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The crafting of uracils with enhanced stacking potential

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Abstract. Uracils having enhanced stacking profile are of interest from diverse vantages ranging from the chemical simulation of transcription to the design of novel anti viral agents. This objective has been realized by synthetic strategies leading to uracils having, *inter alia*, pseudo aromatic and hydrophobic rings crafted to the 5–6 location and ionophore and hydrophobic chains affixed at the C-5 and nitrogen atoms. Endeavours to prepare a 5–2′ uracil-pyrimidine composite have led to novel uracil arising from 2–O → $=CH(COOR)_2$ transformation and a tethered malonic acid pyrimidine complex.

Keywords. Attenuation; uracil; non-covalent interactions; stacking profile.

The vertical stacking of the code nucleotides that are attached to the template nucleic acid by hydrogen bonding is a pre-requisite for their polymerization to the daughter molecules. *In vitro* studies have shown that whilst this is not a problem with the purine nucleotides, the necessary stacking is not achieved by pyrimidine nucleotides. As a consequence, whilst a polypyrimidine nucleotide can produce a polypurine nucleotide *via* processes that could be considered as chemical simulation of transcription, the reverse is not achieved. This is illustrated in scheme 1.

The lack of complementary strand formation in the case of pyrimidine nucleotides is a result of insufficient interpyrimidine attraction, thus resulting in poor alignment. On the other hand, purines, possessing a complete aromatic moiety, stack well (Hamilton 1991). In the present work, it was proposed to synthesize a series of pyrimidines whose stacking properties could be envisaged as better than the parent. The objective, then, would be, the attachment of appropriate ligands to the parent uracil framework that could open up possibilities for stacking interactions, either by means of hydrophobic bonding, or attraction *via* polar substituents. Fortuitously, such systems are of great current interest, since numerous nucleosides and nucleotides and their analogs, harboring modified uracils have shown significant anti-viral activity and some of these have emerged as therapeutic agents against crippling viral afflictions.

Barbituric acid (1), readily prepared from urea and malonic acid or ester, presented itself as an attractive starting material for the preparation of the substituted uracils that would carry polar residues. Nitration of (1) with fuming nitric acid gave 5–nitrobarbituric acid, (2) in 90% yields. Reduction of (2) with tin and hydrochloric acid gave the expected amino compound (3), which, on treatment with sodium

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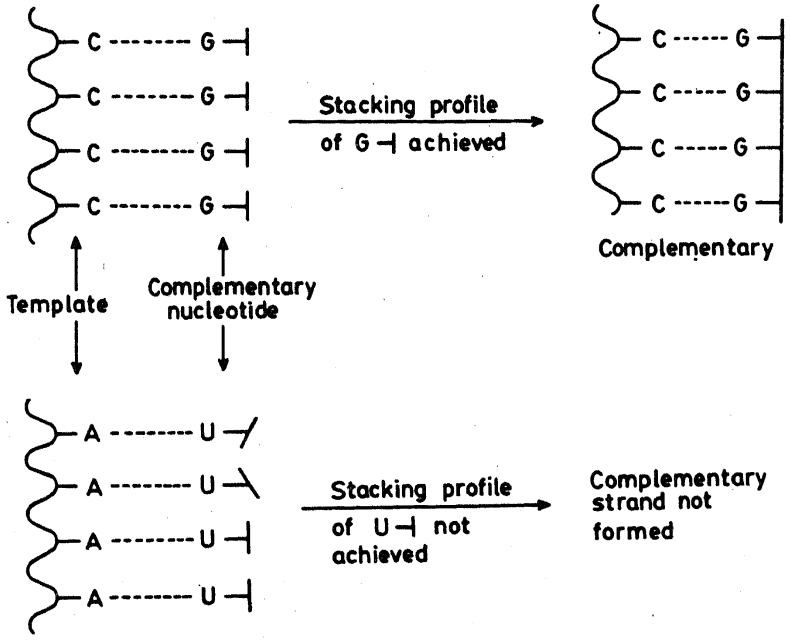
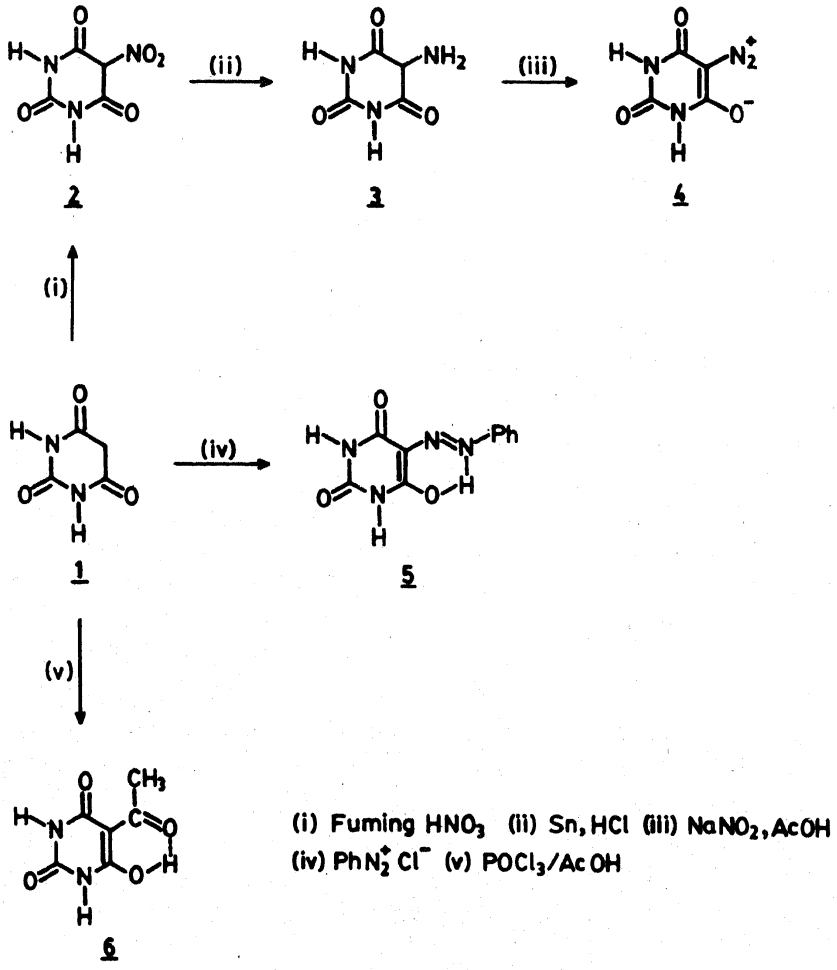


Scheme 1.



Scheme 2.

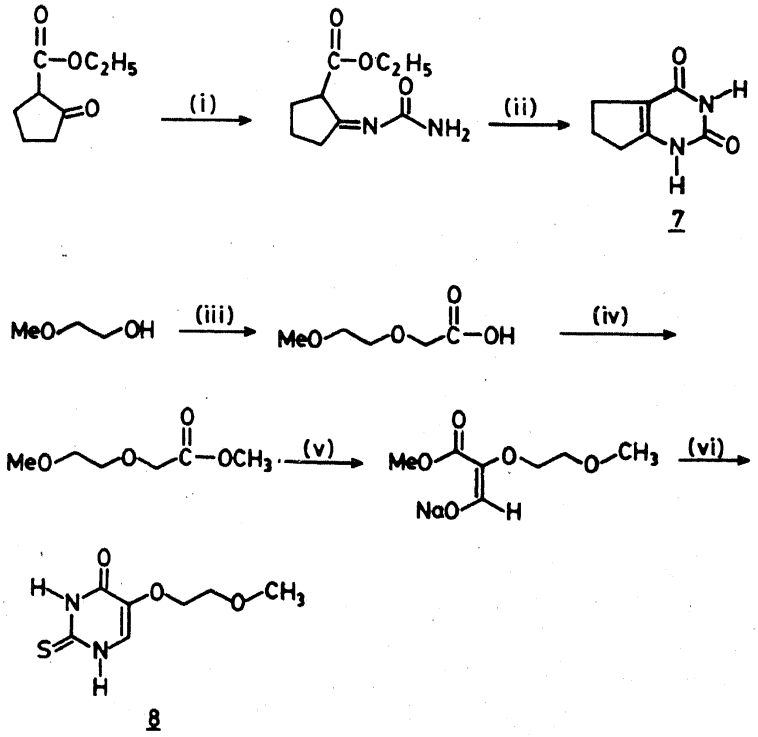
nitrite/acetic acid, gave the key intermediate 5-diazobarbituric acid (4) (Carlo *et al* 1952). In another experiment, barbituric acid, (1), was directly transformed, *via* coupling with benzenediazonium chloride, in 57% yields to the coupled product (5) (Kuhling 1972). The acetylation at the 5-position of (1) was achieved in over 80% yields by reaction with phosphorus oxychloride and acetic acid leading to the acetyl derivative (6) [scheme 2].

Interestingly, whilst (4) had an open structure, compounds (5) and (6) possessed pseudo six-membered hydrogen-bonded structures, as evidenced from spectral data.

To provide a substrate that could improve the stacking properties of uracils *via* hydrophobic bonding, the 5,6-cyclotrimethyleneuracil (7), was prepared from 2-carbethoxycyclopentanone by treatment with urea (Shigeo and Fujimura 1962).

Two impediments have to be overcome in order that appropriately modified uracils could be used for the stacking studies. One of these is the differentiation of two amide units present in the parent ring system. This is commonly achieved *via* selective transformation of the one-peptide unit to the corresponding thio compound, which, then, can specifically be linked to the sugar residues giving rise to the nucleoside. To demonstrate the feasibility of this approach, 2-methoxyethanol was transformed to 5-methoxy-ethoxy uracil-2-thione, (8), in modest overall yields. The structural assignment for (8) is fully supported by spectral and analytical data (scheme 3).

The second problem would be the solubilization of the modified uracils in the common solvents needed for further group attachments. It was felt that this could be achieved by attaching a hydrophobic residue to the heterocentres not directly



(i) Urea, dry EtOH, HCl (ii) Aq. NaOH (iii) $ClCH_2COOH$, Na
(iv) MeOH, H_2SO_4 (v) HCOOMe, Na (vi) Thiourea, MeOH

Scheme 3.

involved in the nucleoside formation. Although alkylated uracils have been prepared, the procedures are not well defined and it appears that no single methodology has been identified as generally useful to bring about such changes. In the present work, it was considered feasible that the readily available dimethyl acetal of dimethylformamide, would be a useful reagent to bring about such alkylation. The DMF acetal, was prepared by a modified procedure from DMF in nearly 60% yields. In the preliminary alkylation studies, no effort was made to distinguish the two nitrogen functions that are present in the uracil, since the primary objective was to identify DMF acetal as a reliable alkylating agent and study the scope of its utility. Additionally, since the 1-nitrogen, which is to be linked to the sugar, would already be protected, in such substrates, the alkylation would take place on the 3-nitrogen which is the point that was to be tested.

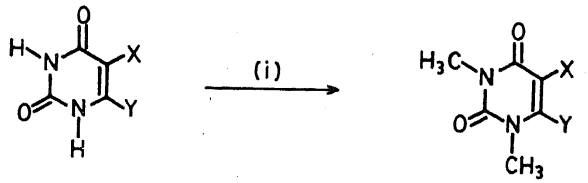
The reaction of uracil (U), 5-bromouracil (9) and the bicyclic uracil (7) with DMF acetal led to the smooth formation of the *bis*-methylated products (10), (11) and (12) in very good yields.

Even substrates carrying highly polar functional groups at uracil 5 and 6 positions underwent smooth alkylation with DMF acetal. Thus, diazobarbituric acid, (4), and the coupled compound (5) led to, in about 60% yields, the expected bisalkylated products (13) and (14). The IR spectrum clearly showed that the diazo grouping present in (4) was retained in this reaction. The NMR spectrum of the alkylated product arising from (5) clearly demonstrated that only the ring nitrogens were alkylated without affecting the other acidic NH function present in the starting material.

An interesting compound was obtained on treatment of 5-acetylbarbituric acid (6), with DMF acetal. The NMR spectrum of the alkylated product clearly showed that 4-methyl groups had been introduced into the substrate, and from the NMR, IR and mass spectra it was concluded that the product obtained in 44% yield was (17), carrying highly polar residues at the 5 and 6 positions of the parent uracil. The formation of (17) from (6) can be readily understood on the basis of enolate alkylation followed by the expected ring 1,3-nitrogen methylation and the insertion of the methyl vinyl ether function to the acidic methyl grouping of the 5-acetyl unit. Compound (17) possessing an extended conjugation and endowed with a number of polar residues, presents itself as an attractive synthon. The alkylation of 5-azauracil, presented interesting possibilities; however, in the event, this compound on treatment with DMF acetal, gave rise to the *bis*-alkylated product (16) in 70% yields. It could be noted that the symmetry of the conjugate base pertaining to the 1- and 5-hydrogens would dictate that alkylation of either of these would lead to the same product (scheme 4).

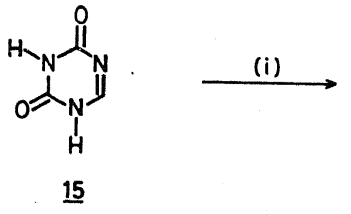
The preferential alkylation of nitrogen over oxygen of the peptide units present in the system show that the conjugate bases of these units rather than the units themselves are involved in the alkylation. The pathway leading to such alkylation with DMF acetal is presented in scheme 5. The present studies have shown that the readily available DMF acetal can be used with confidence for the N-methylation of 1-protected uracils, uracil nucleosides and nucleotides.

The attachment of longer hydrophobic and polar side chains to the uracil system via alkylation was also accomplished in the present work. Thus, the alkylation of 5-azauracil with *n*-butyl bromide in K_2CO_3/DMF gave in over 60% yields, the *bis* alkylated product (18). It is therefore possible to effect alkylation of these nitrogens



A

(U) : X = H, Y = H (10)
(9) : X = Br, Y = H (11)
(7) : X = Y = $(CH_2)_3$ (12)
(4) : X = N_2^+, Y = O^- (13)
(5) : X = N = N-Ph, Y = OH (14)



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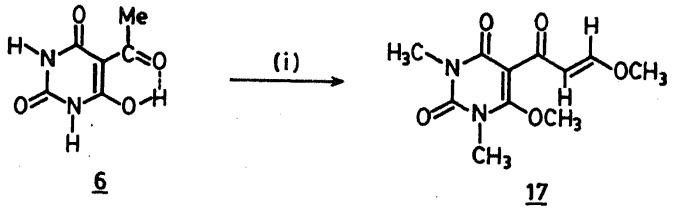

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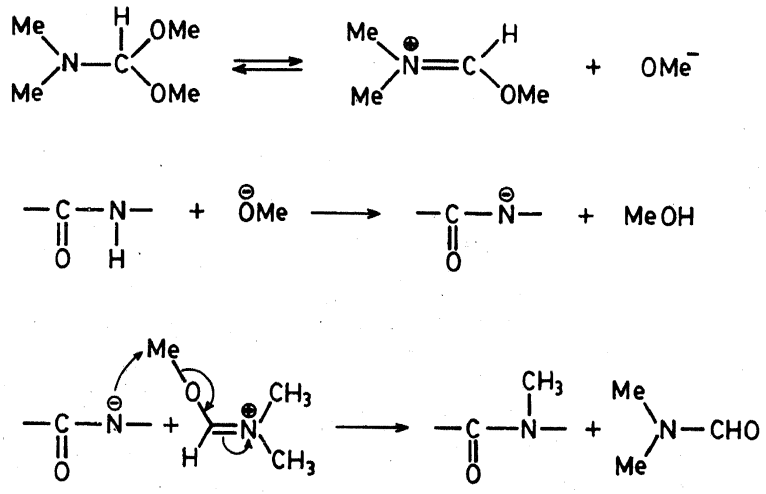
(i) $Me_2NCH(OMe)_2$

Scheme 4.



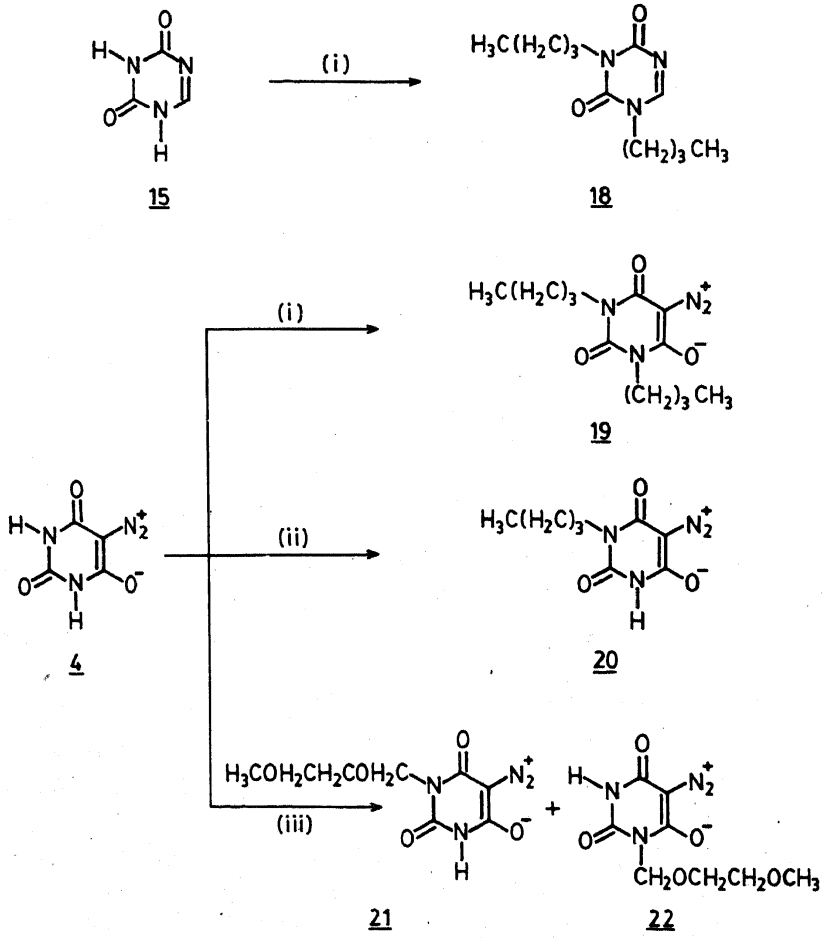
Scheme 5.

with long chain halides leading to the synthesis of nucleotides and nucleic acids having tailor-made hydrophobic qualities. Interestingly, 5-diazobarbituric acid under the same conditions gave, in 65% yields, the *bis*-alkylated product (19); however, when triethylamine was used as base, only the mono-alkylated product was obtained which is tentatively identified as (20). In either case, the diazo unit was retained.

The present work has shown that the polar methoxy ethoxy methyl side chain could also be attached to the uracil frame work. Thus, the reaction of 5-diazobarbituric acid (4), with methoxy ethoxy methyl chloride (MEMCl) in THF and triethylamine, led to the isolation of mono alkylated products (21) and (22) (scheme 6).

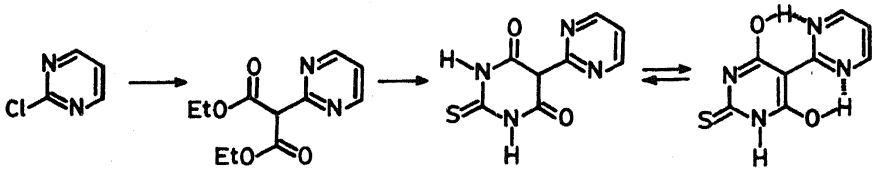
The interesting conclusion, namely that whilst K_2CO_3/DMF promotes *bis*-alkylation, Et_3N/THF results only in mono alkylation, emerges from the above study.

A novel approach to the problem of stacking in the case of uracil explored in the present work was the creation of specifically 5-substituted uracils that would have hydrogen bonding possibilities with the hydroxyl groups arising from the enolization of an appropriately tailored uracil system. It was considered that attachment of the 5-position of the uracil with the 2-position of a pyrimidine unit would lead to a very



(i) n-BuBr, K_2CO_3, DMF (ii) n-BuBr, Et_3N, THF (iii) MEMCl, Et_3N, THF

Scheme 6.



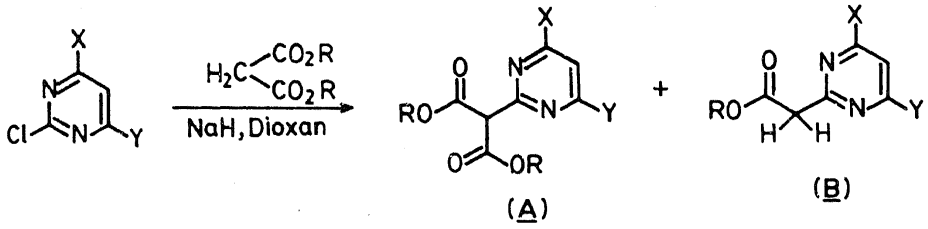
Scheme 7.

attractive structure that could offer hydrogen bonding possibilities with both the nitrogens of the pyrimidine system. This approach is illustrated in scheme 7.

The reaction of 2-chloropyrimidine with the conjugate base of diethyl malonate could be expected to give rise to the adduct, which, on treatment with thiourea, can lead to the desired system. It could be noted that such a species, because of the differentiation of the uracil nitrogens, can be attached to the sugar units by known procedures and, therefore, could readily be adapted into nucleic acids. It was stated earlier that the better stacking profile of purines arises from the presence of the additional aromatic system. Indeed it has been shown that attachment of additional aromatic systems to purines favourably contribute to the stacking profile (Hamilton 1991). In view of this, it could be expected that the *bis*-hydrogen bonded structures, as envisaged in scheme 7 would provide an excellent incentive for the stacking of uracil unit present.

2-Chloropyrimidine, (23) the starting material for the desired malonate alkylation, was prepared by two different pathways in the present work. Malic acid, on reaction with urea in fuming sulphuric acid, afforded uracil which, on treatment with phosphorus oxychloride, yielded in 77%, 2,4-dichloropyrimidine (25), which itself was used in alkylation studies. Compound (25), in turn, could be easily reduced with zinc/ammonium chloride to 2-chloropyrimidine (23) in 56% yields. 2-Chloropyrimidine was also prepared directly from 2-hydroxypyrimidine in good yields by treatment with $PCl_5/POCl_3$. The latter was obtained by reaction of 1,1,3,3-tetraethoxypropane with urea in presence of acid. The 1,1,3,3-tetraethoxypropane used was readily made by reaction of ethyl orthoformate and ethyl vinyl ether in presence of boron trifluoride etherate. 2-Chloro-4,6-dimethylpyrimidine (24) was easily prepared from urea and pentane 1,3-dione- a reaction which resulted in the formation of the 2-hydroxy derivative which, in turn with $POCl_3$, gave the desired compound in excellent yields.

The reaction of 2-chloropyrimidine (23) with the conjugate base of diethylmalonate generated *in situ* with NaH led to, after work up followed by careful chromatography, the expected adduct (26) and the acetate (27) in respectively 23% and 21% yields. The decarboethoxylation associated with the (26)→(27) change most likely occurred during workup, involving evaporation, addition of chilled water and acidification to *p*H 2. Direct acidification to obviate the formation of (27), afforded colloidal suspensions. Interestingly, workup here also gave (26) and (27) in reduced yields. 2-Chloro 4,6-dimethyl pyrimidine, (24), with sodium diethyl malonate gave only 13% of the expected adduct (30) but a vastly enhanced yield of the undesired acetate (31) in 56% yields. The varying yields of the acetate with reference to the expected malonate adduct observed with the three substrates, namely, 2,4-dichloropyrimidine (*vide infra*), 2-chloropyrimidine and 2-chloro-4,6-dimethylpyrimidine, can be attributed to subtle and not so easily discernible factors, either during the course of reaction or during workup.



		(R)	(A)	(B)	(R)	(A)	(B)
(23)	X = Y = H	Et	(26)	(27)	^{t}Bu	(28)	(29)
(24)	X = Y = Me	Et	(30)	(31)	^{t}Bu	(32)	(33)
(25)	X = Cl, Y = H	Et	(34)	(35)	^{t}Bu	(36)	(37)

Scheme 8.

The reaction of 2,4-dichloropyrimidine (25) with the conjugate base of diethyl malonate followed by workup and careful chromatography, led to isolation of two compounds which have been assigned, on the basis of spectral and analytical data, structures (34) and (35). The NMR spectra of these compounds clearly showed that only monoalkylation involving the 2-halogen took place. The expected malonic ester adduct (34) was isolated in 35% yields and the acetate (35) in a modest yield of 8% (scheme 8).

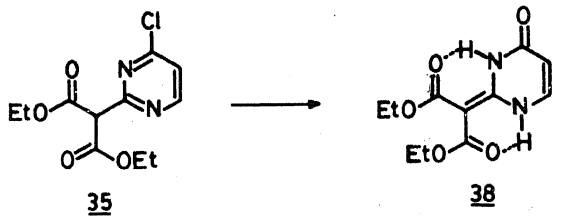
An unexpected transformation of (34) was its slow conversion to (38) on standing at room temperature. The formation of compound (38) could be readily understood on the basis of prototropic shift and hydrolysis of the chlorimine unit. The structural assignment of (38) is fully supported by spectral and analytical data (scheme 9).

Interestingly, although not unexpected, deliberate attempts to hydrolyze (34) → (38), proved infructuous.

A comparison of schemes 7 and 9 is interesting. Whilst the former pertains to routes for a uracil–pyrimidine composite, the latter opens up exciting possibilities for a uracil–uracil tandem duplex. Indeed compound (38) as a synthon, should afford opportunities for the construction of a range of biologically relevant compounds.

A number of experiments were carried with the malonate adducts (26), (30), (34) and urea or thiourea to form the desired uracil-pyrimidine system (scheme 7). Unfortunately, the enhanced reactivity of these systems to undergo degradation in presence of nucleophiles precluded success. Novel and mild methodologies are needed here and endeavours in the direction are being pursued.

The ready availability of the pyrimidine–malonate adducts, revived our interest relating to the recognition of these two entities. The objective here was to sequester malonic acid on polymer immobilized pyrimidine. Earlier endeavours, to prepare either a crystalline 1:1 complex of pyrimidine and malonic acid, or demonstrate their recognition in solution by spectral methods, were not successful and this was attributed to the unfavourable interaction between the pyrimidine 2-H and the CH_2 of malonic acid. As shown in scheme 10, the malonate adducts opened up a route to tethered pyrimidine–malonic acid composites, which are devoid of the unfavourable interaction cited above. The desired di-*t*-butyl malonate ester adducts, identified as precursor to the system envisaged in the scheme 10, were sought along the lines described for the diethylmalonate adducts. The pattern of reactivity was similar to that encounterd earlier in the sense that the reaction of each of the substrates with



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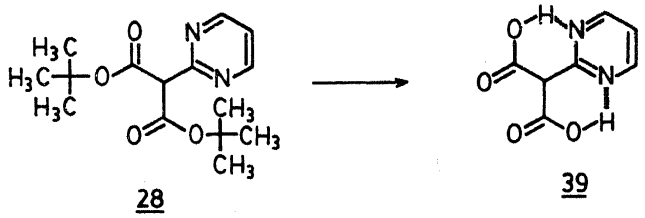
Scheme 9.



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Scheme 10.

di-*t*-butyl malonate – prepared from malonic acid and isobutylene – gave rise to both the malonic ester adduct, and the acetate. The structural assignments for the tertiary butyl malonate ester adducts, namely, (28), (32) and (36) as well as for the acetates (29), (33) and (37) are fully supported by spectral and analytical data (scheme 8). The addition of trifluoroacetic acid to chilled solution of (28), in methylene chloride afforded solutions containing the desired (39) (scheme 10). Rapid and visible decarboxylation ensued on attaining room temperature to afford pyrimidine-2-acetic acid characterized as (27).

Preliminary ^{1}H NMR and thermal osmometric studies of several of the compounds reported here have brought out the dominance of hydrophobic interaction in the enhancement of the stacking profile of uracils. These studies being entirely physicochemical in nature will form a separate publication.

Experimental

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 580 Spectrophotometer either as neat liquids or as thin KBr wafers. NMR spectra were obtained on dilute solutions in $CDCl_3$, CCl_4 or DMSO-d_6 on Hitachi R600 (FT) Spectrometer. The chemical shifts are reported in ppm downfield from internal TMS at 0·00 as standard. Mass spectra were recorded on a Jeol instrument. Elemental analysis were carried out in automatic C,H,N analysers. Silica gel *G* (acme) was used for TLC and column chromatography was done on silica gel (acme, 100–200 mesh) columns, which were invariably made from a slurry in benzene. Reported experimental procedures are provided wherever optimization has been done with respect to yields and reproducibility. Novel procedures for known compounds are, naturally, described.

Preparation of 5-diazobarbituric acid (4) (5-diazo-2,4,6 (1H,3H) pyrimidine trione)

(a) *5-Nitrobarbituric acid (2)*: To an ice cooled and stirred solution of fuming nitric acid (15 ml) in glacial acetic acid (40 ml) was added, over 1 h, barbituric acid

(1), (10 g, 0·078 mol) (Dickey and Gray 1959). The inside temperature was kept below 20°C during addition. The reaction mixture was stirred for 1 h, poured onto crushed ice (~ 80g), filtered, washed with cold water, crystallised from boiling water and dried to give 10·6 g (90%) of 5-nitrobarbituric acid (2), m.p. 178–9°C (lit. m.p. 176°C, Hartmann and Sheppard 1959).

(b) *5-Aminobarbituric acid* (3): To a suspension of 5-nitrobarbituric acid (2) (10 g, 0·065 mol) in conc. HCl (60 ml) at 100°C was gradually added Sn (25g) and HCl (40 ml) over a period of 0·5 h. The reaction mixture was heated on a water bath until no yellow colour persisted. The resulting white solid was taken up in HCl (300 ml), filtered, concentrated to half the volume, left overnight in the refrigerator, the white powdery solid collected, washed with dil. HCl (~ 25 ml), water (~ 100 ml) and dried to give 5·2g (56%) of (3) m.p. > 400°C (lit. m.p. > 400°C, Hartmann and Sheppard 1959).

(c) *5-Diazobarbituric acid* (4): A solution of sodium nitrite (3·73 g, 0·054 mol) in water (30 ml) was added, in drops, over a period of 3·25 h to a stirred suspension of 5-aminobarbituric acid (3) (7·5 g, 0·052 mol) in acetic acid (6 ml). The reaction mixture was left stirred for 4 h, allowed to stand overnight at room temperature, poured onto water (100 ml), heated to boiling, cooled and filtered to give 4·2g (51%) of (4) as yellow shining crystals. m.p. 283–5°C (lit. m.p. 285°C, Carlo *et al* 1952). IR: ν_{max}(KBr) cm^{-1}: 1640 (C=O, *br*), 2185 (diazo), 3290 (–NH). *m/z*: 154 (M^+), 155 ($M^+ + 1$).

The reaction of barbituric acid with benzene diazonium chloride: Isolation of coupled product (5)

A solution of barbituric acid (1) (4·1 g, 0·03 mol) in H_2O:HCl (500:20) was slowly added to phenyl diazonium chloride [prepared at 0°C from aniline (2·8 ml, 0·028 mol) in dil. HCl (7:7) and sodium nitrite (2·4 g, 0·034 mol)]. The reaction mixture was stirred for 5–6 h, left overnight at room temperature, filtered, washed with cold water and dried to give 4·2 g (57%) of (5) as a yellow micro crystalline solid. m.p. 285°C (lit. m.p. 284°C, Kuhling 1972). IR: ν_{max}(KBr) cm^{-1}: 1665 (C = O), 3312 (–NH). *m/z*: 232 (M^+), 233 ($M^+ + 1$).

The reaction of barbituric acid with $POCl_3$–AcOH: Preparation of 5-acetylbarbituric acid (6)

A stirred mixture of barbituric acid (1) (3·0 g, 0·02 mol), AcOH (15 ml, 0·25 mol) and $POCl_3$ (6 ml, 0·063 mol) was held at 130°C for 0·5 h, cooled, poured onto ice (30g), filtered and crystallised from hot water to give 3·2 g, (81%) of 5-acetyl barbituric acid (6). m.p. 297°C (lit. m.p. 297–8°C, Vulfson 1961). IR: ν_{max}(KBr) cm^{-1}: 1610, 1680 (C = O), 3290 (–NH).

Preparation of 5,6-cyclotrimethylene uracil (7)

Urea (4·3 g, 0·713 mol) was added to a solution of 2-carbethoxy cyclopentanone (10·4 g, 0·068 mol), in absolute ethanol (10 ml) admixed with conc. HCl (1 ml). The reaction mixture was refluxed for 2 hours, filtered, the residue taken up in aqueous NaOH (4·4 g, 60 ml), cooled, acidified (*p*H ~ 2) with 6N HCl to give 9·4 g, (87%) of (7) which, on crystallization from EtOH, gave white crystals. m.p. > 300°C (lit. m.p. > 300°C, Shigeo and Fujimura 1962).

m/z: 152 (M^+), 153 ($M^+ + 1$).

Preparation of 5-ethoxymethoxy uracil-2-thione (8)

(a) *Methoxy ethoxy acetic acid*: To a stirred solution of $MeO-CH_2CH_2ONa$ – prepared from Na (2·3 g, 0·1 mol) and $MeO-CH_2CH_2OH$ (30 ml, 0·4 mol) – was added $ClCH_2COOH$ (4·7 g, 0·05 mol). The reaction mixture was refluxed for 2 h, admixed with water, the residue concentrated, acidified to *p*H ~ 2 with 2N H_2SO_4, extracted with ether (3 × 50 ml), dried ($MgSO_4$) and evaporated to give 5.2g (10%) of the acid. b.p. 125–30°C/10 torr.

(b) *Methoxy ethoxy methyl acetate*: To a stirred solution of the above acid (4·2 g, 0·03 mol) in absolute MeOH (20 ml) was added, in drops, conc. H_2SO_4 (0·2 ml). The reaction mixture was stirred overnight, poured onto ice (~ 20g), extracted with benzene (2 × 50 ml), washed with saturated $NaHCO_3$ (2 × 50 ml), dried ($MgSO_4$) and evaporated to give 2·4 g, (52%) of the ester. b.p. 160–5°C/10 torr.

(c) *5-Ethoxy methoxy uracil-2-thione*: A solution of methoxy ethoxy methyl acetate (2·4 g, 0·016 mol) and methyl formate (1·2g. 0·02 mol) was added, in drops, to a stirred suspension of Na (0·230 g, 0·01 mol) in dry ether (10 ml). The reaction mixture was stirred overnight, the ether layer was decanted, and the crude viscous methyl sodio-β-hydroxy-α-ethoxy methoxy acrylate taken up in absolute MeOH (4 ml), admixed with thiourea (1·5g. 0·019 mol) refluxed for 5 h, cooled, filtered, taken up in water (~ 30 ml) and neutralized with 6N HCl (~ 8 ml) to give 0·405g (10%) of (8) as a pale brown solid. m.p. 155°C.
Analysis – Calcd. for $C_7H_{10}N_2O_3S$ (Mol. wt. 202): C, 41·58; H, 4·95; N, 13·86%; Found C, 41·24; H, 4·76; N, 14·02%.
IR: ν_{max}(KBr) cm^{-1}: 1660 (C=O, *br*).
NMR: δ(DMSO-d_6), 60 MHz: 3·5 (*s*, 3H, $-CH_3$), 3·7–3·9 (*t*, 2H, $-O-CH_2CH_2$), 4·0–4·3 (*t*, 2H, $-O-CH_2-CH_2$), 7·1 (*s*, 2H, 2 × NH).
m/z: 202 (M^+).

Preparation of dimethylformamide dimethyl acetal

A mixture of $(MeO)_2SO_2$ (50·4 g, 0·4 mol) and Me_2NCHO (29·2 g, 0·4 mol) was heated at 70°C for 3 h. The resulting faintly yellow liquid was added, in drops, to an ice-cooled and stirred solution of NaOMe – prepared from Na (9·2 g, 0·4 mol) and absolute MeOH (125 ml), left stirred for 1 h and distilled from the white slurry to give 28 g (59%) of dimethyl acetal of dimethylformamide. b.p. 102–3°C/760 torr (lit. b.p. 102–3°C/760 torr, Arnold and Kornilov 1964).

Reaction of uracil with DMF-dimethyl acetal: Isolation of 1,3-dimethyluracil (10)

A stirred mixture of uracil (0·6 g, 0·005 mol), dry DMF (10 ml) and $Me_2NCH(OMe)_2$ (5 ml, 0·037 mol) was refluxed for 8 h, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 50:50 gave 0·605 g (81%) of (10), which on crystallization from benzene:hexane gave white crystals. m.p. 121°C (lit. m.p. 121°C, Yamaguchi *et al* 1976; Denney *et al* 1978; Oglivie *et al* 1979).
TLC: PhH:EtOAc :: 50:50 R_f 0·5
IR: ν_{max}(KBr) cm^{-1}: 1650, 1710 (C=O).
NMR: δ($CDCl_3$), 60 MHz: 3·4 (*s*, 3H, $-N-CH_3$), 3·5(*s*, 3H, $-N-CH_3$), 5·8(*d*, 1H, 5H), 7·4 (*d*, 1H, 6H).

Reaction of 5-bromouracil (9) with DMF - dimethyl acetal: Isolation of 5-bromo-1,3-dimethyluracil (11)

A mixture of 5-bromourcil (1·0 g, 0·005 mol), dry DMF (15 ml) and $Me_2NCH(OMe)_2$ (8 ml, 0·06 mol) was refluxed for 5 h, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 60:40 gave 0·860 g (75%) of (11) which on crystallization from benzene:hexane gave white crystals. m.p. 182–3°C (lit. m.p. 184°C, Wang 1957).
TLC: PhH:EtOAc :: 50:50 R_f 0·5.
IR: ν_{max}(KBr) cm^{-1}: 1650 (C=O, *br*).
NMR: $\delta(CDCl_3)$, 60 MHz: 3·6 (*s, s*, 6H, –N–C<u>H</u>$_3$, –N–C<u>H</u>$_3$), 7·7 (*s*, 1H, 6<u>H</u>).

Reaction of cyclotrimethylene uracil (7) with DMF – dimethyl acetal: Isolation of 1,3-dimethyl cyclotrimethylene uracil (12)

A stirred mixture of cyclotrimethylene uracil (7) (0·608 g, 0·004 mol) and $Me_2NCH(OMe)_2$ (5 ml, 0·036 mol) was refluxed for 2 h, left stirred overnight, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 50:50 gave 0·65 g, (90%) of (12), which on crystallization from ether:hexane gave white crystals. m.p. 84–5°C.
TLC: PhH:EtOAc :: 70:20 R_f 0·5.
Analysis Calcd. for $C_9H_{12}N_2O_2$ (mol. wt. 180): C, 60·0; H, 6·68; N, 15·55%; Found C, 59·73; H, 6·83; N, 15·16%.
IR: ν_{max}(KBr) cm^{-1}: 1650, 1700 (C=O).
NMR: $\delta(CDCl_3)$, 60 MHz: 2·0–2·5 (*q*, 2H, $-CH_2-C\underline{H}_2-CH_2$), 2·7–3·1 (*t*, 4H, $-C\underline{H}_2-CH_2-C\underline{H}_2$) 3·5 (*s, s*, 6H, –N–C<u>H</u>$_3$, –N–C<u>H</u>$_3$).
m/z: 180 (M^+), 181 ($M^+ + 1$).

Reaction of 5-diazobarbituric acid (4) with DMF-dimethyl acetal: Isolation of 1,3-dimethyl-5-diazobarbituric acid (13)

A stirred mixture of diazobarbituric acid (4) (1·0 g, 0·006 mol) and $Me_2NCH(OMe)_2$ (8 ml, 0·06 mol) was refluxed for 3 h, left stirred overnight, solvents evaporated and the residue chromatographed on silica gel. Elution with benzene gave 0·75 g (64%) of (13) which on crystallization from benzene:hexane gave pale yellow crystals. m.p. 164°C (lit. m.p. 164°C, Fischer *et al* 1952).
TLC: PhH:EtOAc :: 70:30 R_f 0·7.
Analysis – Calcd. for $C_6H_6N_4O_3$ (Mol. wt. 182): C, 39·56; H, 3·29; N, 30·76%; Found C, 39·70; H, 3·84; N, 30·48%.
IR: ν_{max}(KBr) cm^{-1}: 1650, 1710 (C=O), 2120 (diazo).
NMR: $\delta(CDCl_3)$, 60 MHz: 3·4 (*s*, 6H, –N–C<u>H</u>$_3$, –N–C<u>H</u>$_3$).
m/z: 182 (M^+), 154 ($M^+ - N_2$).

Reaction of (5) with $Me_2NCH(OMe)_2$: Isolation of (14)

A stirred mixture of (5) (0·928 g, 0·004 mol), dry DMF (15 ml) and $Me_2NCH(OMe)_2$ (15 ml, 0·112 mol) was refluxed for 10 h, cooled, evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 80:20 gave 0·542 g (52%) of (14)

which on crystallization from chloroform:hexane gave a yellow solid. m.p. 235°C.
TLC: PhH:EtOAc :: 70:30 R_f 0·4.
Analysis Calcd. for $C_{12}H_{12}N_4O_3$ (Mol. wt. 260): C, 55·38; H, 4·61; N, 21·53%; Found C, 55·24; H, 5·03; N, 21·36%.
IR: ν_{max}(KBr) cm^{-1}: 1625, 1660, 1705 (C=O).
NMR: δ($CDCl_3$), 60 MHz: 3·5 (*s*, *s*, 6H, –N–C<u>H</u>$_3$, –N–C<u>H</u>$_3$) 7·3–7·7 (*m*, 5H, aromatic).
m/z: 260 (M^+).

Preparation of 5-azauracil (<u>15</u>)

(a) *5-Azauracil-urea adduct*: A mixture of urea (15 g, 0·25 mol), triethyl orthoformate (40 ml, 0·27 mol) and acetic anhydride (15 ml) was held at 120°C until vigorous reaction set in (5–10 min). The resulting slurry was cooled, then refluxed for 1 h, cooled, filtered, washed with ethanol and dried to give 10·6 g (76%) of the urea adduct. m.p. 231–2°C (lit. m.p. 234–5°C, Piskala and Gut 1963).
(b) *5-Azauracil*: A mixture of the urea adduct (19·6 g, 0·055 mol) and conc. HCl (12 ml) was held at 100°C for 0·25 h, the resulting clear solution cooled, diluted with ethanol (50 ml), refrigerated for 0·25 h, filtered, washed with ethanol, dried and recrystallised from water (~ 50 ml) to give 4·2 g (68%) of (<u>15</u>). m.p. 280°C (lit. m.p. 282°C, Piskala and Gut 1963).
m/z: 113 (M^+).

Reaction of 5-azauracil (<u>15</u>) with DMF-dimethyl acetal: Isolation of 5-aza-1,3-dimethyluracil (<u>16</u>)

A stirred mixture of 5-azauracil (<u>15</u>) (0·565 g, 0·005 mol) and $Me_2NCH(OMe)_2$ (5 ml, 0·036 mol) was refluxed for 3 h, left stirred overnight, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 30:70 gave 0·494 g (70%) of (<u>16</u>) which on crystallization from benzene gave white crystals. m.p. 164°C (lit. m.p. 164°C, Chung *et al* 1979).
TLC: PhH:EtOAc :: 50:50 R_f 0·4.
Analysis Calcd. for $C_5H_7N_3O_2$ (Mol. wt. 141): C, 42·55; H, 4·96; N, 29·78%; Found C, 43·02; H, 4·67; N, 30·41%.
IR: ν_{max}(KBr) cm^{-1}: 1675, 1725 (C=O).
NMR: δ($CDCl_3$), 60 MHz: 3·5 (*s*, *s*, 6H, –N–C<u>H</u>$_3$, –N–C<u>H</u>$_3$) 8·1 (*s*, 1H, 6<u>H</u>).
m/z: 141 (M^+).

Reaction of 5-acetylbarbituric acid (<u>6</u>) with DMF-dimethyl acetal: Isolation of (<u>17</u>)

A stirred mixture of 5-acetylbarbituric acid (<u>6</u>) (0·845 g, 0·005 mol) and $Me_2NCH(OMe)_2$ (8 ml, 0·06 mol) was refluxed for 3 h, left stirred overnight, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 90:10 gave 0·556 g, (44%) of (<u>17</u>) as pale yellow solid. m.p. 192°C.
TLC: EtOAc R_f 0·4.
IR: ν_{max}(KBr) cm^{-1}: 1675, 1725 (C=O).
NMR: δ($CDCl_3$), 60 MHz: 3·2 (*s*, 3H, –N–C<u>H</u>$_3$), 3·4 (*s*, 3H, –N–C<u>H</u>$_3$), 3·5 (*s*, 6H, O–C<u>H</u>$_3$, –O–C<u>H</u>$_3$), 6·9–7·2 (*d*, 1H, –CO–C<u>H</u>), 7·9–8·3 (*d*, 1H, –CO–CH = C<u>H</u>).
m/z: 254 (M^+).

*Reaction of 5-azauracil (15) with n-bromobutane: Isolation of 1,3-di-n-*butyl-5-azauracil (*18*)

To a stirred solution of 5-azauracil (15) (1·5 g, 0·013 mol) in dry DMSO (20 ml) was added anhydrous K_2CO_3 (7·0 g, 0·05 mol) followed by, in drops. *n*-bromobutane (6·85 g, 0·05 mol). The reaction mixture was left stirred for 48 h, filtered, solvents evaporated *in vacuo*, the residue poured onto water (~ 50 ml), extracted with CH_2Cl_2 (4 × 40 ml) washed with water (5 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 50:50 gave 1·9 g (64%) of (18). m.p. 42°C.
TLC: PhH:EtOAc :: 50:50 R_f 0·5
Analysis Calcd. for $C_{11}H_{19}N_3O_2$ (Mol. wt. 225): C, 58·66; H, 8·44; N, 18·66%; Found C, 57·98; H, 8·02; N, 18·34%.
IR: ν_{max}(KBr) cm^{-1}: 1640, 1700, 1750 (C=O).
NMR: $\delta(CDCl_3)$, 60 MHz: 0·94–1·02 (*t*, 6H, $-N(CH_2)_3-C\underline{H}_3$, $-N(CH_2)_3-C\underline{H}_3$), 1·26–1·88 (*m*, 8H, $-N-CH_2-C\underline{H}_2-C\underline{H}_2$, $-N-CH_2-C\underline{H}_2-C\underline{H}_2$), 3·75–3·99 (*t*, 4H, $-N-C\underline{H}_2$, $-N-C\underline{H}_2$), 7·2 (*s*, 1H, 6<u>H</u>).
m/z: 225 (M^+).

Reaction of 5-diazobarbituric acid (4) with n-bromobutane in K_2CO_3: Isolation of 1,3-di-n-butyl-5-diazobarbituric acid (19)

To a stirred solution of diazobarbituric acid (4) (0·31 g, 0·02 mol) in dry DMF (15 ml) was added anhydrous K_2CO_3 (2·5 g, 0·018 mol) followed by, in drops, the addition of *n*-bromobutane (2·74 g, 0·02 mol). The reaction mixture was stirred for 2 h, filtered, solvents evaporated *in vacuo* and the residue was poured onto water (~ 20 ml), extracted with EtOAc (4 × 25 ml), washed with water (3 × 25 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 50:50 gave 0·348 g (65%) of (19). b.p. 195–200°C/0·5 torr.
TLC: PhH:EtOAc : 50:50 R_f 0·5
Analysis Calcd. for $C_{12}H_{18}N_4O_3$ (Mol. wt. 266): C, 54·13; H, 6·76; N, 21·05%; Found C, 54·76; H, 6·44; N, 21·34%
IR: ν_{max}(KBr) cm^{-1}: 1680, 1745 (C=O), 2195 (diazo).
NMR: $\delta(CDCl_3)$, 60 MHz: 0·9–1·1 (*t*, 6H, $-N(CH_2)_3-C\underline{H}_3$, $-N(CH_2)_3-C\underline{H}_3$). 1·2–1·8 (*m*, 8H, $-N-CH_2-C\underline{H}_2-C\underline{H}_2$, $-N--CH_2-C\underline{H}_2-C\underline{H}_2$), 3·9 (*t*, 4H, $-N-C\underline{H}_2$, $-N-C\underline{H}_2$).
m/z: 266 (M^+).

Reaction of 5-diazobarbituric acid (4) with n-bromobutane in Et_3N: Isolation of (20)

To a stirred solution of diazobarbituric acid (4) (0·770 g, 0·005 mol) in dry THF (40 ml) was added, in drops, Et_3N (2·8 g, 0·027 ml) followed by *n*-bromobutane (2·7 g, 0·02 mol). The reaction mixture was left stirred for 20 h, solvents evaporated, the residue poured onto water (~ 40 ml), extracted with EtOAc (3 × 50 ml), washed with water (2 × 50 ml), dried ($MgSO_4$), evaporated *in vacuo* and the residue chromatographed on silica gel. Elution with PhH:EtOAc ::20:80 gave 0·210 g (21%) of (20). m.p. 110°C.
TLC:EtOAc R_f 0·5

Analysis Calcd. for $C_8H_{10}N_4O_3$ (Mol. Wt. 210): C, 45·71; H, 4·76; N, 26·66%; Found C, 45·36; H, 4·47; N, 26·66%.
IR: ν_{max}(KBr) cm^{-1}: 1650, 1720, 1750 (C=O), 2200 (diazo), 3220 (–NH).
NMR: δ($CDCl_3$), 60 MHz: 0·9–1·1 (*t*, 3 H, $-C\underline{H}_3$), 1·23–1·9 (*m*, 4 H, $C\underline{H}_2-C\underline{H}_2-CH_3$), 3·6–4·0 (*t*, 2 H, $-N-C\underline{H}_2$), 8·9 (*s*, 1H, N$\underline{H}$).
m/z: 210 (M^+), 195 ($M^+ - CH_3$).

Reaction of 5-diazobarbituric acid (4) with methoxy ethoxy methyl chloride (MEMCl): Isolation of (21) and (22)

To a stirred solution of 5-diazobarbituric acid (4) (0·310 g, 0·002 mol) in dry THF (~ 20 ml) was added, in drops, dry Et_3N (1·5 g, 0·014 mol) followed by MEMCl (2·42 g, 0·01 mol). The reaction mixture was left stirred for 20 h, solvents evaporated, *in vacuo*, the residue poured onto water (30 ml), extracted with CH_2Cl_2 (3 × 50 ml), washed with water (2 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::50:50 gave 0·4 g (82%) of (21) and (22). b.p. 130–135°C/0·5 torr.
TLC: PhH:EtOAc : 50:50 R_f 0·6.
IR: ν_{max}(KBr) cm^{-1}: 1690, 1750 (C=O), 2190 (diazo).
NMR: δ($CDCl_3$), 60 MHz: 3·4 (*s*, 6H, $-O-C\underline{H}_3$, $-O-C\underline{H}_3$), 3·5–4·0 (*m*, 8H, $-O-C\underline{H}_2-C\underline{H}_2-OCH_3$, $-O-C\underline{H}_2-C\underline{H}_2-OCH_3$), 5·0 (*d*, 2H, –N$\underline{H}$, –N$\underline{H}$), 5·5 (*s*, 4H, $-N-C\underline{H}_2$, $-N-C\underline{H}_2$).

Preparation of 2,4-dichloropyrimidine (25)

(a) *Uracil*: To mechanically stirred ice-cooled fuming sulphuric acid (15% SO_3, 40 ml) was added, over a period of 0·5 h, maintaining the temperature below 0°C, urea (10 g, 0·166 mol). Malic acid (10 g, 0·07 mol) was then added in one lot, the reaction mixture heated on a water bath for 1 h, cooled, poured onto crushed ice (~ 120 g), filtered, washed with cold water, crystallized from boiling water and dried at 100°C, to give 4·2 g (50%) of uracil. m.p. > 300°C (lit. m.p. > 300°C, Davidson and Baudish 1926)
(b) *2,4-Dichloropyrimidine (25)*: A suspension of uracil (8 g, 0·071 mol) in $POCl_3$ (40 ml) was refluxed for 3 h. The resulting brown solution was cooled to room temperature, evaporated *in vacuo*, admixed with ether (25 ml), poured onto crushed ice (~ 70 g), extracted with ether (4 × 50 ml), washed with saturated sodium carbonate (2 × 50 ml), dried, evaporated and residue on crystallization from hexane gave 8·2 g (77%) of (25). m.p. 60–61°C (lit. m.p. 61–61·5°C, Gosalapoff and Roy 1961).
NMR: δ($CDCl_3$), 60 MHz: 7·3 (*d*, 1H, 5$\underline{H}$), 8·6 (*d*, 1H, 6$\underline{H}$).

Preparation of 2-chloropyrimidine (23)

(a) *1,1,3,3-tetraethoxypropane*: Under nitrogen, ethyl vinyl ether (18 g, 0·025 mol) was added, in drops, to a stirred solution of triethyl orthoformate (74 g, 0·5 mol) and $BF_3.Et_2O$ (0·35 ml). The reaction mixture was left stirred for 1 h admixed with anhyd. sodium carbonate (2·5 g, 0·023 mol, left stirred for an additional 3 h, filtered and evaporated to give 44 g (80%) of 1,1,3,3-tetraethoxypropane. b.p. 84–5°C/6 torr (lit. b.p. 87–8°C/6 torr, Protopopova and Skolidinov 1951).

(b) *2-Hydroxypyrimidine hydrochloride*: 1,1,3,3-Tetraethoxypropane (17·5 g, 0·079 mol) was added, in drops, maintaining the temperature below 20°C to a stirred solution of urea (4·5 g, 0·075 mol) in absolute ethanol:conc. HCl (30:15 ml). The reaction mixture was left stirred for 3–4 h, cooled in ice, filtered, dried and crystallised from ethanol:ether to give 5·8 g (59%) of 2-hydroxypyrimidine hydrochloride. m.p. 208–9°C (lit. m.p. 210°C, Hunt *et al* 1959).
(c) *2-Chloropyrimidine* (23): A suspension of 2-hydroxypyrimidine hydrochloride (5·3 g, 0·040 mol), PCl_5 (15 g, 0·072 mol) and $POCl_3$ (4 ml) was refluxed for 1 h, the resulting brown solution cooled to rt, evaporated *in vacuo*, admixed with ether (15 ml), poured onto crushed ice (~ 60 g) adjusted to *p*H ~ 8 with aqueous NaOH, extracted with ether (4 × 50 ml), dried, evaporated and the residue on crystallization from hexane gave 3·4 g (74%) of (24). m.p. 64–5°C (lit. m.p. 65°C, Matsukawa and Bohta 1950)
NMR: $\delta(CDCl_3)$, 60 MHz: 7·3 (*t*, 1H, 5H) 8·6 (*d*, 2H, 4H, 6H).

Reaction of 2,4-dichloropyrimidine with Zn and NH_4Cl: Preparation of 2-chloropyrimidine (23)

A mixture of 2,4-dichloropyrimidine (25) (5·1 g, 0·034 mol), NH_4Cl (1·32 g, 0·024 mol), H_2O (15 ml) and zinc dust (6·66 g, 0·0102 mol) was refluxed for 1 h. The clear solution was cooled to 70°, filtered, the residue washed with acetone (5 ml), chloroform (5 × 25 ml), the organic extract dried, evaporated and crystallized from hexane to give 2·2 g (56%) of (23). m.p. 63–4°C (lit. m.p. 64°C, Gosalopoff and Roy 1961)
NMR: $\delta(CDCl_3)$, 60 MHz: 7·3 (*t*, 1H, 5H) 8·6 (*d*, 2H, 4H, 6H).

Preparation of 2-chloro-4,6-dimethylpyrimidine (24)

(a) *2-Hydroxy-4,6-dimethylpyrimidine hydrochloride*: 2,4-Pentanedione (7·5 g, 0·075 mol) was added, in drops, to a stirred solution of urea (4·5 g, 0·075 mol) in absolute EtOH:HCl (60:12 ml) at room temperature. The reaction mixture was left stirred for 8 h, cooled, filtered, and dried to give 9·0 g (76%) of 2-hydroxy-4,6-dimethylpyrimidine hydrochloride. m.p. 268°C (dec) (lit. m.p. 270°C dec, Matsukawa and Bohta 1950)
(b) *2-Chloro-4,6-dimethylpyrimidine* (24): A suspension of 2-hydroxy-4,6-dimethylpyrimidine hydrochloride (8 g, 0·05 mol) and $POCl_3$ (40 ml) was refluxed for 12 h, cooled to room temperature, evaporated *in vacuo*, admixed with ether (50 ml), poured onto crushed ice (~ 70 g), adjusted to *p*H ~ 8 with aqueous NaOH, extracted with ether (4 × 60 ml), dried and evaporated. The residue on crystallisation from hexane gave 6·2 g, (87%) of (25). m.p. 38°C (lit. m.p. 38°C, Matsukawa and Bohta 1950)
NMR: $\delta(CDCl_3)$, 60 MHz: 2·5 (*s*, 6H, 2 × CH_3), 7·0 (*s*, 1H, 5H).

Reaction of 2-chloropyrimidine (23) *with diethyl-malonate: Isolation of the adduct* (26) *and acetate* (27)

Under nitrogen, to a stirred solution of diethyl malonate (1·1 g, 0·068 mol) in dry dioxan (30 ml) was added NaH (0·350 g, 50% oil dispersion), followed by, in drops, a solution of (23) (0·800 g, 0·007 mol) in dry dioxan (10 ml). The mixture was refluxed for 8 h, solvents evaporated, the residue poured onto ice-water (~ 30 ml), acidified to *p*H ~ 2 with 2N H_2SO_4, extracted with CH_2Cl_2 (3 × 50 ml), washed with saturated $NaHCO_3$ (2 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed

on silica gel. Elution with PhH:EtOAc : 90:10 gave 0·370 g (23%) of (26). b.p. 125–130°C/0·5 torr.
TLC: PhH:EtOAc : 80:20, R_f 0·7.
Analysis Calcd. for $C_{11}H_{14}N_2O_4$ (Mol. wt. 238): C, 55·46; H, 5·88; N, 11·76%. Found C, 55·86; H, 6·01; N, 12·01%.
IR: ν_{max}(neat) cm^{-1}: 1750 (ester)
NMR: $\delta(CCl_4)$, 60 MHz: 1·2–1·5 (*t*, 6H, $-CH_2\underline{CH_3}$, $-CH_2\underline{CH_3}$), 4·1–4·5 (*q*, 4H, $-\underline{CH_2}-CH_3$, $-\underline{CH_2}CH_3$), 5·0 (*s*, 1H, –C–C<u>H</u>), 7·3 (*t*, 1H, 5<u>H</u>), 8·7 (*d*, 2H, 4<u>H</u>, 6<u>H</u>).
m/z: 238 (M^+), 239 ($M^+ + 1$).
Further elution with PhH:EtOAc :: 60:40 gave 0·240 g (21%) of the acetate (27). b.p. 100–2°C/4 torr (lit. b.p. 96–8°C/3 torr, Brown and Warring 1973)
TLC: PhH:EtOAc :: 80:20 R_f 0·3.
Analysis Calcd. for $C_8H_{10}N_2O_2$ (Mol. wt. 166): C, 57·83; H, 6·02; N, 16·86%; Found C, 57·76; H, 6·01; N, 16·55%.
IR: ν_{max}(neat) cm^{-1}: 1750 (ester).
NMR: $\delta(CCl_4)$, 60 MHz: 1·2–1·5 (*t*, 3H, $-CH_2-\underline{CH_3}$), 4·0 (*s*, 2H, –C–C<u>H</u>$_2$), 4·1–4·5 (*q*, 2H, $-\underline{CH_2}-CH_3$), 7·3 (*t*, 1H, 5<u>H</u>), 8·8 (*d*, 2H, 4<u>H</u>, 6<u>H</u>).
m/z: 166 (M^+), 167 ($M^+ + 1$).

Reaction of 2-chloro-4,6-dimethylpyrimidine (24) with diethyl malonate: Isolation of adduct (30) and acetate (31)

Under nitrogen, to a stirred solution of diethyl malonate (3·2 g, 0·02 mol) in dry dioxan (50 ml) was added NaH (0·960 g, 50% oil dispersion) followed by, in drops, a solution of (24) (2·84 g, 0·02 mol) in dry dioxan (25 ml). The mixture was refluxed for 8 h, solvents evaporated, the residue poured onto ice-water (~ 60 ml), acidified to *p*H ~ 2 with 2N H_2SO_4, extracted with CH_2Cl_2 (4 × 50 ml), washed with saturated $NaHCO_3$ (3 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 90:10 gave 0·300 g (11%) of unchanged (24). Further elution with PhH:EtOAc :: 80:20 gave 0·615 g (13%) of (30). b.p. 140°C/1·0 torr.
TLC: PhH:EtOAc :: 70:30 R_f 0·6.
Analysis Calcd. for $C_{13}H_{18}N_2O_4$ (Mol. wt. 266): C, 58·64; H, 6·76; N, 10·52%; Found C, 58·95; H, 6·86; N, 11·29%.
IR: ν_{max}(neat) cm^{-1}: 1750 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·3–1·6 (*t*, 6H, $-CH_2-\underline{CH_3}$, $-CH_2-\underline{CH_3}$), 2·6 (*s*, 6H, 4 <u>Me</u>, 6 <u>Me</u>), 4·2–4·4 (*q*, 4H, $-\underline{CH_2}-CH_3$, $-\underline{CH_2}-CH_3$), 4·9 (*s*, 1H, –C–C<u>H</u>), 7·0 (*s*, 1H, 5<u>H</u>).
m/z: 266 (M^+), 267 ($M^+ + 1$).
Further elution with PhH:EtOAc :: 30:70 gave 1·945 g (56%) of (31). m.p. 65°C (lit. m.p. 65°C, Mamaev and Zagulyaeva 1967).
TLC: PhH:EtOAc :: 70:30 R_f 0·3.
Analysis Calcd. for $C_{10}H_{14}N_2O_2$ (Mol. wt. 194): C, 61·85; H, 7·2; N, 14·43%; Found C, 61·96; H, 7·56; N, 14·55%.
IR: ν_{max}(KBr) cm^{-1}: 1745 (ester).
NMR: $\delta(CCl_4)$, 60 MHz: 1·3–1·6 (*t*, 3H, $-CH_2-\underline{CH_3}$), 2·5 (*s*, 6H, 4<u>Me</u>, 6<u>Me</u>), 3·9 (*s*, 2H, –C–C<u>H</u>$_2$), 4·1–4·5 (*q*, 2H, $-\underline{CH_2}-CH_3$), 6·9 (*s*, 1H, 5<u>H</u>).
m/z: 194 (M^+), 195 ($M^+ + 1$).

Reaction of 2,4-dichloropyrimidine (25) with diethyl malonate: Preparation of the mono adduct (34) and acetate (35)

Under nitrogen, to a stirred solution of diethyl malonate (3·2 g, 0·02 mol), in dry dioxan (50 ml) was added NaH (0·960 g, 50% oil dispersion) followed by, in drops, a solution of (25) (2·98 g, 0·02 mol) in dry dioxan (25 ml). The mixture was refluxed for 8 h, evaporated, the residue poured onto ice-water (50 ml), made acidic to $pH \sim 2$ with 2N H_2SO_4, extracted with CH_2Cl_2 (4 × 50 ml), washed with saturated $NaHCO_3$ (3 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 90:10 gave 1·9 g (35%) of (34). b.p. 175–80°C/0·8 torr.
TLC: PhH:EtOAc :: 90:10 R_f 0·7.
Analysis Calcd. for $C_{11}H_{13}ClN_2O_4$ (Mol. wt. 272): C, 48·44; H, 4·77; N, 10·27%; Found C, 47·95; H, 4·78; N, 10·64%.
IR: ν_{max}(neat) cm^{-1}: 1750 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·3–1·6 (*t*, 6H, $-CH_2-C\underline{H}_3$, $-CH_2-C\underline{H}_3$), 4·2–4·6 (*q*, 4H, $-C\underline{H}_2-CH_3$, $-C\underline{H}_2CH_3$), 4·7 (*s*, 1H, $-C-C\underline{H}$), 7·6 (*d*, 1H, 5H), 8·7 (*d*, 1H, 6H).
m/z: 272 (M^+), 274 ($M^+ + 2$).
Further elution with PhH:EtOAc :: 80:20 gave 0·310 g (8%) of (35). m.p. 208°C.
TLC: PhH:EtOAc :: 90:10 R_f 0·5.
Analysis Calcd. for $C_8H_9ClN_2O_2$ (Mol. wt. 200): C, 47·88; H, 4·48; N, 13·96%; Found C, 47·61; H, 4·44; N, 14·64%.
IR: ν_{max}(KBr) cm^{-1}: 1740 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·3–1·7 (*t*, 3H, $-CH_2-C\underline{H}_3$), 4·0 (*s*, 2H, $-C-C\underline{H}_2$), 4·1–4·6 (*q*, 2H, $-C\underline{H}_2-CH_3$), 7·5 (*d*, 1H, 5H), 8·6 (*d*, 1H, 6H).

Hydrolysis and isomerization of adduct (34): Isolation of uracil (38)

When a pure sample of (34) was allowed to stand at room temperature for several days it was slowly transformed to the crystalline product (38). m.p. 155–6°C.
TLC: PhH:EtOAc :: 70:30 R_f 0·4.
Analysis Calcd. for $C_{11}H_{14}N_2O_5$ (Mol. wt. 254): C, 51·96; H, 5·51; N, 11·02%; Found C, 51·54; H, 5·32; N, 10·74%.
IR: ν_{max}(KBr) cm^{-1}: 1640, 1690 (ester), 3300 (–NH).
NMR: $\delta(CDCl_3)$, 60 MHz (20 ppm): 1·2–1·6 (*t*, 6H, $-CH_2-C\underline{H}_3$, $-CH_2-C\underline{H}_3$), 4·2–4·6 (*q*, 4H, $-C\underline{H}_2-CH_3$, $-C\underline{H}_2-CH_3$), 6·6 (*d*, 1H, 5H), 7·1 (*d*, 1H, 6H), 10·2 (*s*, 1H, –NH), 12·1 (*s*, 1H, –NH).
m/z; 254 (M^+).

Reaction of 2-chloropyrimidine (23) with di-t-butyl malonate: Isolation of the adduct (28) and acetate (29)

Under nitrogen, to a stirred solution of di-*t*-butyl malonate (4·75 g, 0·0219 mol) in dry dioxan (70 ml) was added NaH (0·960 g, 50% oil dispersion), followed by, in drops, a solution of (23) (2·5 g, 0·0218 mol) in dry dioxan (30 ml). The mixture was refluxed for 8 h, solvents evaporated, the residue poured onto ice-water (~ 50 ml), acidified to $pH \sim 2$ with 2N H_2SO_4, extracted with EtOAc (4 × 50 ml), washed with saturated $NaHCO_3$ (3 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 90:10 gave 2·4 g (36%) of (28). b.p. 175–80°C/0·8 torr.

TLC: PhH:EtOAc :: 70:30 R_f 0·7.
Analysis Calcd. for $C_{15}H_{22}N_2O_4$ (Mol. wt. 294): C, 61·22; H, 7·48; N, 9·52%; Found C, 60·99; H, 7·78; N, 9·97%.
IR: ν_{max}(neat) cm^{-1}: 1750 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·6 (*s*, 18H, $-(C\underline{H}_3)_3$, $-C-(C\underline{H}_3)_3$), 5·1 (*s*, 1H, $-C-C\underline{H}$), 7·4 (*t*, 1H, 5H), 8·8 (*d*, 2H, 4H, 6H).
m/z: 294 (M^+).
Further elution with PhH:EtOAc :: 50:50 gave 0·240 g (56%) of (29). m.p. 63–4°C.
TLC: PhH:EtOAc :: 70:30 R_f 0·3.
Analysis Calcd. for $C_{10}H_{14}N_2O_2$ (Mol. wt. 194): C, 61·85; H, 7·21; N, 14·43%; Found C, 62·36; H, 6·83; N, 15·02%.
IR: ν_{max}(KBr) cm^{-1}: 1740 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·6 (*s*, 9H, $-C-(C\underline{H}_3)_3$), 3·9 (*s*, 2H, $-C-C\underline{H}_2$), 7·3 (*t*, 1H, 5H), 8·7 (*d*, 2H, 4H, 6H).

Reaction of 2-chloro-4,6-dimethylpyrimidine (24) with di-t-butyl malonate: Isolation of adduct (32) and acetate (33):

Under nitrogen, to a stirred solution of di-*t*-butyl malonate (4·32 g, 0·02 mol) in dry dioxan (50 ml) was added NaH (0·960 g, 50% oil dispersion) followed by, in drops, a solution of (24) (2·84 g, 0·02 mol) in dry dioxan (25 ml). The mixture was refluxed for 8 h, solvents evaporated, residue poured onto ice-water (~ 50 ml), acidified to *p*H ~ 2 with 2N H_2SO_4, extracted with EtOAc (4 × 50 ml), washed with saturated $NaHCO_3$ (4 × 50 ml), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 95:5 gave 0·400 g (14%) of unchanged (24).
TLC: PhH:EtOAc :: 95:5 R_f 0·7.
Further elution with PhH:EtOAc :: 80:20 gave 1·2 g (22%) of (32). m.p. 80°C.
TLC: PhH:EtOAc :: 95:5 R_f 0·5.
Analysis Calcd. for $C_{17}H_{26}N_2O_4$ (Mol. wt. 322): C, 63·35; H, 8·07; N, 8·69%; Found C, 63·25; H, 7·66; N, 8·35%.
IR: ν_{max}(KBr) cm^{-1}: 1740 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·6 (*s*, 18H, $-C-(C\underline{H}_3)_3$, $-C-(C\underline{H}_3)_3$), 2·5 (*s*, 6H, 4 Me, 6 Me), 4·9 (*s*, 1H, $-C-C\underline{H}$), 7·0 (*s*, 1H, 5H). *m/z*: 322 (M^+), 323 ($M^+ + 1$).
Further elution with PhH:EtOAc :: 50:50 gave 0·230 g (6%) of (33). b.p. 140°C/4·0 torr.
TLC: PhH:EtOAc :: 95:5 R_f 0·3.
Analysis Calcd. for $C_{12}H_{18}N_2O_2$ (Mol. wt. 222): C, 64·86; H, 8·10; N, 12·61%; Found C, 64·74; H, 7·76; N, 12·72%.
IR: ν_{max}(neat) cm^{-1}: 1745 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·5 (*s*, 9H, $-C-(C\underline{H}_3)_3$), 2·5 (*s*, 6H, 4 Me, 6 Me), 3·9 (*s*, 2H, $-C-C\underline{H}_2$), 6·9 (*s*, 1H, 5H).
m/z: 222 (M^+).

Reaction of 2,4-dichloropyrimidine (25) with di-t-butyl malonate: Isolation of mono adduct (36) and acetate (37):

Under nitrogen, to a stirred solution of di-*t*-butyl malonate (1·08 g, 0·005 mol) in dry dioxan (25 ml) was added NaH (0·240 g, 50% oil dispersion) followed by, in drops, a solution of (25) (0·745 g, 0·005 mol) in dry dioxan (10 ml). The mixture was refluxed for 8 h, solvents evaporated, the residue poured onto ice-water (~ 25 ml), acidified to

*p*H ~ 2 with 2N H_2SO_4, extracted with EtOAc (3 × 50 ml), washed with saturated $NaHCO_3$ (3 × 50 ml), dried $(MgSO)_4$, evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc :: 90:10 gave 0·325 g (20%) of (36). m.p. 93–94°C.
TLC: PhH:EtOAc :: 90:10 R_f 0·7.
Analysis Calcd. for $C_{15}H_{21}ClN_2O_4$ (Mol. wt. 328): C, 54·79; H, 6·39; N, 8·52%; Found C, 55·12; H, 6·65; N, 8·39%.
IR: ν_{max}(KBr) cm^{-1}: 1720 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·5 (*s*, 18 H, $-C-(C\underline{H}_3)_3$, $-C-(C\underline{H}_3)_3$), 4·8 (*s*, 1 H, $-C-C\underline{H}$), 7·6 (*d*, 1 H, 5H), 8·7 (*d*, 1 H, 6H).
m/z: 328 (M^+).
Further elution with PhH:EtOAc :: 50:50 gave 0·198 g (17%) of (37). b.p. 180°C/4·0 torr.
TLC: PhH:EtOAc :: 90:10 R_f 0·3.
Analysis Calcd. for $C_{10}H_{13}ClN_2O_2$ (Mol. wt. 228): C, 52·51; H, 5·68; N, 12·25%; Found C, 51·86; H, 5·34; N, 12·72%.
IR: ν_{max}(KBr) cm^{-1}: 1740 (ester).
NMR: $\delta(CDCl_3)$, 60 MHz: 1·6 (*s*, 9 H, $-C-(C\underline{H}_3)_3$), 3·8 (*s*, 2 H, $-C-C\underline{H}_2$), 7·4 (*d*, 1 H, 5H), 8·6 (*d*, 1 H, 6H).

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