

(c) *Hydrochloric acid.* A solution of the 5-fluorouracil-1-yl compound (**12c**) (1.5 mmol) in acetic acid (10 ml) was refluxed for 6 h with conc. HCl (10 ml) and the solution was evaporated. Water (2 ml) was added to the semicrystalline residue and insoluble material was filtered off. Evaporation of the filtrate and two recrystallisations from ethanol yielded the *salt* (**13c**).

Trifluoroacetamides (*Table* 4).—*Bicyclic derivatives* (**19**). A stirred slurry of the appropriate amine hydrochloride obtained directly from dephthaloylation (1 mmol) in ethyl acetate (16 ml) was cooled while trifluoroacetic anhydride (13—16 mmol; 5 mmol sometimes gave lower yields) was added dropwise. The mixture was stirred at room temperature until complete solution occurred (usually in less than 15 min but the 2-hydroxyethoxy derivative required 1 h). Water (3—5 ml), added to the evaporated reaction mixture, caused separation of the *amides* (**19**) as gums which gradually crystallised. The u.v. spectrum indicated no contamination in any case by the monocyclic amides (**26**).

O-Acylation occurred simultaneously in the case of the 2-hydroxyethoxy derivative.

Monocyclic derivatives. (**26**). The corresponding bicyclic derivative (**19**) was refluxed for 1 h with 0.1M-NaOMe (1 equiv.) [2 equiv. for the *O*-trifluoroacetate of (**19d**)]. After neutralisation with 0.1M-HCl, methanol was evaporated off. This caused separation of the *isopropoxy derivative* (**26c**) but

Table 2. Phthalimides

Compound	Yield (%)	Crystallisation solvent	M.p. (°C)	$\lambda_{max.}$[a] (nm)	Formula	Analysis (%)[b] C	H	N	S
(12a)	31	MeCN	204—206.5	270 (271)	$C_{16}H_{15}N_3O_4S$	55.5 (55.65)	4.3 (4.3)	12.3 (12.2)	9.4 (9.3)
(6a)	27	MeOH	176—178	267 (297)	$C_{16}H_{15}N_3O_4S$	56.2	4.4	12.2	9.3
(12b)	8.5[c]	MeOH	203—205	262 (262)	$C_{15}H_{13}N_3O_4S$	54.8 (54.4)	4.05 (3.9)	12.7 (12.7)	9.6 (9.7)
(6b)	55	MeOH	174—176	262 (293)	$C_{15}H_{13}N_3O_4S$	54.6	3.95	12.6	9.7
(12)[d]	67	MeOH	209.5—214.5	301 (278)	$C_{17}H_{16}N_4O_4S$	54.3 (54.8)	4.4 (4.3)	14.8 (15.1)	8.9 (8.6)
(7)	35	EtOH	271—273 (decomp.)	302 (321)	$C_{22}H_{18}N_4O_4S$	60.5 (60.8)	4.1 (4.1)	12.7 (12.9)	7.0 (7.4)
(21b)	86	MeOH	238—240[e]	265 (266)					
(21c)	84	Pr^{i}OH	212—215	267 (268)	$C_{17}H_{16}FN_3O_5$	55.9 (56.5)	4.3 (4.4)	11.5 (11.6)	
(21d)	84	MeOH	198.5—201.5	267 (267)	$C_{16}H_{14}FN_3O_6$	52.6 (52.9)	4.0 (3.9)	11.5 (11.6)	
(33b)	67	MeOH	221.5—222.5	263 (293)	$C_{15}H_{13}N_3O_5$	56.8 (57.15)	4.1 (4.2)	13.1 (13.3)	

[a] In parentheses: those in the presence of NaOH. [b] Required values in parentheses. [c] Also obtained (67%) by refluxing (2 h) the N^4-benzoylcytosine derivative (**7**) in 80% AcOH (30 ml mmol^{-1}), followed by evaporation and trituration of the residue with MeOH. [d] B = N^4-Acetylcytosine. [e] Lit.,[1] 238—240 °C.

Table 3. Hydrochlorides

Compound	Reagent	Yield (%)	M.p. (°C)	$\lambda_{max.}$[a] (nm)	Formula	Analysis (%)[b] C	H	N	S
(13a)	H_2NNH_2	90	125[c]	267 (271)	$C_8H_{14}ClN_3O_2S$·EtOH	39.9 (40.3)	6.8 (6.75)	13.9 (14.1)	10.9 (10.75)
(13b)	H_2NNH_2	75	217—219[d]	261 (266)					
(3b)	H_2NNH_2	51	152.5—156.5	261 (291)	$C_7H_{12}ClN_3O_2S$·$\frac{1}{2}H_2O$	34.7 (34.1)	5.25 (5.3)	16.3 (17.0)	
(13c)	HCl	29	228—229[e]	270 (274)	$C_7H_{11}ClFN_3O_2S$	32.7 (32.9)	4.25 (4.3)	16.3 (16.4)	12.5 (12.5)

[a] In parentheses: those in the presence of NaOH. [b] Required values in parentheses. [c] With effervescence. [d] Lit.,[2] 226—227 °C. [e] With decomp.

the *methoxy* (**26b**) and *2-hydroxyethoxy* (**26d**) *derivatives* required extraction by ethyl acetate and crystallisation.

(*2-Chloroethyl*)*ureas* (*Table* 5.)—Considerable experimental detail is given for these compounds and the nitrosoureas because of the difficulty experienced in crystallising many of them.

(*a*) This method gave[2] the bicyclic urea (**17a**) from the free base. In the present work, the appropriate amine was obtained from its hydrochloride (1 mmol) by treatment with 0.2M-NaOMe followed by evaporation of methanol, and was then mixed with DMF (1 ml). The resultant slurry, chilled in ice–water, was treated with 2-chloroethyl isocyanate [2 mmol; 1.1 mmol for the uracil-1-yl derivative (**14b**)]. After 10 min, addition of M-HCl or 5% AcOH (6 ml) precipitated a gum which in general gradually dissolved during refrigeration overnight.

The 5-fluorouracil-1-yl derivative (**24a**) subsequently crystallised from the reaction mixture. The uracil-1-yl derivative (**14b**) remained in solution but was isolated (98%) as a pure (t.l.c.) gum after extraction with methylene dichloride and evaporation of solvents. The *thymine derivative* (**14a**) usually crystallised from the reaction mixture, but method (*b*), below, was found to be more reliable for the preparation of these compounds.

The gummy product which was obtained from the uracil-3-yl hydrochloride (**3b**) (1 mmol) gradually solidified to give material (304 mg), m.p. 112—118 °C, having an anomalous u.v. spectrum ($\lambda_{max.}$ 252 nm). A solution of the solid in 0.2M-NaOMe (10 ml) was acidified with 0.4M-HCl after 15 min and methanol was evaporated off. Extraction of the remaining aqueous solution with methylene dichloride (20 ml) caused separation of the crystalline *uracil-3-yl derivative* (**4b**) (122 mg, 41%) which was, however, obtained (80%) directly by method (*b*) below.

(*b*) The corresponding amine hydrochloride (1 mmol) was dissolved in 0.2M-NaOMe (5 ml). [In the case of the thymine derivative (**13a**) the solution was concentrated to a volume of 2 ml]. For the urea (**4c**) the starting material was the free base which was dissolved in methanol. 2-Chloroethyl isocyanate (1—1.1 mmol) was then added.

The thymine derivative (**14a**) crystallised on addition of a seed crystal and was filtered after dilution with ether (an equal vol.). Though probably contaminated by traces of sodium chloride, the material (358 mg) was suitable for direct conversion into the corresponding nitrosourea (**15a**). The reaction mixture in the other cases was evaporated after 15 min. The *isopropoxy derivative* (**17c**) and the uracil-3-yl derivative (**4b**) crystallised on addition of 5% AcOH and water respectively. The *5-fluorouracil-3-yl derivative* (**4c**) separated

Table 4. Trifluoroacetamides

Compound	Yield (%)	Crystallisation solvent	M.p. (°C)	$\lambda_{max.}$[a] (nm)	Formula	Analysis (%)[b] C	H	N
(19b)	38[c]	EtOAc–LP[d]	175.5—177	229 (236)	$C_9H_9F_4N_3O_4$	36.2 (36.1)	3.1 (3.0)	13.9 (14.0)
(19c)	49[c]	EtOPt–LP	87—89[e]	228 (236)	$C_{11}H_{13}F_4N_3O_4{\cdot}H_2O$	38.5 (38.3)	4.2 (4.3)	12.1 (12.2)
(19d)[f]	42[c]	EtOAc–LP	146—147	228 (235)	$C_{12}H_{10}F_7N_3O_6$	33.7 (33.9)	2.25 (2.4)	10.0 (9.9)
(26b)	70	EtOAc–LP	161.5—163	266 (266)	$C_9H_9F_4N_3O_4$	36.3 (36.1)	3.1 (3.0)	13.9 (14.0)
(26c)	76	EtOAc–LP	176.5—177.5	266 (266)	$C_{11}H_{13}F_4N_3O_4$	40.2 (40.4)	3.85 (4.0)	12.5 (12.8)
(26d)	43	EtOAc	185—186	266 (266)	$C_{10}H_{11}F_4N_3O_5$	36.4 (36.5)	3.4 (3.3)	12.7 (12.8)

[a] In parentheses: those in the presence of NaOH. [b] Required values in parentheses. [c] Overall from the phthalimide (**21**). [d] LP = Light petroleum, b.p. 40—60 °C. [e] With effervescence. [f] *O*-Trifluoroacetate.

Table 5. (2-Chloroethyl)ureas

Compound	Method[a]	Yield (%)	Crystallisation solvent	M.p. (°C)	$\lambda_{max.}$[b] (nm)	Formula	Analysis (%)[c] C	H	N	S
(24a)	(*a*)	67	MeOH	121—124[d]	273 (272)					
(14a)	(*a*)	72[e]	MeOH	92—94.5[f]	270 (271)	$C_{11}H_{17}ClN_4O_3S{\cdot}MeOH$	40.7 (40.85)	6.1 (6.0)	15.9 (15.9)	9.2 (9.1)
(17c)	(*b*)	70	MeOH–H_2O	115—117	228 (238)	$C_{12}H_{18}ClFN_4O_4{\cdot}H_2O$	40.6 (40.6)	5.9 (5.6)	15.8 (15.8)	
(4b)	(*b*)	80[g]	MeCN	154.5—155.5[f]	261 (292)	$C_{10}H_{15}ClN_4O_3S$	38.9 (39.2)	5.0 (4.9)	18.5 (18.3)	
(4c)	(*b*)	19	MeCN	147—148	268 (302)	$C_{10}H_{14}ClFN_4O_3S$	36.8 (37.0)	4.25 (4.3)	17.1 (17.3)	
(24b)	(*c*)	69	MeOH	101—105	268 (266)	$C_{10}H_{14}ClFN_4O_4{\cdot}H_2O$	37.1 (36.8)	4.9 (4.9)	16.5 (17.5)	
(24c)	(*c*)	44	MeOH	150.5—151.5	268 (266)	$C_{12}H_{18}ClFN_4O_4$	43.1 (42.8)	5.4 (5.35)	16.7 (16.6)	
(24d)	(*c*)	33	MeCN	147.5—149	268 (267)	$C_{11}H_{16}ClFN_4O_5$	39.0 (39.0)	4.9 (4.7)	16.4 (16.5)	

[a] Defined in the text. [b] In parentheses: those in the presence of NaOH. [c] Required values in parentheses. [d] Lit.,[2] 121—123 °C (Formula: $C_{10}H_{14}ClFN_4O_3S{\cdot}MeOH$). [e] Method (*b*) gave a product converted (in 76% overall yield) into the nitrosourea (**15a**). [f] With effervescence. [g] Method (*a*) gave a product (λ_{max} 252 nm) converted into the urea [41% based on (**3b**)] by treatment with 0.2M-NaOMe and subsequent acidification.

very slowly from a concentrated solution (0.5 ml $mmol^{-1}$) in acetonitrile.

(*c*) The appropriate trifluoroacetamide (**26**) (1 mmol) was hydrolysed during 1 h at room temperature in a mixture of dioxane (30 ml) and 0.1M-NaOH (30 ml). The chilled solution was then neutralised with 0.1M-HCl and treated with 2-chloroethyl isocyanate (2 mmol). After 1.5 h at room temperature the mixture was concentrated almost to dryness and water (10 ml) was added. Crystals of the *methoxy derivative* (**24b**) separated at this stage and a further amount of product was extracted from the mother liquor by methylene dichloride and was recrystallised from methanol. The *isopropoxy derivative* (**24c**) separated as a gum which was also extracted by methylene dichloride and crystallised from methanol. In the preparation of the 2-*hydroxyethoxy derivative* (**24d**), the small amount of extraneous (t.l.c.) crystals which separated initially was discarded. The authentic material was extracted by ethyl acetate as a gum which was crystallised, under mild conditions, from acetonitrile.

The isopropoxy derivative (**24c**) was also prepared (20—48% overall yield) from the bicyclic precursor (**19c**) without isolation of the intermediate amide (**26c**). Following isomerisation with 0.1M-NaOMe (for 1.5 h) methanol was evaporated off and the residue subjected to the conditions in method (*c*).

N-(2-*Chloroethyl*)-N-*nitrosoureas* (*Table* 6).—These were formed by one of the following two methods and purified (pale yellow crystals) under very mild conditions. Relevant signals in the n.m.r. spectra are given at the end of the Experimental section.

(a) Sodium nitrite (10 mmol) was added in approximately equal portions every 10 min during 3 h at 1—3 °C to a vigorously stirred mixture of the appropriate urea (1 mmol) in chloroform (10 ml) and 2M-HCl (15 ml) [ethyl acetate (10 ml) and M-HCl (20 ml) were used for the urea (**24d**)]. The mixture was stirred and cooled for a further 1 h. Any solid present was filtered off and further product (usually a foam) recovered, if necessary, from the organic layer which in the case of ethyl acetate was shaken with saturated aqueous $NaHCO_3$. The *thymine derivative* (**15a**) separated in good yield as a crystalline solid. By contrast, the *uracil-1-yl derivative* (**15b**) and the 2-*hydroxyethoxy derivative* (**27d**) were isolated only as foams which slowly crystallised from the solvents indicated in Table 6. The *isopropoxy derivative* (**27c**) was obtained as a mixture of solid and gum which were combined and purified similarly.

(*b*) A stirred solution of the corresponding urea (1 mmol) in formic acid (3 ml) was treated at 1—3 °C with sodium nitrite (3 mmol), added in small portions regularly during 30 min. The solution was kept (4 h) at the same temperature. Addition of water (3 ml) caused no separation of product and the solution,

Table 6. *N*-(2-Chloroethyl)-*N*-nitrosoureas

Compound	Method[a]	Yield (%)	Crystallisation solvent	M.p.[b] (°C)	$\lambda_{max.}$[c] (nm)	Formula	Analysis (%)[d] C	H	N
(15a)	(*a*)	72	EtOAc	147—147.5	266 (269)	$C_{11}H_{16}ClN_5O_4S$[e]	37.7 (37.8)	4.7 (4.6)	19.8 (20.0)
(15b)	(*a*)	41[f]	EtOH	128—129	261 (264)	$C_{10}H_{14}ClN_5O_4S$	35.4 (35.8)	4.1 (4.2)	20.2 (20.9)
(27d)	(*a*)[g]	35	EtOAc–LP[h]	103—105.5	262 (263sh)	$C_{11}H_{15}ClFN_5O_6$	35.8 (35.9)	4.2 (4.1)	18.9 (19.0)
(27c)	(*a*)	59	EtOH	111—112.5	263 (266)	$C_{12}H_{17}ClFN_5O_5$	39.3 (39.4)	4.9 (4.65)	19.0 (19.15)
(27b)	(*b*)	17.5	EtOH	139.5—140	264 (264sh)	$C_{10}H_{13}ClFN_5O_5$	35.4 (35.6)	3.85 (3.85)	20.3 (20.7)
(5b)	(*b*)	19	EtOH	136	258 (291)	$C_{10}H_{14}ClN_5O_4S$	35.6 (35.8)	4.3 (4.2)	20.4 (20.9)
(5c)	(*b*)	18	EtOH	144.5—145	263 (303)	$C_{10}H_{13}ClFN_5O_4S$	33.4 (33.95)	3.7 (3.7)	19.4 (19.8)
(29)	(*b*)	30	EtOH	153—154	269 (272)	$C_{10}H_{13}ClFN_5O_5S$	32.2 (32.5)	3.45 (3.5)	18.4 (18.9)

[a] Defined in the text. [b] With effervescence. [c] In parentheses: those in the presence of NaOH. [d] Required values in parentheses. [e] Found: S, 8.9. Required: S, 9.2%. [f] Overall from the amine hydrochloride *via* the crude urea. [g] EtOAc and M-HCl, respectively, used instead of $CHCl_3$ and 2M-HCl. [h] LP = Light petroleum, b.p. 40—60 °C.

after 30 min, was concentrated almost to dryness under mild conditions. Water (3 ml) was again added and the precipitated gum was extracted by ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to yield the product as a foam which was crystallised by the solvent specified in Table 6.

N-(2-*Chloroethyl*)-N′-[2-(p-*tolylsulphinyl*)*ethyl*]*urea* (**20**) (*with C. N. Lucey*).—A solution of 2-phthalimidoethyl *p*-tolyl sulphoxide (1.57 g, 5 mmol) in 2-methoxyethanol (16 ml) containing hydrazine hydrate (0.29 ml, 6 mmol) was heated (1 h; 100 °C) and evaporated. M-HCl (5 ml) was added to the residue and insoluble material removed by filtration. The filtrate was evaporated and the residual oil (1.33 g), in chloroform (40 ml), treated with triethylamine (1 ml) and then, dropwise, 2-chloroethyl isocyanate (0.86 ml, 10 mmol). Next day, the solution was washed with water (100 + 2 × 50 ml), dried ($MgSO_4$), and evaporated to give a crystalline solid (1.72 g) which, on crystallisation from benzene, yielded the *sulphoxide* (**20**) (968 mg, 67%), m.p. 128—130 °C (from benzene) (Found: C, 50.2; H, 6.05; N, 9.8; S, 11.0. $C_{12}H_{17}ClN_2O_2S$ requires C, 49.9; H, 5.95; N, 9.7; S, 11.1%).

N-[2-(p-*Tolylthio*)*ethyl*]*acetamide* (*with C. N. Lucey*) (**16**).—2-Phthalimidoethyl *p*-tolyl sulphide (297 mg, 1 mmol) was dephthaloylated as described above and the reaction mixture was evaporated. M-NaOH (1.2 ml) and water (2 ml) were added to the residue and the mixture was extracted by methylene dichloride (3 × 10 ml). The dried ($MgSO_4$) and evaporated extract (170 mg) was treated overnight with acetic anhydride (0.15 ml). Addition of benzene (2 ml) and light petroleum (b.p. 60—80 °C; 2 ml) caused crystallisation of the *amide* (**16**) (141 mg, 67%), m.p. 73—75 °C (Found: C, 62.8; H, 7.2; N, 6.8; S, 15.6. $C_{11}H_{15}NOS$ requires C, 63.1; H, 7.1; N, 6.7; S, 15.3%).

The amide (10%) was isolated following attempted Pummerer rearrangement of the sulphoxide (**20**) using acetic anhydride at 100 °C for 18 h. Alternative conditions (acetic anhydride–trifluoroacetic anhydride at room temperature in the presence of 2,6-lutidine) also failed to give a normal rearrangement product.

N-(2-*Chloroethyl*)-N′-[2-(5-*fluorouracil*-1-*yl*)-2-(*methylsulphinyl*)*ethyl*]*urea* (**28**; R = CH_2CH_2Cl). A solution of *m*-chloroperbenzoic acid (95%; 381 mg, 2.1 mmol) in acetic acid (4 ml) was added dropwise at room temperature to a stirred solution of the urea (**24a**) (713 mg, 2 mmol)[2] in acetic acid (12 ml). Next day, the oxidant was shown (negative starch–KI test) to have been consumed and the reaction mixture was evaporated to give a crystalline residue which was triturated with ether (40 ml) to dissolve *m*-chlorobenzoic acid. The slightly sticky, insoluble material (841 mg) dissolved very easily in methanol (2 ml) and the solution subsequently deposited the *sulphoxide* (**28**; R = CH_2CH_2Cl) (a mixture of isomers) as crystals (326 mg, 48%), m.p. 155—157.5 °C. Repeated recrystallisation gradually raised the m.p. The analytical sample, probably a single isomer, had m.p. 196—197 °C (with effervescence) (Found: C, 35.1; H, 4.1; N, 16.4; S, 9.4. $C_{10}H_{14}ClFN_4O_4S$ requires C, 35.25; H, 4.1; N, 16.45; S, 9.4%).

Reaction of HBr–AcOH *with* N-[2-*Alkoxy*-2-(5-*fluorouracil*-1-*yl*)*ethyl*]*phthalimides* (**21b** and **c**).—A solution of the isopropoxyphthalimide (**21c**) (361 mg, 1 mmol) in 45% w/v HBr–AcOH (5 ml), obtained by stirring the mixture (10 min), was kept overnight at room temperature and was then evaporated. The semi-crystalline residue was triturated with propan-2-ol and crystals (92 mg, 71%), decomp. 277——281 °C, of 5-fluorouracil were filtered off. From the evaporated mother liquors were obtained, similarly, crystals (63 mg), m.p. < 200 °C. The u.v. spectrum was consistent with an *N*-[2-bromo-2-(5-fluorouracil-3-yl)ethyl]phthalimide structure, but no pure material could be isolated. The mechanism of the $N^1 \rightarrow N^3$ rearrangement brought about by HBr—CF_3CO_2H in orotidine derivatives[10] is unlikely in the present case.

Treatment of the methoxy phthalimide (**21b**) in the same way as the isopropoxy compound yielded 5-FU (38%).

N-[2-(p-*Tolylthio*)-2-(*uracil*-3-*yl*)*ethyl*]*phthalimide* (**31b**).—A solution, cooled in ice–water, of 2-phthalimidoethyl *p*-tolyl sulphoxide (626 mg, 2 mmol) in benzene (8 ml) was treated with trifluoroacetic anhydride (0.37 ml, 2.6 mmol). The cooling bath was removed and, after 5 min, dry pyridine (0.37 ml, 4.6 mmol) was added. After a further 20 min, the reaction mixture was diluted with ether (10 ml) and the solution was shaken successively with M-HCl (10 ml), saturated aqueous $NaHCO_3$ (10 ml), and water (3 × 10 ml). The organic layer was dried ($MgSO_4$) and evaporated to yield an oil (845 mg) which crystallised.

The above crude product, in methylene dichloride (14 ml), was condensed[3] with uracil (224 mg, 2 mmol), as the bis(trimethylsilyl) derivative, in the presence of tin(IV) chloride. The reaction mixture was poured into M-HCl (8 ml) and the organic layer was shaken successively with water and saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). On evaporation it yielded a foam (820 mg) consisting almost entirely (u.v. spectrum) of the *uracil-3-yl derivative* (**31b**) which separated from its solution in methanol as crystals (498 mg, 61%), m.p. 190.5—192 °C (Found: C, 61.7; H, 4.2; N, 10.2; S, 7.8. $C_{21}H_{17}N_3O_4S$ requires C, 61.9; H, 4.2; N, 10.3; S, 7.9%); $\lambda_{max.}$ 257sh nm (291 in the presence of NaOH).

N[2-*Chloro*-2-(*uracil-3-yl*)*ethyl*]*phthalimide* (**32b**).—The *p*-tolyl sulphide (**31b**) (407 mg, 1 mmol) dissolved rapidly in methylene dichloride (24 ml), with formation of a yellow colour, on addition of sulphuryl chloride (0.09 ml, 1.1 mmol). After 2 h, the now somewhat cloudy solution was clarified by filtration, and was then evaporated. The crystalline residue, on trituration with methanol, afforded the *chloride* (**32b**) as crystals (152 mg, 45%), m.p. 166—168.5 °C (with effervescence) (from methanol) (Found: C, 49.5; H, 3.3; N, 12.3. $C_{14}H_{10}ClN_3O_4 \cdot H_2O$ requires C, 49.8; H, 3.6; N, 12.4%); $\lambda_{max.}$ 266 nm (298 in the presence of NaOH).

N-[2-*Acetoxy*-2-(p-*chlorophenylthio*)*ethyl*]*phthalimide* (**34**) (*with C. N. Lucey*).—(*a*) *p*-Chloro(thiophenol) (12.7 g, 8 mmol), followed by a solution (at 35 °C) of *N*-(2-bromoethyl)-phthalimide (20.3 g, 80 mmol) in methanol (80 ml), was added to a solution of sodium (1.84 g, 0.08 g-atom) in methanol (80 ml), and the resulting slightly cloudy reaction mixture was kept overnight at room temperature, when crystals were found to be present. Methylene dichloride (100 ml) and 5% NaOH (200 ml) were added after evaporation. The aqueous layer was extracted by methylene dichloride (100 ml) and the combined organic solutions were washed with saturated brine and dried ($MgSO_4$). Removal of solvent left N-[2-(p-*chlorophenylthio*)*ethyl*]-*phthalimide* (20.6 g, 81%), m.p. 96—98 °C (from methanol) (Found: C, 60.3; H, 3.85; N, 4.45; S, 10.3. $C_{16}H_{12}ClNO_2S$ requires C, 60.45; H, 3.8; N, 4.4; S, 10.1%).

(*b*) A stirred, partial solution of the above sulphide (20.5 g, 64.5 mmol) in ethanol (130 ml) and acetic acid (130 ml) was treated dropwise during 3 min with 30% w/v hydrogen peroxide (7.3 ml, 64.5 mmol) below 10 °C. The mixture was stirred for 30 min at this temperature and then for 40 h at room temperature. Complete solution occurred during this time. Untreated oxidant was destroyed by addition of dimethyl sulphide (4 ml) and the solution was then evaporated. The residual oil was dissolved in methylene dichloride (220 ml) and the solution was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give N-[2-(p-*chlorophenylsulphinyl*)*ethyl*]*phthalimide* (18.3 g, 85%), m.p. 128—130 °C (from methanol) (Found: C, 57.7; H, 3.6; N, 4.35; S, 9.3. $C_{16}H_{12}ClNO_3S$ requires C, 57.55; H, 3.6; N, 4.2; S, 9.6%).

(*c*) The sulphoxide (18.2 g, 54.4 mmol) was refluxed (3 h) with anhydrous sodium acetate (18.5 g) in acetic anhydride (248 ml) and the mixture was then evaporated. The product was extracted with boiling benzene (100 + 3 × 50 ml) and the extract was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The resultant sticky solid was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to afford the *acetate* (**34**) (11.9 g, 58%), m.p. 99—101 °C (from methanol) (Found: C, 57.7; H, 3.7; N, 3.65; S, 8.2. $C_{18}H_{14}ClNO_4S$ requires C, 57.55; H, 3.75; N, 3.75; S, 8.55%).

Condensation of the Acetate (**34**) *with 5-Fluorouracil*.—The acetate (1.13 g, 3 mmol) in methylene dichloride (21 ml) was condensed as already described[3] with 5-fluorouracil (390 mg, 3 mmol), as the bis(trimethylsilyl) derivative, in the presence of tin(IV) chloride (0.3 ml). The crude product (a foam; 1.07 g) obtained after work-up with saturated aqueous $NaHCO_3$ had a u.v. spectrum indicating the presence of N^1- and N^3-substituted derivatives, but failed to crystallise. Reaction with sulphuryl chloride gave only a little impure product.

N.m.r. and I.r. Spectra of N-(2-*Chloroethyl*)-N-*nitrosoureas*.—The ^1H spectrum of the thymine derivative (**15a**) at 20 MHz had δ 11.25 (s, pyrimidine N^3-H), 9.13 (t, *J* 6 Hz, CH_2NH), 7.66 (d, *J* 1 Hz, pyrimidine 6-H), 5.82 (t, *J* 8 Hz, SCHN), 3.70 (t, *J* 6 Hz, CH_2NH), 3.56 and 4.06 (both t, *J* 6 Hz, CH_2CH_2Cl), 2.05 (s, SCH_3), 1.8 (br s, pyrimidine 5-CH_3). The assignments were confirmed by decoupling experiments. The spectra of other compounds were similar, doublets and triplets having *J ca.* 6—7 Hz in all cases.

The alkoxy compounds (**27b—d**) had signals respectively at δ 11.76, 11.72, 11.75 (d, N^3-H), 9.00, 8.99, 8.98 (t, CH_2NH), 7.94, 7.96, 7.95 (d, 6-H), and 5.68, 5.91, 5.81 (t, OCHN). For the isopropoxy compound (**27c**) there were additional signals at δ 1.14 (d), 1.09 (d) (non-equivalent $CHMe_2$), and for the methoxy compound (**27b**) δ 3.25 (s, OMe). The analytical samples of compounds (**27b** and **d**) showed the presence of 10—15% of presumably the other *N*-nitroso isomer.

It was of interest that the samples of the uracil-3-yl derivatives (**5b** and **c**) consisted of 50:50 mixtures of *N*-nitroso isomers even though sharp m.p.s had been noted. Chemical shifts for (**5b**) were δ 11.2 (br s, N′-H), 8.88 (br s, CH_2NH), 7.5—7.4 (m, 5- and 6-H), 5.7—5.4 (m, SCHN), and for (**5c**) were: δ 11.24 (br s, N′-H), 8.91 (br s, CH_2NH), 7.91 (d, 6-H), and 5.6 (m, SCHN).

The i.r. spectrum of each compound in the region 1 580—1 480 cm^{-1} was very characteristic. The peak at 1 575—1 560 cm^{-1}, always present for the parent ureas, was missing, and the nitrosoureas had 2 peaks of which that at 1 500—1 490 cm^{-1} was probably due to N–NO: (**15a**), 1 500 and 1 530; (**15b**), 1 490 and 1 528; (**27b**), 1 490 and 1 518; (**27c**), 1 490 and 1 526; (**27d**), 1 488 and 1 540—and 3 340 (OH); (**5b**), 1 490 and 1 540; (**5c**), 1 500 and 1 535; (**29**), 1 498 and 1 528—and 1 022 (SO) cm^{-1}.

Acknowledgements

Microanalyses and spectra were obtained by May & Baker Ltd. (Dagenham), and the comments of Mr. M. B. Vine on the n.m.r. results are acknowledged with thanks. We are grateful to Neil Lucey for help with the experimental work.

References

1 Part 1, J. E. McCormick and R. S. McElhinney, *J. Chem. Res.*, 1983, (*S*) 176; (*M*) 1736.
2 J. E. McCormick and R. S. McElhinney, *J. Chem. Res.*, 1981, (*S*) 310; (*M*) 3601.
3 J. E. McCormick and R. S. McElhinney, *J. Chem. Res.*, 1980, (*S*) 126; (*M*) 1914.
4 K. V. B. Rao, V. E. Marquez, J. A. Kelley, and M. T. Corcoran, *J. Chem. Soc., Perkin Trans. 1*, 1983, 127.
5 J. P. Scannell and F. W. Allen, *J. Org. Chem.*, 1960, **25**, 2143.
6 M. Yasumoto, I. Yamawaki, T. Marunaka, and S. Hashimoto, *J. Med. Chem.*, 1978, **21**, 738.
7 J. E. McCormick and R. S. McElhinney, *J. Chem. Res.*, 1981, (*S*) 12; (*M*) 256.
8 A. Rosowsky, S.-H. Kim, and M. Wick, *J. Med. Chem.*, 1981, **24**, 1181.
9 S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, 1975, **97**, 5582.
10 C. V. Z. Smith, R. K. Robins, and R. L. Tolman, *J. Org. Chem.*, 1972, **37**, 1418.

Received 25*th April* 1984; *Paper* 4/657