Purines, Pyrimidines, and Imidazoles. Part XLIV.[1] Syntheses of Some Dihydro-1,3-oxazine Derivatives and Related Substituted Uracils

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6-Methyl-1,3-oxazine-2,4(3*H*)-dione has been prepared from ethyl acetoacetate by reaction with *NN*-dimethyl- or *NN*-diethyl-urea in acetic acid–acetic anhydride solution, and by heating with ethyl carbamate in the presence or absence of solvent. The oxazinedione was also produced by heating ethyl *N*-acetoacetylcarbamate, and by heating *N'*-acetoacetyl-*NN*-dimethylurea with acetic acid–acetic anhydride or sulphuric acid. The compound was identical with material prepared from diketen and *NN*-dimethylurea, and its structure was confirmed by ^{1}H and ^{13}C n.m.r. spectroscopy. Similar reactions of various β-oxo-esters, including *C*-methyl and *C*-benzyl derivatives, with ethyl carbamate and with *NN*-dimethylurea provided various 6-aryl- and 6-alkyl-oxazinediones and 5,6-dialkyloxazinediones. Treatment of the oxazinediones and their *N*-alkyl derivatives with ammonia and with primary amines gave substituted uracils and with secondary amines, acylated ureas. The 6-methyloxazinedione dimerised when heated with sodium hydroxide to give (6-hydroxy-4-methyl-2-pyridyl)acetic acid.

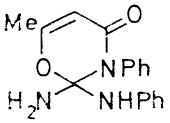
LACEY [2,3] has recorded that the reaction of diketen with various urea derivatives produces compounds thought to be derivatives of 1,3-oxazine. In particular,[2] *NN'*-diphenylguanidine with diketen produced a compound thought to have the structure (I), which when hydrolysed with hydrochloric acid gave successively the isocytosine derivative (II) and 6-methyl-3-phenyluracil (IIIa). Diketen similarly with *NN'*-disubstituted ureas (alkyl, aryl, or aralkyl) or *S*-alkylisothioureas [3] produced 2-imino-1,3-oxazine derivatives (IV), which could be hydrolysed to *N*-substituted 1,3-oxazine-2,4-diones (V) or to uracils by rearrangement of the imino-oxazine structure. A similar reaction of diketen with *NN*-dimethylurea to give the 1,3-oxazine (Va) has also been recorded.[4] The identification of the oxazines was based on a comparison of light absorption data with those of crotonic acid derivatives [2,3] and on the conversion of the oxazine-2,4-diones (V) with ammonia and with alkyl- and aralkylamines into substituted uracils.[2-4] Lacey records [3] that it was not possible to replace diketen by a β-oxo-ester, so that his syntheses were restricted (by the difficulty of producing other diketens) to the production of 6-methyloxazines or the corresponding uracils.

The lack of ready availability of substituted diketens makes the aforementioned syntheses of limited value, and we have been examining alternative routes to oxazines from the readily available β-oxo-esters. The recent isolation of a naturally occurring 1,3-oxazine derivative [oxazinomycin [5] (Vc) (minimycin [6,7])] has added special interest to this work.

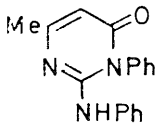
The 6-methyloxazine (Va) was produced in various reactions involving ethyl acetoacetate. It was obtained

[1] Part XLIII, G. Mackenzie, P. W. Rugg, and G. Shaw, *J.C.S. Perkin I*, 1976, 1446.
[2] R. N. Lacey, *J. Chem. Soc.*, 1954, 839.
[3] R. N. Lacey, *J. Chem. Soc.*, 1954, 845.
[4] V. I. Gunar, L. F. Ovechkina, and S. I. Zav'yalov, *Izvest. Akad. Nauk S.S.R. Ser. khim.*, 1965, **6**, 1036.
[5] T. Haneishi, T. Okazaki, T. Hata, C. Tamura, M. Nomura, A. Naito, I. Seki, and M. Arai, *J. Antibiotics*, 1971, **24**, 797.
[6] Y. Kusakabe, J. Nagatsu, M. Shibuya, O. Kawaguchi, C. Hirose, and S. Shirato, *J. Antibiotics*, 1972, **25**, 44.
[7] K. Sasaki, Y. Kusakabe, and S. Esumi, *J. Antibiotics*, 1972, **25**, 151.

by the reaction of the oxo-ester with *NN*-dimethyl- or *NN*-diethyl-urea with acetic acid–acetic anhydride.[8]



(I)



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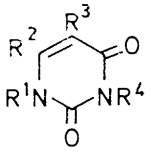
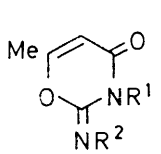
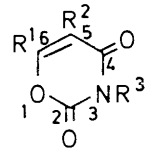


(III) a; $R^1 = R^3 = H, R^2 = Me, R^4 = Ph$
b; $R^1 = R^3 = R^4 = H, R^2 = Me$
c; $R^1 = R^2 = Me$ $R^3 = R^4 = H$
d; $R^1 = OH, R^2 = Me, R^3 = R^4 = H$
e; $R^1 = CH_2CO_2H, R^2 = Me, R^3 = R^4 = H$
f; $R^1 = R^3 = H, R^2 = R^4 = Me$
g; $R^1 = R^2 = R^4 = Me, R^3 = H$
h; $R^1 = NH_2, R^2 = R^4 = Me, R^3 = H$
i; $R^1 = R^3 = R^4 = H, R^2 = Ph$
j; $R^1 = Me, R^2 = Ph, R^3 = R^4 = H$
k; $R^1 = R^3 = H, R^2 = Ph, R^4 = Me$
l; $R^1 = R^4 = Me, R^2 = Ph, R^3 = H$
m; $R^1 = R^4 = H, R^2 = R^3 = Me$
n; $R^1 = H, R^2 = R^3 = R^4 = Me$

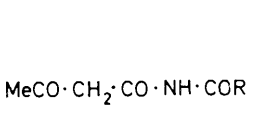


(IV)

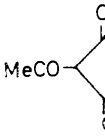


(V) a; $R^1 = Me$ $R^2 = R^3 = H$
b; $R^1 = R^3 = Me, R^2 = H$
c; $R^1 = R^3 = H, R^2 = \beta$-D-ribofuranosyl
d; $R^1 = Ph, R^2 = R^3 = H$
e; $R^1 = p\text{-}NO_2{\cdot}C_6H_4, R^2 = R^3 = H$
f; $R^1 = p\text{-}FC_6H_4, R^2 = R^3 = H$
g; $R^1 = Pr^n, R^2 = R^3 = H$
h; $R^1 = EtO_2C{\cdot}CH_2, R^2 = R^3 = H$
i; $R^1 = R^2 = Me, R^3 = H$
j; $R^1 = Me, R^2 = PhCH_2$ $R^3 = H$
k; $R^1 = R^3 = Me, R^2 = H$
l; $R^1 = Me, R^2 = H, R^3 = CH_2{\cdot}CO_2Et$
m; $R^1 = Me, R^2 = H, R^3 = PhCH_2$
n; $R^1 = Ph, R^2 = H$ $R^3 = Me$
o; $R^1 = Ph, R^2 = H$ $R^3 = CH_2{\cdot}CO_2Et$
p; $R^1 = R^2 = R^3 = Me$

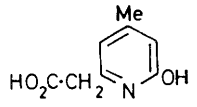
Alternatively the ureas could be replaced by the more readily available ethyl carbamate. The oxazine was also produced from the oxo-ester and ethyl carbamate alone, or by heating ethyl *N*-acetoacetylcarbamate [9] (VIb) either with acetic acid–acetic anhydride or in xylene. The reaction of the oxazine (Va) with dimethylamine gave the acyclic acylurea (VIa). This compound, when heated in acetic acid–acetic anhydride or when treated with sulphuric acid, gave the oxazine (Va).



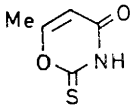
(VI) a; R = NMe_2
b; R = OEt



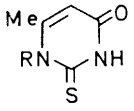
(VII)



(VIII)

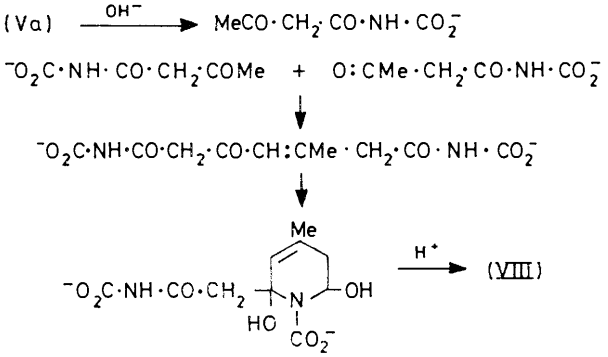


(IX)



(X) a; R = $CH_2CH_2{\cdot}OH$
b; R = $CH_2{\cdot}CO_2H$

The structure of compound (Va) followed from elemental analysis and i.r. and mass spectra (M — 127 84.021 127); HCNO and not CH_3CO is eliminated. These data however did not exclude the alternative acetylmalonimide structure (VII). Some support for structure (VII) came from the fact that the substance was relatively and surprisingly stable in alkaline solution, from which it could be precipitated with acid, and readily gave an iodoform reaction. In addition, long boiling with sodium hydroxide solution produced the pyridine derivative (VIII) in good yield, identical with a sample prepared from ethyl β-aminocrotonate and acid. Compound (VIII) is in fact the result of self condensation, by a mechanism such as outlined in Scheme 1.



SCHEME 1

The best evidence for the oxazine structures has come from n.m.r. spectra. The ^1H n.m.r. spectrum of (Va)

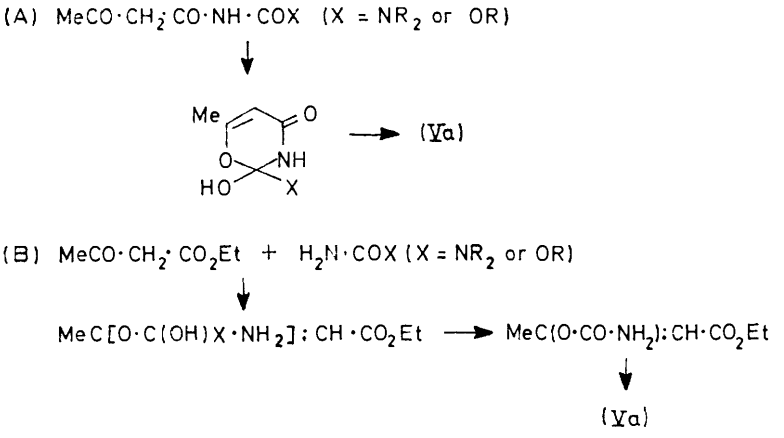
[8] Preliminary report, S. Ahmed, R. Lofthouse, and G. Shaw, *J.C.S. Chem. Comm.*, 1974, 959.
[9] R. K. Ralph, G. Shaw, and R. N. Naylor, *J. Chem. Soc.*, 1959, 1169.

(solvent Me_2SO) showed singlet methyl, CH, and NH signals. In D_2O only the NH proton is exchanged, whereas the acetylmalonimide structure (VII) might be expected to possess two acidic protons. More conclusive evidence came from ^{13}C n.m.r. Fourier transform spectra. The decoupled spectra (solvent Me_2SO) showed five well separated singlets, confirming the presence of five different carbon atoms, whereas the four-membered ring in (VII) would presumably have C-1 and C-3 indistinguishable. The methylated derivative (Vb) (in which tautomerisation is not possible) prepared from (Va) and diazomethane still shows five ^{13}C singlets, and an extra methyl singlet.

The coupled ^{13}C n.m.r. spectrum of (Va) in Me_2SO showed a doublet for C-5, which must therefore retain its proton. This in turn indicates that no tautomerisation is taking place; thus the hypothetical malonimide structure would give a singlet for C-1 and C-3 instead of the observed doublet. This further confirms the oxazine (Va). The coupled spectrum showed in the methyl region a quartet of doublets (three methyl protons), resulting from coupling of the methyl carbon atom with the single C-5 proton. The C-5 doublet was split into two quartets owing to coupling with the three methyl protons. In the carbonyl region two singlets occurred due to C-2 and C-4, with no coupling, and a doublet of quartets for C-6 due to coupling with the three methyl protons and the single C-5 proton.

The various reactions described probably involve two separate routes to the 1,3-oxazine system (Scheme 2). The direct formation of (Va) from either ethyl *N*-acetoacetylcarbamate or *N'*-acetoacetyl-*NN*-dimethylurea provides a firm foundation for mechanism (A). The reaction requires relatively high temperatures and/or acid catalysis to facilitate elimination of HX. Mechanism (B), involving the oxo-ester and an appropriate urea or carbamate derivative, seems possible, and would involve prior reaction of the enol ester to produce an *O*-carbamoyl derivative, which would be expected to cyclise readily. This last sequence offers scope for the development of milder routes to the oxazine system.

The same reactions could be applied to the synthesis of other oxazines. In particular, reactions of ethyl benzoyl-, *p*-nitrobenzoyl-, *p*-fluorobenzoyl-, and n-butyroyl-acetate, and diethyl acetonedicarboxylate produced the oxazines (Vd—h), respectively. In preliminary experiments, condensation of ethyl α-methylacetoacetate with *NN*-dimethylurea in acetic acid–acetic anhydride did not produce an oxazine. However when the urea was replaced by ethyl carbamate, the oxazine (Vi) was obtained. Similarly from ethyl α-benzylacetoacetate the oxazine (Vj) was produced. These last syntheses of 5-substituted derivatives are of special interest, since they produce the skeletal features of oxazinomycin (Vc). The corresponding oxazinethione (IX) was made by a similar reaction of *NN*-dimethylthiourea with diketen. The preparation of this compound from diketen and ammonium thiocyanate in acetone has also been reported, as has its conversion by hydrogen peroxide in acetic acid into the oxazine (Va).[4]



SCHEME 2

The oxazines are a useful source of substituted uracils. Thus reactions of the 6-methyloxazine (Va) with ammonia, methylamine, hydroxylamine, and glycine produced the uracils (IIIb—e), respectively. Alkylations of (Va) with diazomethane, ethyl bromoacetate, and benzyl chloride gave the *N*-alkyloxazines (Vk—m), respectively. The oxazine (Vk) with ammonia, methylamine, and hydrazine produced the uracils (IIIf—h), respectively. In a similar manner the phenyloxazine (Vd) with ammonia and methylamine gave the 6-phenyluracils (IIIi and j), respectively, whereas the alkylated phenyloxazines (Vn), prepared from (Vd) and diazomethane, and (Vo), prepared from (Vd) and ethyl bromoacetate, with ammonia gave the uracils (IIIk and l), respectively.

The dimethyloxazine (Vi) also reacted smoothly with aqueous ammonia to produce 5,6-dimethyluracil (IIIm), and the trimethyloxazine (Vp), from (Vi) and diazomethane, with ammonia gave 3,5,6-trimethyluracil (IIIn).

The analogous reaction of oxazinomycin (Vc) with ammonia or ammonium carbonate to produce pseudouridine has been reported.[7]

The oxazinethione (IX) was converted into the 2-thiouracils (Xa and b) with 2-amino-ethanol and glycine, respectively. The structures assigned to the various uracil derivatives were confirmed by elemental analysis, mass, u.v., and i.r. spectra, and (in most cases) comparison with authentic samples.

EXPERIMENTAL

Evaporations were carried out with a Büchi rotary evaporator under water-pump vacuum with a flask temperature $\leqslant$50 °C unless otherwise stated. U.v. absorption spectra were measured with a Unicam SP 800 spectrophotometer, ^{1}H n.m.r. spectra with a JEOL-MH-100 spectrometer (tetramethylsilane as internal standard), and mass spectra with an A.E.I. MS902 spectrometer. ^{13}C N.m.r. spectra were recorded by the P.C.M.U., Harwell. Silica gel $60F_{254}$ (0.25 mm) precoated glass plates (Merck) were used for t.l.c. with chloroform–methanol (10 : 1) or butan-1-ol–acetic acid–water (12 : 3 : 5) as developing solvent.

6-*Methyl*-1,3-*oxazine*-2,4(3H)-*dione* (Va).—(*a*) A mixture of *NN*-dimethylurea (4,4 g), acetic acid (10 ml), acetic anhydride (50 ml), and ethyl acetoacetate (13 g) was boiled for 1 h in a flask fitted with a short air condenser which allowed slow evaporation of the more volatile components. The temperature of the mixture was maintained below 150 °C by addition from time to time of acetic acid–acetic anhydride (1 : 5). The solution was cooled and the crystalline precipitate of the oxazine (1 g) recovered. The same oxazine was obtained in similar yield when *NN*-dimethylurea was replaced by *NN*-diethylurea or when ethyl acetoacetate was replaced by an equivalent amount of benzyl acetoacetate. On the other hand when the preparation was carried out by boiling the components under reflux a smaller yield of the oxazine (0.4 g) was obtained. The oxazine crystallised from acetonitrile as prisms, m.p. 243° (lit.,[4] 231—232°) (Found: C, 47.5; H, 4.1; N, 10.85%; M^+, 127. Calc. for $C_5H_5NO_3$: C, 47.25; H, 3.95; N, 11.05%; *M*, 127), δ_H [$(CD_3)_2SO$] 2.19 (CH_3), 3.44 (NH, exchanged in D_2O), and 5.92 (:CH); δ_C [$(CD_3)_2SO$; ^{1}H-decoupled] 18.59, 100.86, 148.24, 162.54, and 166.44 (all s; Me, :CH, C·*C*O·N, MeC·O·, and O·CO·N, respectively); δ_C [coupled; $(CD_3)_2SO$] 18.59 (q), 100.86 (d), 148.24 (s), 162.54 (s) and 166.44 (d) (Me, :CH, C·*C*O·N, Me*C*·O, and O·CO·N, respectively).

(*b*) A mixture of ethyl carbamate (44.5 g), ethyl acetoacetate (130 g), acetic acid (30 ml), and acetic anhydride (70 ml) was boiled under reflux for 6 h. The solution was evaporated to about half volume, cooled, and set aside. The oxazine (7 g) separated. More (1.5 g) of the oxazine was recovered from the mother liquor.

(*c*) A mixture of ethyl acetoacetate (13.9 g) and ethyl carbamate (8.8 g) was boiled for 30 min in a flask provided with an air condenser. The cooled solution deposited a crystalline precipitate of the oxazine (0.5 g). In a similar experiment at this stage a further quantity of oxo-ester (12 ml) was added and the solution boiled for 40 min (the temperature varied between 150 and 185 °C). The cooled solution produced a precipitate of the oxazine (1.5 g).

(*d*) A solution of ethyl *N*-acetoacetylcarbamate [9] (20 g), acetic acid (12 ml), and acetic anhydride (40 ml) was boiled under reflux for 10 h, evaporated to about half volume, and cooled. The oxazine (3.6 g) separated and was collected. More (total 0.9 g) of the oxazine was obtained by evaporation and cooling of the mother liquor. Similar yields were obtained by repeating the experiment but with an air condenser and allowing the more volatile materials to evaporate.

(*e*) Ethyl *N*-acetoacetyl carbamate (5 g) was heated for 2 h at 170—175 °C (oil-bath). The cooled melt deposited crystals of the oxazine, which were washed out with a little acetic acid; yield, including material recovered from mother liquors, 1.5 g. In a similar experiment ethyl *N*-acetoacetylcarbamate (3 g) was boiled under reflux in xylene (50 ml) for 14 h. The cooled solution precipitated the oxazine (1.6 g).

(*f*) A solution of *N'*-acetoacetyl-*NN*-dimethylurea (0.05 g; for preparation see later) in acetic anhydride (2 ml) and acetic acid (3 drops) was boiled for a few min. The cooled solution was set aside, and a crystalline precipitate of the oxazine (0.03 g) was obtained.

(*g*) *N'*-Acetoacetyl-*NN*-dimethylurea (0.025 g) was dissolved in concentrated sulphuric acid (0.5 ml) to produce a clear yellow solution, which was set aside at room temperature for 30 min, then added to water (20 ml). The mixture was cooled and a precipitate (0.01 g) of the oxazine collected.

Reactions of 6-*Methyl*-1,3-*oxazine*-2,4(3H)-*dione* (Va) *with Amines.—General method.* To a suspension of the oxazine in ethanol or water an aqueous or alcoholic solution of the amine was added, and the mixture was boiled for a few min, then cooled, and if necessary acidified. Hydrazine (95%) produced 5-methylpyrazolone as needles, m.p. 215°, identical with an authentic specimen (from ethyl acetoacetate and hydrazine). Hydroxylamine gave 1-*hydroxy*-6-*methyluracil* (IIId), which was purified by dissolution in 2M-sodium hydroxide, treatment with charcoal, and reprecipitation with 2M-hydrochloric acid. It formed a white solid, m.p. 300° (decomp.) (Found: C, 42.1; H, 4.15; N, 19.55%; M^+, 142. $C_5H_6N_2O_3$ requires C, 42.25; H, 4.25; N, 19.7%; *M*, 142), $\lambda_{max.}$ (H_2O) 210 and 271 nm (ε 28 000) (in water), $\lambda_{max.}$ (NaOH) 245 and 300 nm, $\lambda_{max.}$ (HCl) 210 and 271 nm, δ_H [$(CD_3)_2SO$] 2.22 (CH_3), 3.60 (NH exchanged in D_2O), 5.45 (:CH), and 12.08 (OH, exchanged in D_2O). A substance claimed [10] to be 1-hydroxy-6-methyluracil has been shown to be the 3-hydroxy-derivative.[11] Reaction with ammonia gave 6-methyluracil (IIIb), m.p. 275°, identical (mixed m.p. and i.r., u.v., and mass spectra) with an authentic specimen.[12] Methylamine gave 1,6-dimethyluracil (IIIc), which crystallised from ethanol as needles, m.p. 221°, identical with an authentic specimen (from diketen and *N*-methylurea [13]). Glycine gave 1-*carboxymethyl*-6-*methyluracil* (IIIe), which separated from ethanol as needles, m.p. 258—260° (Found: C, 45.4; H, 4.45; N, 15.0%; M^+, 184. $C_7H_8N_2O_5$ requires C, 45.65; H, 4.4; N, 15.25%; *M*, 184). Dimethylamine gave 1-*acetoacetyl*-3,3-*dimethylurea* (VIa), which crystallised from ethanol as needles, m.p. 110° (Found: C, 48.6; H, 6.7; N, 16.0%; M^+, 172. $C_7H_{12}N_2O_3$ requires C, 48.85; H, 7.05; N, 16.3%; *M*, 172), $\lambda_{max.}$ (H_2O) 307 nm (ε 9 461), δ_H ($CDCl_3$) δ 2.52 (CMe), 3.04 (NMe_2), 5.68 (CH_2), and 7.68 (NH).

3,6-*Dimethyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vb).—The foregoing 6-methyloxazine (1 g) with ethereal diazomethane gave a clear solution after 2 h. Evaporation gave a solid. The *dimethyloxazine* (1 g) separated from carbon tetrachloride as plates, m.p. 104° (Found: C, 50.9; H, 5.1; N, 9.65%; M^+,

[10] E. Ajello, T. Ajello, and V. Sprio, *Ricerca sci.*, 1964, **4**, 105.
[11] A. L. Cossey and J. N. Phillips, *Chem. and Ind.*, 1970, **2**, 58.
[12] R. Behrend, *Annalen*, 1885, **229**, 1.
[13] A. D. Ainley, F. H. S. Curd, W. Hepworth, A. G. Murray, and G. H. Vasey, *J. Chem. Soc.*, 1953, 59.

141. $C_6H_7NO_3$ requires C, 51.05; H, 5.0; N, 9.95%; *M*, 141), $\lambda_{max.}$ (H_2O) 223 nm (ε 5 810), δ_H (D_2O) 2.26 (CH_3), 3.30 (NCH_3), and 6.02 (:CH), δ_H($CDCl_3$) 2.12 (CH), 3.24 (NCH_3), and 5.76 (:CH), δ_C [decoupled; $(CD_3)_2SO$] 18.39, 27.8, 100.54, 148.96, 161.31, and 164.68 (C*Me*, NMe, :CH, C·*C*O·N, Me·C·O·, and O·*C*O·N, respectively).

The dimethyloxazine with aqueous ammonia (*d* 0.88) gave 3,6-dimethyluracil (IIIf), which crystallised from ethanol as needles, m.p. 260°, identical with a specimen prepared from 6-methyluracil with dimethyl sulphate.[14] Similarly the dimethyloxazine with hot aqueous methylamine gave 1,3,6-trimethyluracil (IIIg), m.p. 113°, identical with a specimen prepared from 6-methyluracil.[13] The dimethyloxazine and hydrazine in ethanol gave 1-*amino*-3,6-*dimethyluracil* (IIIh), which crystallised from ethanol as needles, m.p. 112° (Found: C, 46.25; H, 5.9; N, 27.15%; M^+, 155. $C_6H_9N_3O_2$ requires C, 46.45; H, 5.85, N, 27.1%; *M*, 155), $\lambda_{max.}$ (H_2O) 239 nm (ε 8 380).

3-*Ethoxycarbonylmethyl*-6-*methyl*-1,3-*oxazine*-2,4(3H)-*dione* (VI).—The 6-methyloxazine (1.3 g) was added to a solution of sodium (0.25 g) in ethanol (15 ml). The clear resulting solution was evaporated to a foam. This was dissolved in dimethylformamide (10 ml), and ethyl chloroacetate (1.2 g) was added. The solution was boiled under reflux for 5 min then evaporated to a syrup which soon crystallised. The *ethoxycarbonylmethyloxazine* (0.6 g), m.p. 66°, was washed out with ethanol–ether (75 : 25) (Found C, 50.55; H, 5.2; N, 6.55%; M^+, 213. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.55%; *M*, 213). $\lambda_{max.}$ (H_2O) 236 nm (ε 18 620). The 6-methyloxazine (3 g) with benzyl chloride similarly produced 3-*benzyl*-6-*methyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vm) (2 g), which crystallised from ethanol as needles, m.p. 80° (Found: C, 66.2; H, 5.3; N, 6.4%; M^+, 217. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%; *M*, 217), $\lambda_{max.}$ (H_2O) 245 nm (ε 6 895).

(6-*Hydroxy*-4-*methyl*-2-*pyridyl*)*acetic Acid* (VIII).—A solution of the 6-methyloxazine (Va) (1.5 g) in water (25 ml) containing sodium hydroxide (4.5 g) was boiled under reflux for 5 h. Evolution of ammonia had then ceased, and the cooled solution was acidified with 2M-hydrochloric acid to produce a precipitate. The pyridine derivative (1.5 g) crystallised from ethanol as needles, m.p. 189° (decomp.) (Found: C, 57.8; H, 5.6; N, 7.95%; M^+, 167. Calc. for $C_8H_9NO_3$: C, 57.7; H, 5.45; N, 8.4%; *M*, 167), identical (m.p., mixed m.p., and i.r., u.v., and mass spectra) with a sample prepared from hydrogen chloride and ethyl β-aminocrotonate.[15] A small amount of the pyridine derivative was heated at 190 °C; carbon dioxide was rapidly evolved and the crystalline sublimate was collected. It had m.p. 180° and was identical with 2-hydroxy-4,6-dimethylpyridine prepared by heating 4,6-dimethyl-2-hydroxypyridine-3-carboxylic acid.[16]

6-*Phenyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vd).—(*a*) A mixture of *NN*-dimethylurea (44 g), acetic acid (75 ml), acetic anhydride (300 ml), and ethyl benzoylacetate (192 g) was boiled for 2 h in a flask fitted with an air condenser. Volatile components were allowed to distil off slowly while the temperature of the solution was maintained below 160 °C by occasional addition of acetic acid–acetic anhydride (1 : 5). The solution (volume *ca.* 150 ml) was cooled to give a crystalline precipitate. The *oxazine* (13 g) separated from acetic acid as prisms, m.p. 242—244° (Found: C, 63.2; H, 3.8; N, 7.6%; M^+, 189. $C_{10}H_7NO_3$ requires C, 63.5; H, 3.7; N, 7.4%; *M*, 189). After heating the mother liquor for a further 1 h, more oxazine (6 g) was obtained. When the mother liquor was heated for 30 min (final b.p. 220°) and cooled, a solid was precipitated. 6-Phenyluracil crystallised from acetic acid as prisms, m.p. 280—282°, identical with an authentic sample (lit.,[17] m.p. 272—274°).

(*b*) A solution of ethyl benzoylacetate (19.5 g), ethyl carbamate (4.4 g), acetic acid (3 ml), and acetic anhydride (7 ml) was boiled in a flask with an air condenser so that volatile material could escape. After 45 min the b.p. was 130—140 °C and the volume of solution *ca.* 10 ml. The cooled solution gave a crystalline precipitate. The oxazine (3.4 g) was collected and washed with water, ethanol, and ether. The filtrate was treated with acetic anhydride (10 ml) and acetic acid (3 ml) and the mixture boiled as before for 40 min to produce a syrup (10 ml). This was diluted with a little acetic anhydride and set aside overnight; more of the oxazine (1 g) separated. The oxazine was identical (m.p., t.l.c., and i.r., u.v., and mass spectra) with the material described under (*a*). T.l.c. of the mother liquor indicated the presence of another u.v. absorbing substance. This slowly crystallised out and was separated from traces of the oxazine by crystallisation from acetic acid to give needles (0.8 g), m.p. 164°, identical with authentic 3-benzoyl-6-phenyl-2*H*-pyran-2,4(3*H*)-dione (Found: C, 73.95; H, 4.1%; M^+, 292. Calc. for $C_{18}H_{12}O_4$: C, 74.05; H, 4.15%; *M*, 292) (lit.,[18] m.p. 171—172°).

(*c*) A mixture of ethyl benzoylacetate (19.2 g) and ethyl carbamate (8.8 g) was boiled in a flask fitted with an air condenser until the temperature of the solution had risen from 140 to 180 °C. The cooled solution gave a crystalline precipitate of the phenyloxazine (4.5 g). More (0.5 g) was recovered from the mother liquors after heating for 45 min.

(*d*) A solution of *N'*-benzoylacetyl-*NN*-dimethylurea (0.115 g; for preparation see later) in acetic anhydride (3 ml) was boiled for 2 min, then set aside overnight at 0 °C; a crystalline precipitate of the oxazine (0.085 g) had then separated. In a separate experiment the foregoing urea (0.2 g) with sulphuric acid (1 ml) was set aside at room temperature for 2 h. Water (20 ml) was added with cooling and the mixture was set aside overnight at 0 °C. A crystalline precipitate (0.1 g) of the oxazine was collected.

Reactions of 6-*Phenyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vd) *with Amines*.—The oxazine with aqueous ammonia gave 6-phenyluracil (IIIi), which separated from acetic acid as prisms, m.p. 282—284° (Found: C, 63.55; H, 4.35; N, 14.8%; M^+, 188. Calc. for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9%; *M*, 188). Similarly, aqueous methylamine gave 1-methyl-6-phenyluracil (IIIj) monohydrate as prisms, m.p. 182—184° (Found: C, 59.9; H, 5.4; N, 12.65%; M^+, 202. Calc. for $C_{11}H_{10}N_2O_2$, H_2O: C, 60.0; H, 5.5; N, 12.75%; *M*, 202) (lit.,[17] m.p. 194—195°). Hydrazine (95%) gave 3-phenylpyrazol-5-one, m.p. 238—240°, identical with a sample prepared from ethyl benzoylacetate and hydrazine, and dimethylamine gave *N'*-*benzoylacetyl*-*NN*-*dimethylurea*, which crystallised from ethyl acetate as needles, m.p. 112—114° (Found: C, 61.55; H, 5.85; N, 11.85%; M^+, 234. $C_{12}H_{14}N_2O_3$ requires C, 61.6; H, 6.0; N, 11.95%; *M*, 234).

3-*Methyl*-6-*phenyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vn).—A

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[15] J. N. Collie, *J. Chem. Soc.*, 1897, **71**, 303.
[16] G. Knoevenagle and W. Cremer, *Chem. Ber.*, 1902, **35**, 2394.
[17] J. Evans and T. B. Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 4993.
[18] W. H. Perkin, jun., *J. Chem. Soc.*, 1885, **47**, 278.

solution of diazomethane in ether (2%; 30 ml) was treated with the phenyloxazine (2 g). The solid slowly dissolved. After 2 h the solution was filtered and the solid treated with more ethereal diazomethane (35 ml). The process was repeated (20 ml of diazomethane solution). The combined ethereal solutions were evaporated to leave a solid. The *oxazine* (2 g) separated from water as needles, m.p. 138—140° (Found: C, 65.0; H, 4.4; N, 6.95%; M^+, 203. $C_{11}H_9NO_3$ requires C, 65.05; H, 4.45; N, 6.9%; *M*, 203). The compound (1 g) was boiled with aqueous ammonia (9 ml; *d* 0.88) and ethanol (5 ml) for 5 min. The solution was cooled and set aside at 0 °C overnight; the crystalline precipitate gave 3-methyl-6-phenyluracil (IIIk) (0.75 g) as plates, m.p. 230—232° (from water) (Found: C, 65.0; H, 4.95; N, 13.95%; M^+, 202. Calc. for $C_{11}H_{10}N_2O_2$: C, 65.4; H, 4.95; N, 13.8%; *M*, 202) (lit.,[17] m.p. 228—230°).

3-*Ethoxycarbonylmethyl*-6-*phenyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vo).—The phenyloxazine (Vd) (1.89 g) was added to a solution of sodium (0.23 g) in ethanol (20 ml). The solution was evaporated to leave a solid. This was suspended in dimethylformamide (10 ml) and ethyl bromoacetate (1.75 g) was added. The solution was boiled under reflux for 5 min then evaporated to leave a solid. The *product* (Vo) (1.5 g) crystallised from ethanol as prisms, m.p. 110—112° (Found: C, 61.35; H, 4.7; N, 5.1%; M^+, 275. $C_{14}H_{13}NO_5$ requires C, 61.15; H, 4.75; N, 5.1%; *M*, 275). The compound (0.275 g) was boiled with aqueous ammonia (2 ml; *d* 0.88) and ethanol (3 ml) for a few min. The cooled solution gave a solid precipitate. 3-Ethoxycarbonylmethyl-6-phenyluracil (0.25 g) separated from ethanol as needles, m.p. 212—214° (Found: C, 61.25; H, 5.25; N, 10.4%; M^+, 274. Calc. for $C_{14}H_{14}N_2O_4$: C, 61.35; H, 5.15; N, 10.2%; *M*, 274) (lit.,[17] m.p. 205—208°).

6-p-*Fluorophenyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vf).—A solution containing *NN*-dimethylurea (2.2 g), acetic acid (3 ml), acetic anhydride (12 ml), and ethyl *p*-fluorobenzoylacetate (4 g) was boiled under reflux for 4 h. The cooled solution gave a solid precipitate. The *oxazine* (0.5 g) crysallised from acetic acid as prisms, m.p. 208° [sublimes then m.p. (decomp.) 292°] (Found: C, 57.45; H, 2.9; F, 9.5; N, 6.8%; M^+, 207. $C_{10}H_6FNO_3$ requires C, 58.0; H, 2.9; F, 9.2%; N, 6.75; *M*, 207).

6-p-*Nitrophenyl*-1,3-*oxazine*-2,4(3H)-*dione* (Ve).—A solution containing *NN*-dimethylurea (8.8 g), acetic acid (10 ml), acetic anhydride (50 ml), and ethyl *p*-nitrobenzoyl acetate (20 g) was boiled for 30 min in a flask fitted with an air condenser, then boiled under reflux for 24 h. The cooled solution slowly deposited a crystalline solid. This was washed with ether to remove unchanged oxo-ester. The *oxazine* (2.5 g) crystallised from acetic acid as needles, m.p. 262—264° (Found: C, 50.95; H, 2.35; N, 11.8%; M^+, 234. $C_{10}H_6N_2O_5$ requires C, 51.3; H, 2.6; N, 11.95%; *M*, 234). More oxazine (1 g) was recovered from the mother liquors. The oxazine (1.5 g) was boiled with aqueous ammonia (70 ml; *d* 0.88) until a clear solution was obtained. The solution was evaporated and cooled to give a solid precipitate. 6-p-*Nitrophenyluracil* (1.15 g) crystallised from acetic acid as prisms, m.p. >330° (Found: C, 51.25; H, 3.05; N, 17.5%; M^+, 233. $C_{10}H_7N_3O_4$ requires C, 51.55; H, 3.0; N, 18.05%; *M*, 233).

6-*n*-*Propyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vg).—A solution of ethyl n-butyroylacetate (23.3 g) and ethyl carbamate (8.8 g) in acetic acid (5 ml) and acetic anhydride (15 ml) was boiled in a flask fitted with an air condenser for 2 h; the volume had then been reduced to *ca.* 15 ml. The cooled solution was set aside and a crystalline solid separated. The *propyloxazine* (4 g) crystallised from water as needles, m.p. 143° (Found: C, 54.5; H, 5.4; N, 9.1%; M^+, 155. $C_7H_9NO_3$ requires C, 54.2; H, 5.85; N, 9.05%; *M*, 155). The oxazine (0.3 g) was boiled with aqueous ammonia (8 ml; *d* 0.88) for 5 min. The cooled solution gave a solid precipitate. 6-n-Propyluracil (0.26 g) had m.p. 220° (Found: M^+, 154. Calc. for $C_7H_{10}N_2O_2$: *M*, 154) (lit.,[19] m.p. 217—219°). The oxazine (0.4 g) was suspended in ether (5 ml) and treated with ethereal diazomethane (12 ml; 2%); it slowly (8 min) dissolved. The solution was evaporated to leave a solid. 3-*Methyl*-6-*n*-*propyl*-1,3-*oxazine*-2,4(3H)-*dione* (0.35 g) crystallised from carbon tetrachloride as prisms, m.p. 131° (Found: N, 8.9%; M^+, 169. $C_8H_{11}NO_3$ requires N, 8.3%; M, 169).

6-*Ethoxycarbonylmethyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vh).—A mixture of *NN*-dimethylurea (4.49 g), acetic acid (5 ml), acetic anhydride (15 ml), and diethyl acetonedicarboxylate (9 g) was boiled under reflux for 8 h. The cooled solution gave a precipitate of cyanuric acid (0.2 g), m.p. 300°. This was removed and the filtrate evaporated to a small volume, evaporated with ethanol, then set aside at 0 °C after addition of light petroleum (b.p. 40—60 °C). A crystalline precipitate slowly appeared. The *oxazine* (0.8 g) crystallised from ether (containing a little ethanol) as needles, m.p. 110—112° (Found: C, 48.45; H, 4.5; N, 7.15%; M^+, 199. $C_8H_9NO_5$ requires C, 48.3; H, 4.55; N, 7.05%; *M*, 199).

5,6-*Dimethyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vi).—(*a*) A solution of ethylcarbamate (4.5 g) and ethyl α-methylacetoacetate (144 g) in acetic anhydride (70 ml) and acetic acid (30 ml) was boiled in a flask fitted with a short air condenser for 4 h; the volume was then *ca* 50 ml. The cooled solution deposited a crystalline precipitate. The *oxazine* (8 g) crystallised from diethyl ether as needles, m.p. 160—162° (Found: C, 50.95; H, 4.95; N, 10.0%; M^+, 141. $C_6H_7NO_3$ requires C, 51.1; H, 5.0; N, 9.95%; *M*, 141). More (1.5 g) was recovered from the mother liquors. The oxazine (0.75 g) was boiled with aqueous ammonia (20 ml; *d* 0.88) for 5 min. The solution was evaporated and cooled to give a precipitate. 5,6-Dimethyluracil (IIIm) (0.56 g) crystallised from water as needles, m.p. 297° (Found: C, 51.25; H, 5.7; N, 20.15%; M^+, 140. Calc. for $C_6H_8N_2O_2$: C, 51.45; H, 5.75; N, 20.0%; *M*, 140) (lit.,[20] m.p. 294—297°). The oxazine (2 g) with ethereal diazomethane gave a solution which was evaporated to a syrup, which soon crystallised. 3,5,6-*Trimethyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vp) (1.6 g) crystallised from light petroleum (b.p. 80—100°C) as needles, m.p. 76—78° (Found: C, 54.25; H, 5.85; N, 9.1%; M^+, 155. $C_7H_9NO_3$ requires C, 54.25; H, 5.85; N, 9.05%; *M*, 155.)

(*b*) A solution of ethyl α-methylacetoacetate (15 g) and ethyl carbamate (8.8 g) was boiled for 30 min in a flask fitted with an air condenser. The b.p. of the solution increased from 155 to 175 °C. More of the oxo-ester (15 ml) was added, and the solution boiled for 1 h. The cooled solution gave a precipitate of the oxazine (2.5 g). More (1 g) was recovered from the mother liquors.

5-*Benzyl*-6-*methyl*-1,3-*oxazine*-2,4(3H)-*dione* (Vj).—A solution of ethyl carbamate (4.4 g) and ethyl α-benzylacetoacetate (15.5 g) in acetic acid (8 ml) and acetic anhydride (20 ml) was boiled in a flask fitted with an air condenser for 1 h. Acetic acid (5 ml) and acetic anhydride (15 ml) were

[19] R. H. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 1956, 4106.

[20] R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 1946, 357.

added, and the solution was boiled for 30 min until its volume was *ca.* 8 ml. The solution was set aside, and crystals were slowly deposited. The *oxazine* (1.8 g) crystallised from carbon tetrachloride as needles, m.p. 116° (Found: C, 66.05; H, 4.95; N, 6.6%; M^+, 217. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.45%; *M*, 217).

6-*Methyl*-2-*thioxo*-1,3-*oxazin*-4(3H)-*one* (IX).—To a hot solution of *NN*-dimethylthiourea (10.4 g) in acetic acid (40 ml) was added diketen (16.8 g), dropwise over 15 min. The solution was cooled to give a crystalline precipitate. The oxazinethione (3 g) separated from ethyl acetate as needles, m.p. 210° (lit.,[4] 201—203°), identical with a sample made from diketen and ammonium thiocyanate.[4] A solution of the oxazinethione (1.43 g) and 2-aminoethanol (1.25 g) in water (10 ml) was boiled for a few min. The cooled solution gave a solid precipitate. 1-*Hydroxyethyl*-6-*methyl*-2-*thiouracil* (Xa) (1 g) separated from water as prisms, m.p. 220° (Found: C, 45.2; H, 5.45; N, 14.95; S, 17.25%; M^+, 186. $C_7H_{10}N_2O_2S$ requires C, 45.2; H, 5.45; N, 15.05; S, 17.25%; *M*, 186). The oxazinethione (1.43 g) was boiled with ethanolic dimethylamine (33%; 7 ml) for 3 min. The solution was cooled to give a crystalline precipitate. *N'*-Acetoacetyl-*NN*-dimethylthiourea (0.8 g) crystallised from diethyl ether containing a little ethanol as needles, m.p. 88—90°, M^+, 188. The oxazinethione (1.42 g) was added to a solution of glycine (0.75 g) in 2M-sodium hydroxide (11 ml) and the solution was heated on a steam-bath for 15 min. The cooled solution with hydrochloric acid gave a pale yellow precipitate. 1-*Carboxymethyl*-6-*methyl*-2-*thiouracil* (Xb) (1.3 g) crystallised from water as prisms, m.p. 255° (Found: C, 41.10; H, 4.2; N, 14.7; S, 16.15%; M^+, 200. $C_7H_8N_2O_3S$ requires C, 42.05; H, 4.05; N, 14.0; S, 16.05%; *M*, 200).

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