Novel Reaction of Uracil Derivatives Possessing Electron-withdrawing Groups at the 5-Position with Amines: Exchange Reaction between the N¹-Portion of Uracils and Amines[1]

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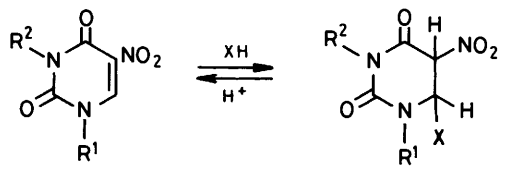
The reaction of 1,3-disubstituted uracils possessing an electron-withdrawing group such as nitro, carbamoyl, and cyano at the 5-position with primary amines resulted in the exchange of the N¹-portion of the uracil ring with the amine moiety. The exchange reactions were influenced by the nature of substituents at the 5- and N¹-position. The reaction sequence is explained in terms of addition, ring-opening, and ring-closure.

Reactions of uracil derivatives with various nucleophiles have been extensively studied in connection with the biosynthesis of thymidylate,[2] the chemical modification of nucleic acids,[3] and ring-transformation reactions for the synthesis of heterocycles.[4–6] The uracil ring system is susceptible to nucleophilic attack at the 6-position. In particular, the presence of electron-withdrawing groups at the 5-position markedly increases the reactivity towards nucleophiles. 5-Nitrouracils are most reactive and suffer smooth addition of nucleophiles, such as ^-OEt,[7] ^-OH,[8] SO_3^{2-},[9] and ^-CN,[10] across the 5,6-double bond to form 5,6-dihydrouracils, which revert to the nitrouracils upon treatment with acid (Scheme 1).



Scheme 1.

The reaction of 5-nitrouracils with amines, however, has never been studied in detail.† During our investigation on the ring transformation of uracils to various heterocycles, we found that 5-nitrouracils reacted with amines to afford exchange reaction of the N¹-portion in the uracil ring for the employed amine.[11] This type of reaction was also observed in the 5-carbamoyl- and 5-cyano-uracil derivatives. This paper describes in full detail the novel type of exchange reaction which is operated by a sequence of addition, ring-opening, and ring-closure processes, and is influenced by virtue of the nature of substituents at the 5- and N¹-positions in the uracil ring.

Upon refluxing of 1,3-dimethyl-5-nitrouracil (**1a**) with an excess of butylamine in absolute ethanol under argon atmosphere for 20 h, 1-butyl-3-methyl-5-nitrouracil (**1b**) was produced in 71% yield along with recovered (**1a**) (18% recovery) (run 1 in Table 1). The structure of compound (**1b**) was confirmed by direct comparison with an authentic sample prepared by reaction of 3-methyl-5-nitrouracil (**1h**) with dimethylformamide (DMF) dibutyl acetal. This reaction was extremely affected by the presence of water. When the nitrouracil (**1a**) was heated with butylamine in ethanol containing a small amount of water, a decomposition product, acrylamide derivative (**2**), was exclusively obtained. The acrylamide (**2**) was shown to be a mixture of (*Z*) and (*E*) isomers by ^1H n.m.r. analysis.

On the basis of above observation, reactions of (**1a**) with propylamine, isopropylamine, cyclohexylamine, and ethanolamine were carried out under anhydrous condition to afford the uracils (**1d—g**) incorporating employed amines at the N¹-position (runs 2—5). The reaction with bulky amines such as isopropylamine and cyclohexylamine gave the products in low yields (runs 3 and 4). 1-Butyl-3-methyl-5-nitrouracil (**1b**) also underwent the N¹-exchange reaction upon treatment with propylamine to give 3-methyl-5-nitro-1-propyluracil (**1d**) in good yield (run 6).

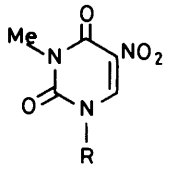
Our previous works[6] have demonstrated that the presence of a phenyl group at the N¹-position of 5-bromo- and 5-cyano-uracil derivatives facilitates the N¹–C⁶ bond cleavage by attack of nucleophiles at the 6-position, resulting in the formation of ring-transformation products. Along this line, 3-methyl-5-nitro-1-(*p*-nitrophenyl)uracil (**1c**)‡ was chosen as a reactant. When the nitrouracil (**1c**) was allowed to react with methylamine in ethanol at ambient temperature, 1-(3-methylamino-2-nitroacryloyl)-3-(*p*-nitrophenyl)urea methylammonium salt (**3**)§ deposited after a few minutes. Upon continued stirring for 30 min the salt (**3**) disappeared and the 1-methyluracil (**1a**) was formed in high yield (run 8). Formation of yellow *p*-nitroaniline was confirmed by t.l.c. analysis of the reaction mixture. Structural proof of the intermediate product (**3**) rests upon its spectral data and the following experimental results. The intermediate (**3**) was stable in ethanol at room temperature, but was easily converted into the N¹-exchange product (**1a**) upon refluxing it in ethanol or treatment with triethylamine at ambient temperature. Acid treatment of (**3**) caused reversion to the starting material (**1c**). When compound (**3**) was treated with excess of ethylamine in ethanol at ambient temperature, 1-ethyl-3-methyl-5-nitrouracil (**1i**) was obtained in 71% yield together with (**1a**) in 27% yield. The occurrence of these

† Fox and his co-workers report in a footnote of ref. 8 that the reaction of 1,3-dimethyl-5-nitrouracil with amines and hydrazine furnishes the corresponding 5,6-dihydro-adducts and that these amine adducts are hydrolysed easily by traces of water to give back the starting material.
‡ The nitration of 3-methyl-1-phenyluracil gave the dinitro compound (**1c**) rather than the expected product (**1**; R = Ph).
§ The ^1H n.m.r. spectrum analysis of (**3**) suggests that the anion site is at the urea moiety; the chemical shift for *ortho*-protons of the *p*-nitrophenyl group was observed at higher field (δ 6.46) compared with those (δ 7.66—7.78) for other ring-opening products (**6**) and (**14**).

Table 1. Reaction of 1,3-disubstituted uracil derivatives with amines

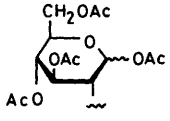
Run	Starting compound	Amine	Molar ratio (uracil:amine)	Reaction conditions	Product	Yield (%)
1	(1a)	$BuNH_2$	1:15	80 °C; 20 h[a]	(1b)	71 (87)[b]
2		$PrNH_2$	1:5	80 °C; 60 h[a]	(1d)	69 (75)[b]
3		Pr^iNH_2	1:15	80 °C; 27 h[a]	(1e)	19 (22)[b]
4		c-$C_6H_{11}NH_2$	1:15	80 °C; 30 h[a]	(1f)	18
5		$HOC_2H_4NH_2$	1:3	80 °C; 66 h[a]	(1g)	33 (37)[b]
6	(1b)	$PrNH_2$	1:15	80 °C; 20 h[a]	(1d)	64
7	(1c)	NH_3	c	r.t.; 4 h	(1h)	93
8		$MeNH_2$	1:10	r.t.; 30 min	(1a)	95
9		$EtNH_2$	1:10	r.t.; 2 h	(1i)	81
10		$BuNH_2$	1:10	80 °C; 3 h	(1b)	59
11		c-$C_6H_{11}NH_2$	1:1.5	80 °C; 1 h	(1f)	77
12		$HOC_2H_4NH_2$	1:1.5	80 °C; 15 min	(1g)	54
13		D-glucosamine	1:1.5	60 °C; 24 h	(1j)[d]	67
14	(7a)	$MeNH_2$	1:10	60 °C; 24 h[e]	(7b)	85
15		$PrNH_2$	1:20	120 °C; 48 h[e]	(7c)	77
16		$BuNH_2$	1:10	120 °C; 24 h[e]	(7d)	97
17		$HOC_2H_4NH_2$	1:10	120 °C; 24 h[e]	(7e)	60
18	(10a)	$MeNH_2$	1:10	r.t.; 12 h	(10b)	97
19	(11a)	$MeNH_2$	1:10	r.t.; 12 h	(11b)	55

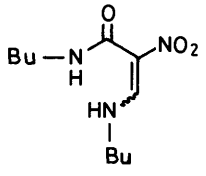
[a] Under Ar atmosphere. [b] Values in parentheses are based on consumed (1a). [c] In absolute ethanol saturated with ammonia. [d] This tetra-acetyl product was isolated after acetylation with acetic anhydride and pyridine. [e] In a sealed tube.



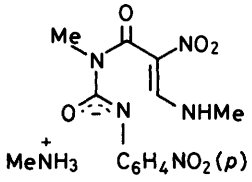
(1)

a; R = Me
b; R = Bu
c; R = p-$C_6H_4NO_2$
d; R = Pr
e; R = Pr^i
f; R = c-C_6H_{11}
g; R = CH_2CH_2OH
h; R = H
i; R = Et
j; R =

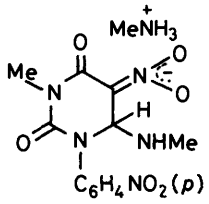




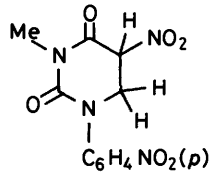
(2)



(3)



(4)



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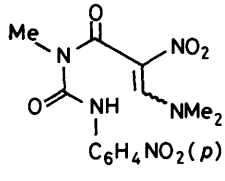


(6)

reactions is also explicable by considering the 5,6-dihydrouracil structure (4)* as an alternative to the ring-opening structure (3) for the structure of the isolated intermediate. The structure (3), however, is more favourable on the basis of the presence of an olefinic proton signal (δ 8.70) in its ^1H n.m.r. spectrum and its u.v. spectrum ($\lambda_{max.}$ 324 nm, ε 20 900), different from that of 5,6-dihydro-3-methyl-5-nitro-1-(*p*-nitrophenyl)uracil (5) ($\lambda_{max.}$ 298 nm, ε 11 300), which was prepared by reduction of compound (1c) with sodium borohydride.[12]

Analogously, the nitrouracil (1c) reacted smoothly even with the less nucleophilic ammonia and with bulky amines, such as cyclohexylamine and glucosamine, as well as with ethylamine, propylamine, and ethanolamine, under mild conditions to give the corresponding N^1-exchange products in good yields (runs 7 and 9—13). In the reaction with ethylamine, *p*-nitroaniline was isolated.

The reaction of (1c) with a secondary amine, dimethylamine, afforded a ring-opening product (6)† corresponding to the intermediate (3) in the reaction of (1c) with methylamine. The structure (6) was determined on the basis of ^1H n.m.r. and u.v. spectral data (see Table 2). An aromatic amine, aniline, did not react even under reflux in ethanol, and starting materials were recovered unchanged.

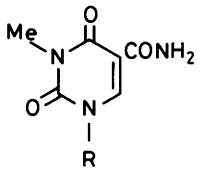
5-Carbamoyl-3-methyl-1-phenyluracil (7a) also easily underwent the N^1-exchange reaction upon treatment with methylamine at 60 °C to give 5-carbamoyl-1,3-dimethyluracil (7b) (run 14), whose structure was confirmed by an alternative synthesis.[13] In the reactions with propylamine, butylamine, and ethanolamine, more drastic conditions (heating at 120 °C in a sealed tube) were required (runs 15—17). On the other hand, treatment of 5-carbamoyl-1,3-dimethyluracil (7b), which has no phenyl group at the N^1-position, with butylamine under various conditions resulted in the recovery of the starting material. These results again indicate that the N^1-phenyl groups plays an accelerating role in the present N^1-exchange reaction.

* In a preliminary report,[11] we presented the structure (4) for the isolated reaction intermediate (3) on the basis of its ^1H n.m.r. spectrum: no olefinic proton was observed in $(CD_3)_2SO$ solution. A detailed n.m.r. study of solutions in both $CDCl_3$ and [$^2H_6$]acetone, however, showed that the structure (4) is an erroneous assignment.

† The ^1H n.m.r. study indicated that the crude product (6) was contaminated with a small amount of amine-adduct, 6-dimethylamino-5,6-dihydro-1-methyl-3-(*p*-nitrophenyl)uracil, which could not be isolated in a pure form.

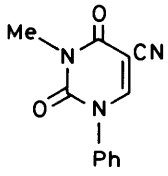
Table 2. Formation of ring-opening products (**3**), (**6**), (**14**), and (**16**)

Product	M.p (°C)	Yield (%)	^{1}H N.m.r. (olefinic proton)	U.v. $\lambda_{max.}^{EtOH}$/nm (ε)
(**3**)	135—137	62	8.70	324 (20 900)
(**6**)	200	71	8.78	320 (17 100)
(**14a**)	232	57	8.48	320 (23 800), 269sh (10 000)
(**14b**)	245	91	8.63	320 (27 600), 272sh (14 700)
(**14c**)	184—185	75	8.68	321 (31 800), 270sh (15 700)
(**14d**)	240—241	74	8.66	322 (29 900), 275sh (14 200)
(**16**)	197—199	84		300 (29 500), 228 (16 000)

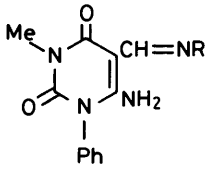


(**7**)

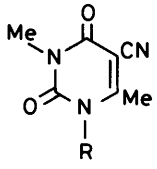
a; R = Ph
b; R = Me
c; R = Pr
d; R = Bu
e; R = CH_2CH_2OH



(**8**)

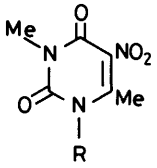


(**9**)



(**10**)

a; R = Ph
b; R = Me



(**11**)

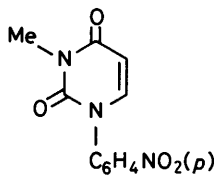
a; R = $C_6H_4NO_2(p)$
b; R = Me

Recently, we have reported[6d] that the reaction of 5-cyano-3-methyl-1-phenyluracil (**8**) with amines induces the Dimroth type of rearrangement, in place of N^1-exchange reaction, to give 6-amino-3-methyl-1-phenyl-5-(*N*-substituted iminomethyl)-uracil (**9**). Treatment of 5-cyano-3,6-dimethyl-1-phenyluracil (**10a**) with methylamine at ambient temperature, however, resulted in the formation of an N^1-exchange reaction product (**10b**) in 97% yield (run 19). At present, it is hard to account for the alternation of reactivities between substrates (**8**) and (**9**) due to the introduction of the 6-methyl grouping. 3,6-Dimethyl-5-nitro-1-(*p*-nitrophenyl)uracil (**11a**) also reacted with methylamine, to give 1,3,6-trimethyl-5-nitrouracil (**11b**) in 55% yield (run 18).

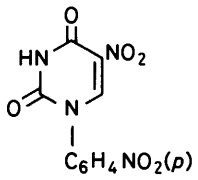
3-Methyl-1-(*p*-nitrophenyl)uracil (**12**) possessing no electron-withdrawing group at the 5-position was inert to reaction with amines. Thus, the presence of an electron-withdrawing group is a prerequisite for the occurrence of the N^1-exchange reaction.

When the 3-unsubstituted 5-nitro-1-(*p*-nitrophenyl)uracil (**13**) was allowed to react with amines such as ammonia, methylamine, butylamine, and cyclohexylamine under analogous conditions, the corresponding ring-opening products (**14a—d**) were isolated in high yields. Assignment of the structures for products (**14a—d**) mainly rests upon their ^{1}H n.m.r. and u.v. spectral data (Table 2). Attempts to cyclize compound (**14b**) into the corresponding N^1-exchanged uracil derivative by using acid, base, or heat were unsuccessful.

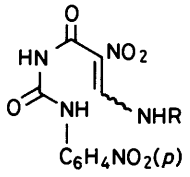
The 3-unsubstituted 5-cyano-6-methyluracil (**15a**) was converted into the corresponding ring-opened product (**16**) in 84% yield upon treatment with methylamine at ambient temperature. Although the product was stable under reflux in ethanol, refluxing of (**16**) in DMF for 2 h caused ring-closure to give 5-cyano-1,6-dimethyluracil (**15b**) in 50% yield. Treatment of compound (**16**) with sodium ethoxide at room temperature, however, gave back the starting uracil (**15a**). These facts are in



(**12**)

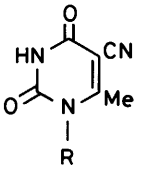


(**13**)



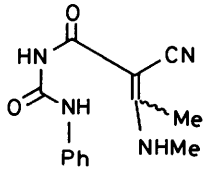
(**14**)

a; R = H
b; R = Me
c; R = Bu
d; R = c-C_6H_{11}

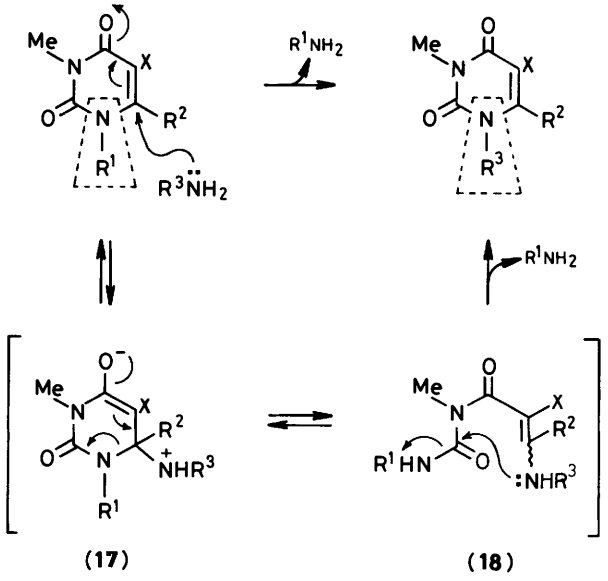


(**15**)

a; R = Ph
b; R = Me

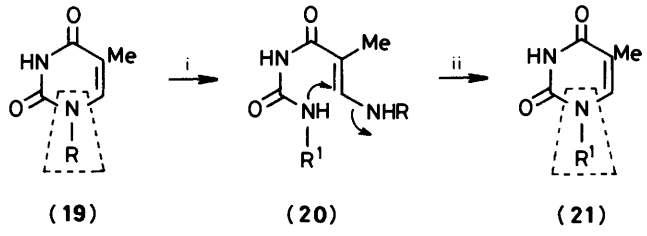


(**16**)



(**17**) (**18**)

Scheme 2.



Scheme 3. *Reagents and conditions:* i, R^1NH_2, *hν*; ii, heat

accord with our hypothesis that the present N^1-thermal exchange-reaction involves an initial nucleophilic attack of amines at the C^6-position and subsequent ring-opening and ring-closure steps.

A plausible reaction sequence to explain the above results can be formulated as shown in Scheme 2 for the N^1-exchange reaction. An initial nucleophilic attack at the 6-position of the uracil ring by an amine could give rise to an adduct (**17**). Scission of the N^1–C^6 bond would give a ring-opening intermediate (**18**), which would then cyclize to N^1-exchange products with release of amine (R^1NH_2) arising from the N^1-portion of the uracils. This reaction mode is mechanistically similar to the reaction of 6-chloro-1,3-dimethyl-5-nitrouracil with 2-aminothiophenol involving an intramolecular N^1-exchange reaction.[14]

Although the reaction of 1,3-*disubstituted uracils with ambident nucleophiles causes various ring transformations involving the apparent displacement of the urea portion of the uracil by the nucleophile employed,*[5a,5c,5d,5g,5h] *the present* N^1-*exchange reaction is the first example of thermal displacement of the* N^1-*portion of the uracil by the amine employed.*

Previously, Saito *et al.* have found that photochemical reaction of thymine derivatives (**19**) with alkylamines induces an exchange reaction between the thymine N^1-portion and alkylamines employed (Scheme 3).[15] This reaction involves an initial nucleophilic attack of amines at the 2-position of the photoexcited thymine as evidenced by isolation of the intermediate urea (**20**) and its cyclization to the N^1-exchange product (**21**). It is worthwhile to note that an initial attack site in the photoinduced N^1-exchange reaction is different from that in the present thermal reaction.

Experimental

M.p.s were determined on a Yanagimoto melting-point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our university. ^1H N.m.r. spectra were recorded on a Hitachi Perkin-Elmer R-20B (60 MHz), JEOL JNM-PS-100 (100 MHz), or JEOL TNM-GX270 (270 MHz) spectrometer with tetramethylsilane (TMS) in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) in $(CD_3)_2SO$ as internal standards. Chemical shifts are reported in parts per million (δ) and *J*-values are first order. I.r. spectra were taken on a Hitachi 215 instrument as KBr pellets. Mass spectra were obtained in a JEOL JMS-D300 machine operating at 70 eV. U.v. spectra were obtained from ethanol on a Shimdazu UV-260 spectrophotometer. Column chromatography was carried out on a silical gel (Wakogel C-300).

Reaction of 1,3-*Dimethyl-5-nitrouracil* (**1a**) *with Amines. General Procedure* (*Table* 1).—A mixture of compound (**1a**)[16] (0.50 g, 2.7 mmol) and an amine in absolute ethanol (50 ml) was refluxed under argon and the conditions specified in Table 1. The solvent was removed under reduced pressure and water (30 ml) was added to the residue. The mixture was extracted with chloroform, and the extract was dried over $MgSO_4$. The solvent was evaporated to dryness and the residue was chromatographed on a silica gel column, with benzene–ethyl acetate (1:0—20:1) as the eluant to give the 1-substituted 3-methyl-5-nitrouracil (**1b—g**) and the starting compound (**1a**).

1-*Butyl*-3-*methyl*-5-*nitrouracil* (**1b**). M.p. 66—70 °C; δ_H(60 MHz; $CDCl_3$) 0.99 (3 H, t, *J* 6 Hz), 1.10—2.22 (4 H, m), 3.36 (3 H, s), 4.07 (2 H, t, *J* 6.5 Hz), and 8.94 (1 H, s) (Found: C, 47.3; H, 5.85; N, 18.35. $C_9H_{13}N_3O_4$ requires C, 47.57; H, 5.77; N, 18.49%).

3-*Methyl*-5-*nitro*-1-*propyluracil* (**1d**). M.p. 98—99 °C (from butan-1-ol); δ_H[60 MHz; $(CD_3)_2SO$] 0.90 (3 H, t, *J* 7.5 Hz), 1.66 (2 H, m), 3.21 (3 H, s), 3.87 (2 H, t, *J* 7.5 Hz), and 9.30 (1 H, s) (Found: C, 45.3; H, 5.15; N, 19.85. $C_8H_{11}N_3O_4$ requires C, 45.07; H, 5.20; N, 19.71%).

1-*Isopropyl*-3-*methyl*-5-*nitrouracil* (**1e**). M.p. 151—152 °C (from butan-1-ol); δ_H[60 MHz; $(CD_3)_2SO$] 1.40 (6 H, d, *J* 7 Hz), 3.22 (3 H, s), 4.77 (1 H, m), and 9.03 (1 H, s) (Found: C, 45.3; H, 5.25; N, 19.6%).

1-*Cyclohexyl*-3-*methyl*-5-*nitrouracil* (**1f**). The extract was evaporated under reduced pressure and the residue was treated with carbon tetrachloride to give compound (**1f**), which was identical with an authentic sample.[5f]

1-(2-*Hydroxyethyl*)-3-*methyl*-5-*nitrouracil* (**1g**). The reaction mixture was evaporated under reduced pressure and water (30 ml) was added to the residue. The mixture was extracted with ethyl acetate, and the extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in methanol and the insoluble portion was filtered off. The filtrate was subjected to dry column chromatography on a silica gel with chloroform as the eluant to give *compound* (**1g**), m.p. 215 °C (from water); δ_H[60 MHz; $(CD_3)_2SO$] 3.26 (3 H, s), 3.34—4.29 (5 H, m), and 9.14 (1 H, s) (Found: C, 38.8; H, 4.2; N, 19.6. $C_7H_9N_3O_5$ requires C, 39.07; H, 4.22; N, 19.53%).

Alternative Synthesis of 1-*Butyl*-3-*methyl*-5-*nitrouracil* (**1b**).—A mixture of 3-methyl-5-nitrouracil (**1h**)[17] (0.34 g, 2 mmol) and DMF dibutyl acetal (2.03 g, 10 mmol) in DMF (10 ml) was heated at 100 °C for 10 h. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with chloroform–hexane (1:1) as eluant to give compound (**1b**) (0.21 g, 47%), which was identical with compound (**1b**) obtained by the N^1-exchange reaction of (**1a**) with butylamine.

3-*Methyl*-5-*nitro*-1-(p-*nitrophenyl*)*uracil* (**1c**). White fuming nitric acid (15 ml) was added dropwise to a stirred suspension of 3-methyl-1-phenyluracil[18] (5.0 g, 25 mmol) in conc. sulphuric acid (30 ml) at −5 to 5 °C. The mixture was stirred at 10 °C for 30 min and then poured over ice. The resulting precipitate was collected, washed successively with water and hot methanol, and dried to give the *title compound* (**1c**) (5.30 g, 73%). An analytical sample was obtained by recrystallization from ethanol, m.p. 198—199 °C; δ_H[60 MHz; $(CD_3)_2SO$] 3.29 (3 H, s), 7.88 and 8.46 (each 2 H, each d, each *J* 9 Hz), and 9.32 (1 H, s) (Found: C, 45.2; H, 2.75; N, 19.3. $C_{11}H_8N_4O_6$ requires C, 45.21; H, 2.76; N, 19.18%).

3-*Methyl*-5-*nitro*-1-*propyluracil* (**1d**) *from* (**1b**).—A mixture of compound (**1b**) (0.50 g, 2.2 mmol) and propylamine (1.95 g, 33 mmol) in absolute ethanol (25 ml) was treated as described in the general procedure for the reaction of (**1a**) with amines to give the title compound (**1d**) (Table 1), which was identical with compound (**1d**) obtained by the N^1-exchange reaction of (**1a**) with propylamine.

Reaction of 3-*Methyl*-5-*nitro*-1-(p-*nitrophenyl*)*uracil* (**1c**) *with Amines* (*Table* 1).—1,3-*Dimethyl*-5-*nitrouracil* (**1a**). A mixture of compound (**1c**) (0.25 g, 0.86 mmol) and methylamine (30% in

methanol) (0.90 g, 8.60 mmol) in methanol (15 ml) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was triturated with ether. The resulting precipitate was collected by filtration and washed with ether to give compound (**1a**), which was identical with an authentic sample.[16]

1-*Butyl*-3-*methyl*-5-*nitrouracil* (**1b**). A mixture of compound (**1c**) (1.00 g, 3.42 mmol) and butylamine (2.50 g, 34 mmol) in ethanol (35 ml) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with chloroform as the eluant, to give compound (**1b**), was identical with the product obtained from the reaction of compound (**1a**) with butylamine.

1-*Cyclohexyl*-3-*methyl*-5-*nitrouracil* (**1f**). A mixture of compound (**1c**) (0.30 g, 1.03 mmol) and cyclohexylamine (0.15 g, 1.54 mmol) in ethanol (10 ml) was refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was triturated with ether. The resulting precipitate was collected by filtration and washed with ether to give compound (**1f**), which was identical with the product obtained from the reaction of compound (**1a**) with cyclohexylamine.

1-(2-*Hydroxyethyl*)-3-*methyl*-5-*nitrouracil* (**1g**). A mixture of compound (**1c**) (0.50 g, 1.71 mmol) and ethanolamine in ethanol (17 ml) was refluxed for 15 min. The resulting precipitate was filtered off and recrystallized from water to give compound (**1g**), which was identical with the product obtained from the reaction of compound (**1a**) with ethanolamine.

3-*Methyl*-5-*nitrouracil* (**1h**). A mixture of compound (**1c**) (0.35 g, 1.20 mmol) and ethanolic ammonia (5 ml) was stirred at room temperature for 4 h. The resulting precipitate was filtered off, washed successively with dil. hydrochloric acid (10%) and water, and recrystallized from ethanol to give compound (**1h**), m.p. 280 °C (lit.,[17] 263—265 °C); δ_H[60 MHz; $(CD_3)_2SO$] 3.66 (3 H, s), 6.30 (1 H, br), and 8.90 (1 H, s) (Found: C, 33.45; H, 3.65; N, 27.3. Calc. for $C_5H_5N_3O_4$: C, 33.48; H, 3.53; N, 27.52%).

1-*Ethyl*-3-*methyl*-5-*nitrouracil* (**1i**) *and* p-*nitroaniline*. A mixture of compound (**1c**) (0.20 g, 0.68 mmol) and aqueous ethylamine (70%) (0.44 g, 6.8 mmol) in ethanol (10 ml) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column with chloroform–methanol (100:1) as the eluant to give compound (**1i**) and *p*-nitroaniline (0.04 g, 42%). *Compound* (**1i**) was recrystallized from chloroform–ether, m.p. 103—105 °C; δ_H(60 MHz; $CDCl_3$) 1.45 (3 H, t, *J* 7 Hz), 3.38 (3 H, s), 4.07 (2 H, q, *J* 7 Hz), and 8.82 (1 H, s) (Found: C, 42.15; H, 4.5; N, 21.25. $C_7H_9N_3O_4$ requires C, 42.21; H, 4.55; N, 21.10%). The isolated *p*-nitroaniline was identical with a commercially available sample.

3-*Methyl*-5-*nitro*-1-(1,3,4,6-*tetra*-O-*acetyl*-2-*deoxy*-D-*glucopyranos*-2α-*yl*)*uracil* (**1j**). A mixture of D-glucosamine hydrochloride (1.11 g, 5.13 mmol) and triethylamine (0.52 g, 5.13 mmol) in ethanol (20 ml) was stirred at room temperature for 5 min. Compound (**1c**) (1.00 g, 3.42 mmol) was added to the reaction mixture, which was then stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in a mixture of acetic anhydride (20 ml) and pyridine (10 ml). The mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform–methanol (100:1) as the eluant to give a crude mass, which was chromatographed on a silica gel column again with chloroform as the eluant and recrystallized from light petroleum * to give *compound* (**1j**) (Table 1), m.p. 103 °C; δ_H(60 MHz; $CDCl_3$) 2.00, 2.06, 2.09, 2.20, and 3.36 (each 3 H, each s), 3.96—6.45 (7 H, m), and 8.79 (1 H, s) (Found: C, 44.95; H, 4.55; N, 8.5. $C_{19}H_{23}N_3O_{13}$·0.5H_2O requires C, 44.71; H, 4.74; N, 8.23%).

N-*Butyl*-3-*butylamino*-2-*nitroacrylamide* (**2**).—A mixture of compound (**1a**) (0.59 g, 3.19 mmol), butylamine (3.50 g, 47.85 mmol), and water (0.05 g, 2.78 mmol) in ethanol (30 ml) was refluxed for 24 h. The solvent was removed under reduced pressure and the resulting residue was dissolved in chloroform. The solution was washed with water and dried over $MgSO_4$. Removal of the solvent afforded a mass, which was chromatographed on a silica gel with chloroform–hexane (1:1) as eluant and recrystallized from hexane–ether to give compound (**2**) (0.42 g, 54%), m.p. 43.5—46 °C; δ_H(270 MHz; $CDCl_3$) 0.80—1.07 (6 H, m), 1.15—2.86 (8 H, m), 3.27—3.60 (4 H, m), 8.53 (0.25 H, d, *J* 15.6 Hz), 8.67 (0.75 H, d, *J* 14.2 Hz), and 8.82 (1 H, br) (Found: C, 54.05; H, 8.8; N, 17.0. $C_{11}H_{21}N_3O_3$ requires C, 54.30; H, 8.70; N, 17.27%).

1-*Methyl*-1-(3-*methylamino*-2-*nitroacryloyl*)-3-(p-*nitrophenyl*)*urea Methylammonium Salt* (**3**).—A mixture of compound (**1c**) (2.00 g, 6.84 mmol) and methylamine (30% in methanol) (3.54 g, 3.42 mmol) in ethanol (150 ml) was stirred at room temperature for 1 min. The resulting precipitate was immediately filtered off and washed with ethanol to give the *salt* (**3**) (1.58 g, 62%). This compound was unstable and was used without further purification, m.p. 135—137 °C; δ_H(100 MHz; $CDCl_3$) 3.40 and 3.59 (each 3 H, each s), 4.40 (2 H, br), 6.61 and 8.04 (each 2 H, each d, each *J* 8.9 Hz), and 8.70 (1 H, s); δ_H[100 MHz; $(CD_3)_2CO$] 3.27 and 3.62 (each 3 H, each s), 6.00 (1 H, br), 6.72 and 7.96 (each 2 H, each d, each *J* 9.1 Hz), and 9.10 (1 H, s); $\lambda_{max.}$(EtOH) 324 nm (ε 20 900) (Found: C, 44.05; H, 5.25; N, 22.8. $C_{13}H_{18}N_6O_6$·0.25C_2H_5OH requires C, 44.32; H, 5.37; N, 22.97%).

Reactions of 1-*Methyl*-1-(3-*methylamino*-2-*nitroacryloyl*)-3-(p-*nitrophenyl*)*urea Methylammonium Salt* (**3**).—*Reaction with hydrochloric acid.* A mixture of compound (**3**) (0.16 g, 0.45 mmol) and conc. hydrochloric acid (35%) (0.06 g, 0.58 mmol) in ethanol (10 ml) was stirred at room temperature for 1 min. The resulting precipitate was filtered off and washed with ether to give compound (**1c**) (0.13 g, 99%). This product was identical with compound (**1c**) obtained by the nitration of 3-methyl-1-phenyluracil.

Heating in ethanol.—A suspension of compound (**3**) (0.50 g, 1.41 mmol) in ethanol (50 ml) was refluxed for 5 min. The resulting precipitate was filtered off to give 1,3-dimethyl-5-nitrouracil (**1a**) (0.15 g, 58%), which was identical with an authentic sample.[16]

Reaction with triethylamine. A mixture of compound (**3**) (0.50 g, 1.41 mmol) and triethylamine (0.47 g, 4.65 mmol) in ethanol (20 ml) was stirred at room temperature for 6 h. The resulting precipitate was filtered off and washed with ether to give compound (**1a**) (0.24 g, 92%), which was identical with an authentic sample.[16]

Reaction with ethylamine. A mixture of compound (**3**) (0.32 g, 0.9 mmol) and aqueous ethylamine (70%) (0.58 g, 9 mmol) in ethanol (20 ml) was stirred at room temperature for 10 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform–methanol (100:1) as the eluant to give compounds (**1a**) (0.05 g, 27%) and (**1i**) (0.14 g, 71%). These products were identical with compounds (**1a**) and (**1i**) obtained by the N^1-exchange reactions of compound (**1c**) with methylamine and ethylamine, respectively.

5,6-*Dihydro*-3-*methyl*-5-*nitro*-1-(p-*nitrophenyl*)*uracil* (**5**).—Sodium borohydride (0.07 g, 1.85 mmol) was added to a

* Boiling range 75—120 °C.

suspension of 3-methyl-5-nitro-1-(*p*-nitrophenyl)uracil (**1c**) (0.25 g, 0.86 mmol) in methanol (10 ml). The mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was dissolved in water (15 ml) and the solution was neutralized with conc. hydrochloric acid (35%). The resulting precipitate was filtered off and recrystallized from ethanol to give *compound* (**5**) (0.23 g, 91%), m.p. 70.5—73 °C; δ_H(270 MHz; $CDCl_3$) 3.37 (3 H, s), 4.40 and 4.53 (each 1 H, each dd, each *J* 13.7 and 4.4 Hz), 5.41 (1 H, t, *J* 4.4 Hz), and 7.45 and 8.31 (each 2 H, each d, each *J* 9.3 Hz); $\lambda_{max.}$(EtOH) 298 nm (ε 11 300) (Found: C, 44.95; H, 3.45; N, 19.0. $C_{11}H_{10}N_4O_6$ requires C, 44.90; H, 3.43; N, 19.04%).

1-(3-*Dimethylamino*-2-*nitroacryloyl*)-1-*methyl*-3-(p-*nitrophenyl*)*urea* (**6**).—A mixture of compound (**1c**) (0.50 g, 1.71 mmol) and aqueous dimethylamine (50%) (1.54 g, 17.10 mmol) in ethanol (20 ml) was stirred at room temperature for 4 h. The resulting precipitate was filtered off and recrystallized from ethyl acetate to give *compound* (**6**) (0.41 g, 71%), m.p. 200 °C; δ_H(270 MHz; $CDCl_3$) 2.62 (6 H, s), 3.49 (3 H, s), 7.65 and 8.45 (each 2 H, each d, each *J* 9 Hz), and 8.78 (1 H, s); $\lambda_{max.}$ 320 nm (ε 17 100) (Found: C, 46.2; H, 4.85; N, 20.65. $C_{13}H_{15}N_5O_6$ requires C, 46.29; H, 4.48; N, 20.77%).

Reaction of 5-*Carbamoyl*-3-*methyl*-1-*phenyluracil* (**7a**) *with Amines. General Procedure* (*Table* 1).—A mixture of compound (**7a**)[18] (3 mmol) and methanolic methylamine (30%) (10 mmol), propylamine (20 mmol), butylamine (10 mmol), or ethanolamine (10 mmol) in ethanol (30 ml) was heated in a sealed tube under the conditions specified in Table 1. The reaction mixture was treated as described below unless otherwise stated. The solvent was removed under reduced pressure and the residue was triturated with ether to give a crude product. Recrystallization from an appropriate solvent gave the N^1-exchange products (**7b—e**).

5-*Carbamoyl*-1,3-*dimethyluracil* (**7b**). The resulting precipitate was collected by filtration to give compound (**7b**), identical with an authentic sample.[13]

5-*Carbamoyl*-3-*methyl*-1-*propyluracil* (**7c**). M.p. 166—167 °C (from EtOH); δ_H[60 MHz; $(CD_3)_2SO$] 0.87 (3 H, t, *J* 7 Hz), 1.62 (2 H, m), 3.22 (3 H, s), 3.85 (2 H, t, *J* 7 Hz), 7.50 and 8.19 (each 1 H, each br), and 8.51 (1 H, s) (Found: C, 51.0; H, 6.2; N, 19.95. $C_9H_{13}N_3O_3$ requires C, 51.17; H, 6.20; N, 19.90%).

1-*Butyl*-5-*carbamoyl*-3-*methyluracil* (**7d**). M.p. 173.5—174 °C (from water); δ_H[60 MHz; $(CD_3)_2SO$] 0.97 (3 H, t, *J* 6 Hz), 1.07—2.32 (4 H, m), 3.38 (3 H, s), 3.88 (2 H, t, *J* 7 Hz), 6.00 (1 H, br), 8.40 (1 H, s), and 8.65 (1 H, br) (Found: C, 53.05; H, 6.7; N, 18.65. $C_{10}H_{15}N_3O_3$ requires C, 53.32; H, 6.71; N, 18.66%).

5-*Carbamoyl*-1-(2-*hydroxyethyl*)-3-*methyluracil* (**7e**). M.p. 123—124 °C (from water); δ_H[60 MHz; $(CD_3)_2SO$] 3.23 (3 H, s), 3.64 and 3.95 (each 2 H, each t, each *J* 5 Hz), 4.88 (1 H, t, *J* 6 Hz), 7.48 and 8.18 (each 1 H, each br), and 8.42 (1 H, s) (Found: C, 45.3; H, 5.25; N, 19.75. $C_8H_{11}N_3O_4$ requires C, 45.07; H, 5.20; N, 19.71%).

5-*Cyano*-1,3,6-*trimethyluracil* (**10b**).—A mixture of 5-cyano-3,6-dimethyl-1-phenyluracil (**10a**)[19] (0.72 g, 3 mmol) and methanolic methylamine (40%) (2.33 g, 30 mmol) was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the residue was triturated with ether. The resulting precipitate was filtered off and recrystallized from ethanol to give compound (**10b**) (Table 1), which was identical with an authentic sample.[19]

3,6-*Dimethyl*-5-*nitro*-1-(p-*nitrophenyl*)*uracil* (**11a**).—3,6-Dimethyl-1-phenyluracil[20] (5.0 g, 23 mmol) was treated with white fuming nitric acid (14 ml) in sulphuric acid (28 ml) under similar conditions to those employed for the preparation of compound (**1c**). The resulting precipitate was collected, washed with water, and recrystallized from propan-1-ol to give the *title compound* (**11a**) (3.67 g, 52%), m.p. 223—225 °C; δ_H[60 MHz; $(CD_3)_2SO$] 2.00 and 3.29 (each 3 H, each s) and 7.74—8.65 (4 H, m) (Found: C, 46.9; H, 3.25; N, 18.1. $C_{12}H_{10}N_4O_6$ requires C, 47.06; H, 3.29; N, 18.30%).

1,3,6-*Trimethyl*-5-*nitrouracil* (**11b**).—A mixture of compound (**11a**) (0.50 g, 1.63 mmol) and aqueous methylamine (40%) (1.30 g, 16.3 mmol) in ethanol (20 ml) was stirred at room temperature for 12 h. The insoluble portion was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in benzene and the insoluble portion was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was triturated with ether. The resulting precipitate was filtered off and washed with ether to give compound (**11b**) (Table 1), which was identical with an authentic sample.[21]

3-*Methyl*-1-(p-*nitrophenyl*)*uracil* (**12**).—A mixture of 5-cyano-3-methyl-1-(*p*-nitrophenyl)uracil[6d] (2.76 g, 10.14 mmol) and hydrobromic acid (47%; 20 ml) was refluxed for 4 h. The reaction mixture was poured over ice and the resulting precipitate was filtered off and recrystallized from ethanol to give the title compound (**12**) (2.19 g, 87%), m.p. 193—195 °C; δ_H[60 MHz; $(CD_3)_2SO$] 3.23 (3 H, s), 5.91 (1 H, d, *J* 8.5 Hz), 7.76 (2 H, d, *J* 9 Hz), 7.84 (1 H, d, *J* 8.5 Hz), and 8.38 (2 H, d, *J* 9 Hz) (Found: C, 51.65; H, 3.55; N, 16.15. $C_{11}H_9N_3O_4 \cdot 0.5H_2O$ requires C, 51.57; H, 3.93; N, 16.40%).

1-(3-*Amino*-2-*nitroarcyloyl*)-3-(p-*nitrophenyl*)*urea* (**14a**).—A mixture of 5-nitro-1-(*p*-nitrophenyl)uracil (**13**)[12] (0.50 g, 1.8 mmol) and ethanol saturated with ammonia (20 ml) was stirred at room temperature for 3 h. The resulting precipitate was filtered off and recrystallized from acetone to give the *title compound* (**14a**) (0.30 g, 57%), m.p. 232 °C; δ_H[60 MHz; $(CD_3)_2SO$] 7.78 and 8.22 (each 2 H, each d, each *J* 9 Hz), 8.48 (1 H, s), and 8.80—11.31 (4 H, br); $\lambda_{max.}$(EtOH) 320 (ε 23 800) and 269sh nm (10 000) (Found: C, 40.7; H, 3.0; N, 23.85. $C_{10}H_9N_5O_6$ requires C, 40.68; H, 3.07; N, 23.73%).

1-(3-*Methylamino*-2-*nitroacryloyl*)-3-(p-*nitrophenyl*)*urea* (**14b**).—A mixture of 5-nitro-1-(*p*-nitrophenyl)uracil (**13**)[12] (1.88 g, 6.8 mmol) and methanolic methylamine (40%) (5.28 g, 68 mmol) in ethanol (20 ml) was stirred at room temperature for 5 min. The resulting precipitate was filtered off and recrystallized from acetic acid to give the *title compound* (**14b**) (1.90 g, 91%), m.p. 245 °C; δ_H[60 MHz; $(CD_3)_2SO$] 3.30 (3 H, s), 7.76 and 8.23 (each 2 H, each d, each *J* 9 Hz), 8.63 (1 H, br s), and 10.27—11.27 (3 H, br); $\lambda_{max.}$(EtOH) 320 (ε 27 600) and 272sh nm (14 700) (Found: C, 42.65; H, 3.6; N, 22.65. $C_{11}H_{11}N_5O_6$ requires C, 42.87; H, 3.59; N, 22.65%).

1-(3-*Butylamino*-2-*nitroacryloyl*)-3-(p-*nitrophenyl*)*urea* (**14c**).—A mixture of 5-nitro-1-(*p*-nitrophenyl)uracil (**13**)[12] (0.50 g, 1.8 mmol) and butylamine (1.30 g, 18 mmol) in ethanol (17 ml) was refluxed for 1.5 h. The resulting precipitate was filtered off and recrystallized from ethanol to give the *title compound* (**14c**) (0.47 g, 75%), m.p. 184—185 °C; δ_H[60 MHz; $(CD_3)_2SO$] 0.95 (3 H, t, *J* 6 Hz), 1.00—2.01 (4 H, m), 3.65 (2 H, t, *J* 6 Hz), 7.78 and 8.25 (each 2 H, each d, each *J* 9.5 Hz), 8.68 (1 H, s), and 10.78 (3 H, br); $\lambda_{max.}$(EtOH), 321 (ε 31 800) and 270sh (15 700) (Found: C, 47.9; H, 4.8; N, 20.1. $C_{14}H_{17}N_5O_6$ requires C, 47.86; H, 4.88; N, 19.94%).

1-(3-*Cyclohexylamino*-2-*nitroacryloyl*)-3-(p-*nitrophenyl*)*urea* (**14d**).—A mixture of 5-nitro-1-(*p*-nitrophenyl)uracil (**13**)[12] (0.50 g, 1.8 mmol) and cyclohexylamine (3.60 g, 36 mmol) in

ethanol (17 ml) was refluxed for 1.5 h. The resulting precipitate was filtered off and recrystallized from acetic acid to give the *title compound* (**14d**) (0.50 g, 74%), m.p. 240—241 °C; δ_H[60 MHz; $(CD_3)_2SO$] 0.76—2.16 (10 H, m), 3.68 (1 H, m), 7.77 and 8.22 (each 2 H, each d, each *J* 9 Hz), 8.66 (1 H, s), and 10.16—11.06 (3 H, br); $\lambda_{max.}$(EtOH) 322 (ε 29 900) and 275sh nm (14 200) (Found: C, 51.1; H, 5.15; N, 18.65. $C_{16}H_{19}N_5O_6$ requires C, 50.92; H, 5.08; N, 18.56%).

5-*Cyano*-6-*methyl*-1-*phenyluracil* (**15a**).—A suspension of compound (**16**) (see later) (0.29 g, 1.12 mmol) in ethanolic sodium ethoxide [prepared from Na (0.23 g, 10 mg-atom) in absolute ethanol (30 ml)] was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was dissolved. in water. The solution was acidified with conc. hydrochloric acid (35%) and the resulting precipitate was filtered off and washed with water to give the *title compound* (**15a**) (0.21 g, 82%), which was identical with an authentic sample.[22]

5-*Cyano*-1,6-*dimethyluracil* (**15b**).—A solution of compound (**16**) (0.22 g, 0.85 mmol) in DMF (5 ml) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give the title compound (**15b**) (0.07 g, 50%), which was identical with an authentic sample.[19]

1-(2-*Cyano*-3-*methyl*-3-*methylaminoacryloyl*)-3-*phenylurea* (**16**).—A mixture of 5-cyano-6-methyl-1-phenyluracil (**15a**)[22] (0.68 g, 3 mmol) and methanolic methylamine (40%) (2.33 g, 30 mmol) in ethanol (30 ml) was stirred at room temperature for 3 h. The resulting precipitate was filtered off and washed with ether to give the title compound (**16**) (84%). An analytical sample was obtained by recrystallization from acetone, m.p. 197—199 °C; δ_H[60 MHz; $(CD_3)_2SO$] 2.28 (3 H, s), 3.06 (3 H, d, *J* 5 Hz), 6.63—7.80 (5 H, m), 8.41 (1 H, br s), and 10.33 (2 H, br); $\nu_{max.}$ 2 190 cm^{-1} (CN); $\lambda_{max.}$(EtOH) 300 (ε 29 500) and 228 nm (16 000) (Found: C, 60.5; H, 5.45; N, 21.7. $C_{13}H_{14}N_4O_2$ requires C, 60.45; H, 5.46; N, 21.70%).

References

1 This paper is part 64 of a series entitled 'Pyrimidines.' For part 63 see the preceding paper.

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