Triazines and Related Products. Part XV.[1] 2,4-Diaminopyrimidines and 2-Aminopyrimidin-4(3*H*)-ones bearing 1,2,3-Benzotriazinyl Groups as Potential Dihydrofolic Reductase Inhibitors

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Interaction of α-methoxy-*o*-nitrobenzylidenemalononitrile (8) and guanidinium carbonate afforded 2,4-diamino-6-*o*-nitrophenylpyrimidine-5-carbonitrile (9) which, on reduction, gave not the expected diamino(aminophenyl)-pyrimidine (10) but the triaminopyrimidoquinoline *N*-oxide (13).

Electrophilic nitration and bromination of 2-amino-6-phenylpyrimidin-4(3*H*)-one (7) yielded 5-substituted derivatives: when the 5-position was blocked the substituent entered the *para*-position of the phenyl group. Rearrangement of 2-nitroamino-6-phenylpyrimidin-4(3*H*)-one (14) in concentrated sulphuric acid afforded the 2-amino-5-nitropyrimidine (18), whereas attempted photorearrangement gave a complex mixture. Efforts to effect homolytic *o*-nitrophenylation of uracil with *o*-nitrophenyl radicals generated from two sources were unsuccessful.

Three pyrimidine derivatives bearing 1,2,3-benzotriazinyl units [(24), (30), and (31)] were prepared by diazotisation of the appropriate *o*-aminobenzamido-precursors. None of the pyrimidines displayed inhibitory activity against lymphoid leukaemia (L-1210) in mice.

DERIVATIVES of 2,4-diaminopyrimidine[2,3] and 2,4-diamino-*s*-triazine[4] can complex reversibly with the enzyme dihydrofolic reductase, and are toxic to micro-organisms and proliferating cells. Baker[5] has identified the structural features of these inhibitors, which bind to complementary areas on the surface of the enzyme.

[1] Part XIV, M. S. S. Siddiqui and M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 2482.

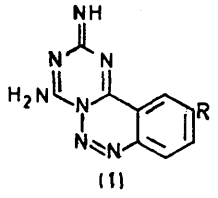
[2] G. H. Hitchings and J. J. Burchall, *Adv. Enzymol.*, 1965, **27**, 417.

[3] B. S. Hurlbert, R. Ferone, T. A. Herrmann, G. H. Hitchings, M. Barnett, and S. R. M. Bushby, *J. Medicin. Chem.*, 1968, **11**, 711.

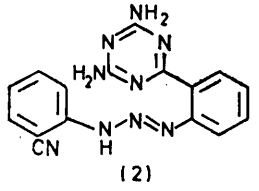
[4] B. R. Baker and Beng-Thong Ho, *J. Heterocyclic Chem.*, 1965, **2**, 340.

[5] B. R. Baker, 'Design of Active-site-directed Irreversible Enzyme Inhibitors,' Wiley, New York, 1967.

The triazines (1; R = H, Me, or Br) [6] were prepared with the intention of exploiting these areas, but proved to be biologically inactive. The related diaryltriazene (2),[7] however, displayed inhibitory activity against L-1210 (lymphoid leukaemia) and P 388 (lymphocytic leukaemia) in mice, and human epidermoid carcinoma of the nasopharynx (cell culture);[8] the piperidinoazo-derivative (3) and its heteroalicyclic analogues were also active in the tissue culture test.[9]



(1)



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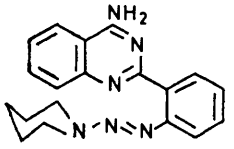


(3)

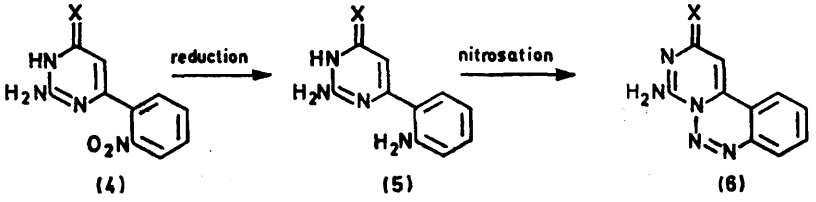
In order to clarify the structure–activity relationships in these series we have prepared pyrimidine derivatives bearing the masked diazo-fragment, since, in general, 2,4-diaminopyrimidines are better inhibitors of dihydrofolic reductase than the corresponding *s*-triazines.[4] This paper records our unsuccessful efforts to synthesise the pyrimido[1,6-*c*][1,2,3]benzotriazines (6) and the successful syntheses of pyrimidines bearing more distant 1,2,3-benzotriazinyl and azido-groups with potential covalent labelling capacity.

Attempted Synthesis of Pyrimido[1,6-c][1,2,3]*benzotriazines*.—We considered that these pyrimidobenzotriazines might be obtainable by the synthetic sequence (4) ⟶ (6) outlined in Scheme 1. Accordingly, our efforts were concentrated on devising a synthesis of the *o*-nitrophenylpyrimidines (4).

(i) *Cyclisation of o-nitroaroyl compounds and guanidines*. Although ethyl benzoylacetate reacts with guanidinium carbonate to afford 2-amino-6-phenylpyrimidin-4(3*H*)-one (7),[10] when methyl *o*-nitrobenzoylacetate was refluxed with guanidinium carbonate in ethanol no pyrimidine was obtained. In strongly alkaline solution a dark gum was obtained from which no identified products were isolated. Possibly the coloured material is an isatogen which is readily formed from methyl *o*-nitrobenzoylacetate in bases.[11]

Modest and his co-workers [12] prepared 2,4-diaminopyrimidines in one step by condensation of monofunctional ketones with cyanoguanidine: by using acetophenone as the ketone, 2,4-diamino-6-phenylpyrimidine was obtained in modest yield. However, cyanoguanidine did not react with *o*-nitroacetophenone under a range of thermal, basic, or acidic conditions.

The reaction of *o*-nitrobenzoyl chloride with malononitrile in tetrahydrofuran containing triethylamine afforded *o*-nitrobenzoylmalononitrile, which was alkylated with dimethyl sulphate to yield the enol ether (8). Cyclisation of the ether with guanidinium carbonate in ethanolic sodium ethoxide furnished the pyrimidine (9). Unfortunately, the cyano-group proved resistant to hydrolysis by concentrated sulphuric or hydrochloric acid, and by hydrogen peroxide in alkali. Reduction of the nitropyrimidine (9) under a range of conditions gave, not the triaminopyrimidine (10), but in all cases the triaminopyrimidoquinoline *N*-oxide (13). Evidently the hydroxylamine (11) formed as an intermediate in these reductions undergoes intramolecular nucleophilic addition to the favourably positioned nitrile group to afford the *N*-hydroxy-tautomer (12) of the pyrimidoquinoline oxide (13). Assignment of the *N*-oxide structure was based on the following evidence: the compound gave a blue colour with iron(III) chloride solution [of the *N*-hydroxy-tautomer (12)]; its electronic absorption spectrum was similar to that of 6-aminophenanthridine 5-oxide (which can itself be prepared by reduction of 2-cyano-2′-nitrobiphenyl [13,14]); its mass spectrum showed the expected molecular ion at *m/e* 242 with a base peak at *m/e* 226 (*M* − 16). Loss of oxygen is a common fragmentation of heteroaromatic *N*-oxides [15]



(4) (5) (6)

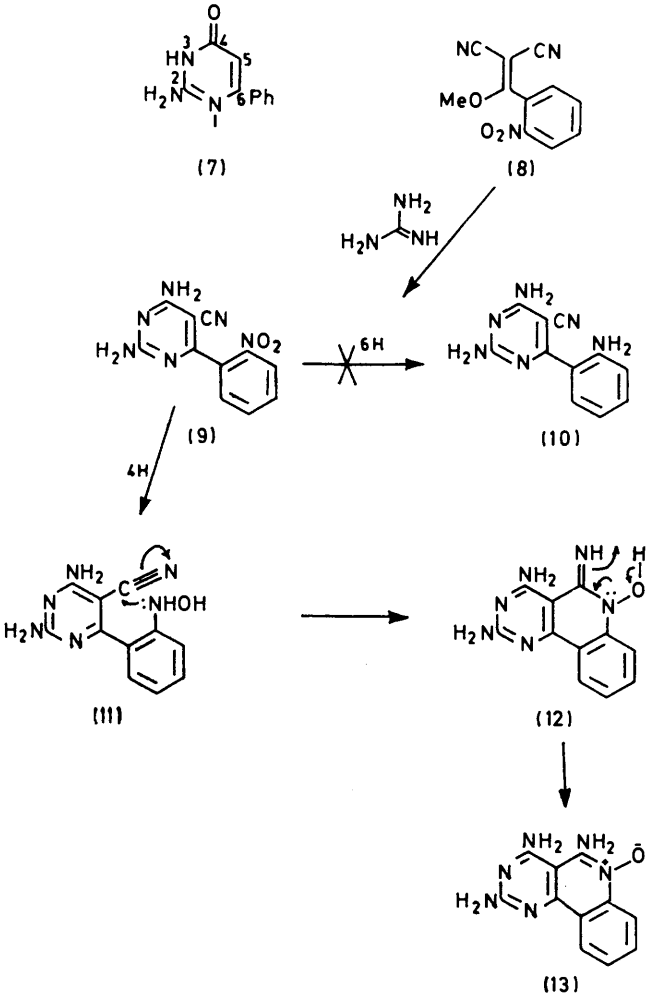
X = O or NH

SCHEME 1

[6] S. M. Mackenzie and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 2298.
[7] S. M. Mackenzie and M. F. G. Stevens, *J.C.S. Perkin I*, 1972, 295.
[8] M. F. G. Stevens, unpublished results.
[9] M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 615.
[10] K. D. Kulkarni, S. S. Sabris, and B. S. Kulkarni, *J. Sci. Ind. Res., India*, 1960, **19***C*, 6.
[11] R. T. Coutts, M. Hooper, and D. G. Wibberley, *J. Chem. Soc.*, 1961, 5205.
[12] E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, 1962, **27**, 2708.
[13] M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1968, 348.
[14] C. W. Muth, J. R. Elkins, M. L. DeMotte, and S. T. Chiang, *J. Org. Chem.*, 1967, **32**, 1106.
[15] Q. N. Porter and J. Baldas, ' Mass Spectrometry of Heterocyclic Compounds,' eds. A. Weissberger and E. C. Taylor, Wiley–Interscience, New York, 1971, p. 409.

and accounts also for the base peak at *m/e* 194 in the mass spectrum of 6-aminophenanthridine 5-oxide.

(ii) *Electrophilic substitution of 6-phenylpyrimidinones.* The ^{1}H n.m.r. spectrum of the pyrimidinone (7) in $(CD_3)_2SO$ shows a sharp singlet at δ 6·1 (H-5), an exchangeable broad singlet at δ 6·6 (NH_2), and the



SCHEME 2

phenyl proton signals as multiplets at δ 7·8—8·0 (2H) and 7·3—7·5 (3H). Nitration of the pyrimidinone (7) with 70% nitric acid in concentrated sulphuric acid at 50° afforded the 5-nitro-6-*p*-nitrophenyl derivative, as evidenced by the disappearance of the singlet at δ 6·1 and the appearance of an AA'XX' pattern for the *para*-disubstituted ring. 6-Phenyluracil also gave a 5-nitro-6-*p*-nitrophenyl derivative under the same conditions. When the susceptible 5-position of the pyrimidinone (7) was blocked by bromination, the resulting 5-bromopyrimidinone also underwent subsequent nitration in the *para*-position of the phenyl group.

Nitration of the pyrimidinone (7) with acetic anhydride–nitric acid gave mixtures of 5-nitro-6-phenyl- and 5-nitro-6-*p*-nitrophenyl-pyrimidinones depending on the conditions. In all these electrophilic substitutions substantial *ortho*-nitration might have been expected because of the possibility of intramolecular assistance by the pyrimidine N(1) atom (*cf.* the high *ortho* : *para* ratio in the nitration of biphenyl-2-carboxylic acid by nitrogen pentaoxide).[16]

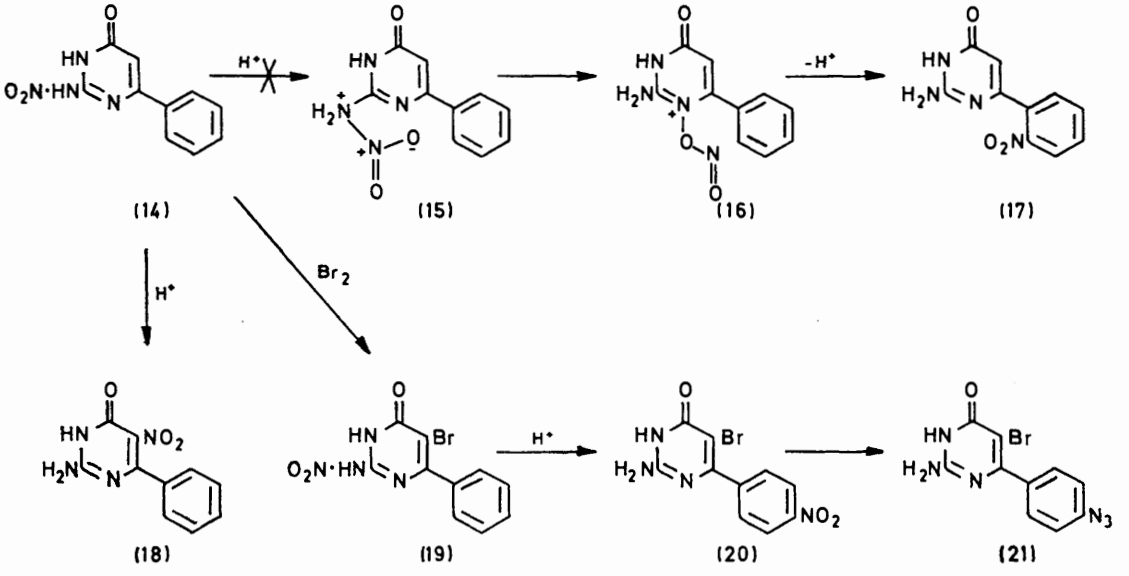
Rearrangement of the nitramine (14) was next examined, because an acid-catalysed 'cartwheel' mechanism involving an *N*-nitro (15) ⟶ *N*-nitrito (16) ⟶ *C*-nitro (17) transformation can be readily envisaged (Scheme 3), analogous to that proposed for the acid-catalysed rearrangement of *N*-nitroaniline.[17] However, the nitramine (14), prepared from ethyl benzoylacetate and nitroguanidine, rearranged in concentrated sulphuric acid exclusively to the 5-nitropyrimidinone (18). Bromination of the nitramine blocked the 5-position and yielded the strongly acidic bromo-nitramine (19), which could be characterised as its ammonium nitronate salt. Rearrangement of this bromonitramine (19) in acid afforded the 5-bromo-6-*p*-nitrophenylpyrimidinone (20), identical with the product formed by the aforementioned direct nitration of 2-amino-5-bromo-6-phenylpyrimidin-4(3*H*)-one. This bromonitropyrimidinone (20) was then successively reduced, diazotised, and converted into the azide (21). This azide could possibly act as a photolabile reagent for dihydrofolic reductase receptor-site labelling.[18]

Nitro ⟶ nitrito rearrangements can also be initiated photochemically.[19] Accordingly, the nitramines (14) and (19) were photolysed in solutions in ethanol and acetone. Only complex mixtures of uncharacterised yellow products were obtained. Even if the desired *o*-nitrophenylpyrimidinones were formed as minor components in these reactions, the route has no preparative use.

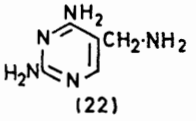
In view of the susceptibility of the 5-position of pyrimidines towards electrophilic substitution, we considered (following a suggestion by Dr. F. L. Rose) that homolytic substitution might involve the 6-position. Accordingly diazotised *o*-nitroaniline was decomposed at pH 9 in the presence of uracil under the conditions of the Gomberg reaction.[20] The red, acidic unidentified product isolated in low yield was not the required 6-*o*-nitrophenyluracil. When 1,3-bis-*o*-nitrophenyltriazene was thermolysed with uracil in xylene or biphenyl, the uracil remained unchanged; in boiling collidine or quinaldine extensive decomposition led to intractable black tar. Evidently the *o*-nitrophenyl radicals which should be generated in these thermolyses[21] do not selectively attack the 6-position, possibly because of the availability of more reactive sites on the uracil molecule.

[16] D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1962, 4579.
[17] D. V. Banthorpe, E. D. Hughes, and D. L. H. Williams, *J. Chem. Soc.*, 1964, 5349.
[18] J. R. Knowles, *Accounts Chem. Res.*, 1972, **5**, 155.
[19] H. A. Morrison, 'The Chemistry of the Nitro and Nitroso Groups,' ed. H. Feuer, Interscience, New York, 1969, part I, p. 177.
[20] M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339.
[21] R. L. Hardie and R. H. Thomson, *J. Chem. Soc.*, 1958, 1286.

Pyrimidines with a 1,2,3-Benzotriazinyl Fragment at the 5-Position.—Reaction of 5-aminomethyl-2,4-diaminopyrimidine (22) with either *o*- or *p*-nitrobenzoyl chloride under Schotten–Baumann conditions afforded the nitrobenzoylpyrimidines (23a and b), which were reduced to the aminobenzoyl analogues (23c and d). Diazotisation of the anthraniloyl isomer (23c) in 2N-hydrochloric acid followed by neutralisation with sodium acetate yielded the triazinone (24). A similar course of reactions starting with 5-amino-6-methyluracil (26) and 2,5-diamino-5-methylpyrimidin-4(3*H*)-one [written as the 2(1*H*)-imino-tautomer (27) for convenience] gave the triazinones (30) and (31), respectively, *via* the aroyl intermediates (28) and (29).



SCHEME 3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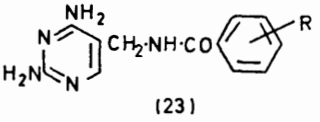
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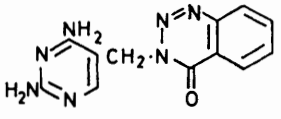
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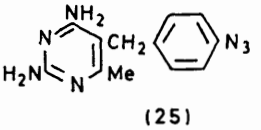
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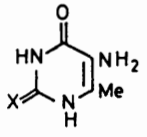
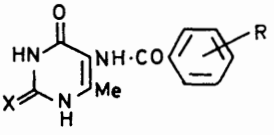
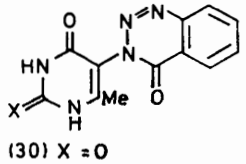

(26) X = O
(27) X = NH


(28) X = O
(29) X = NH


(30) X = O
(31) X = NH

a: R = *o*-NO_2
b: R = *p*-NO_2
c: R = *o*-NH_2
d: R = *p*-NH_2
e: R = *o*-N_3
f: R = *p*-N_3

If diazotisation of the anthraniloylpyrimidine (23c) was carried out in a medium sufficiently acidic to inhibit the competing intramolecular cyclisation, the intermediate diazonium salt could be intercepted with hydrazoic acid to afford the azide (23e). In contrast, the strength of the acid had no effect on the diazotisation of the anthraniloylpyrimidinones (28c) and (29c): intramolecular cyclisation proceeded directly to the triazinones (30) and (31) even in 10N-hydrochloric acid. It is significant that *N*-alkyl- and *N*-aralkyl-*o*-azidobenzamides can be prepared from the corresponding anthranilamides by diazotisation–azidation, but *N*-aryl-*o*-azidobenzamides are not available by this route.[22] No such difficulties attended the preparation of the *p*-azidoarenes (23f), (25), and (29f).

Many of the pyrimidines prepared in the course of this work were screened for tumour-inhibitory activity against lymphoid leukaemia (L-1210) in mice. Preliminary results (which will be reported in full elsewhere) do not indicate any significant activity in the series.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 for potassium bromide discs.

α-Methoxy-o-nitrobenzylidenemalononitrile (8).—A solution of malononitrile (16·5 g) and triethylamine (50·5 g) in tetrahydrofuran (300 ml) was treated at 25° with a solution of *o*-nitrobenzoyl chloride (46·5 g) in anhydrous benzene (100 ml). The mixture was shaken for 30 min, the triethylamine hydrochloride was filtered off, and the benzene layer

[22] A. C. Mair and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1971, 2317.

was shaken with ice–water (500 ml) containing 4N-sulphuric acid (120 ml). The benzene layer was separated, and the aqueous layer was re-extracted with ether (5 × 50 ml). The combined, dried (Na_2SO_4), organic phase was evaporated to leave, as a viscous brown oil, *o*-nitrobenzoylmalononitrile [$\nu_{max.}$ 2250 (C≡N), and 1530 and 1350 cm^{-1} (NO_2)] which was not further purified.

The crude oil (10·0 g), dimethyl sulphate (10 ml), sodium hydrogen carbonate (20·0 g), dioxan (100 ml), and water (10 ml) were refluxed together until carbon dioxide evolution ceased (3 h). The solution was quenched with water and extracted with ether. Evaporation of the extract and crystallisation of the residue from aqueous ethanol furnished the *product* (8) (60%) as white crystals, m.p. 106—107° (Found: C, 57·8; H, 3·3; N, 18·1. $C_{11}H_7N_3O_3$ requires C, 57·7; H, 3·1; N, 18·3%), $\nu_{max.}$ 2220 (C≡N), and 1530 and 1345 cm^{-1} (NO_2); δ ($CDCl_3$) 3·86 (s, OMe).

2,4-*Diamino*-6-o-*nitrophenylpyrimidine*-5-*carbonitrile* (9).—The dinitrile (8) (11·5 g) and guanidinium carbonate (5·0 g) were refluxed (5 h) in sodium ethoxide solution [from sodium (1·2 g) in ethanol (100 ml)], and then poured into ice–water acidified with acetic acid. The precipitated *pyrimidine* (77%) crystallised from ethanol as yellow crystals, m.p. 250—252° (Found: C, 49·6; H, 3·3. $C_{11}H_8N_6O_2$ requires C, 49·4; H, 3·3%); $\nu_{max.}$ 3500 and 3380 (NH_2), 2210 (C≡N), and 1525 and 1360 cm^{-1} (NO_2).

2,4,5-*Triaminopyrimido*[5,4-c]*quinoline* 6-*Oxide* (13).—Catalytic hydrogenation of the nitrile (9) (1·5 g) over 10% palladium–charcoal (0·2 g) (uptake 2 mol. equiv.) gave the buff-coloured *quinazoline oxide* (84%), m.p. 306—307° (from ethanol) (Found: C, 54·9; H, 4·2; N, 34·5%; M^+, 242. $C_{11}H_{10}N_6O$ requires C, 54·5; H, 4·1; N, 34·7%; *M*, 242); $\nu_{max.}$ 3480 and 3380 (NH_2), and 1310 cm^{-1} (N–O); $\lambda_{max.}$ (EtOH) 236, 258, 291, 334, and 388infl nm (log ε 4·53, 4·54, 4·11, 4·07, and 3·47).

Reduction of the nitropyrimidine (9) with either Raney nickel in methanol saturated with ammonia gas at a pressure of 120 atm of hydrogen, or with tin(II) chloride in ethanol gave the same *N*-oxide (74 and 77% yield, respectively).

2-*Amino*-5-*nitro*-6-p-*nitrophenylpyrimidin*-4(3H)-*one*.—Powdered 2-amino-6-phenylpyrimidin-4(3*H*)-one (3·0 g) [10] was added (10 min) to a mixture of concentrated sulphuric acid (18 ml) and 70% nitric acid (18 ml) at 50°. The solution was cooled to 25°, stirred for an additional 20 min, and poured into an excess of ice–water. The precipitated *dinitropyrimidinone* (60%) afforded yellow crystals, m.p. 324—325° (from dimethylformamide) (Found: C, 43·7; H, 2·7. $C_{10}H_7N_5O_5$ requires C, 43·3; H, 2·6%).

5-*Nitro*-6-p-*nitrophenyluracil*.—Nitration of 6-phenyluracil [23] under the conditions described above afforded the *dinitrouracil* (55%), m.p. 228—230° (from water) (Found: C, 42·9; H, 2·4; N, 19·9. $C_{10}H_6N_4O_6$ requires C, 43·2; H, 2·2; N, 20·1%).

2-*Amino*-5-*bromo*-6-*phenylpyrimidin*-4(3H)-*one*.—To 2-amino-6-phenylpyrimidin-4(3*H*)-one (12·0 g) in acetic acid (50 ml) at 70° was added bromine (11·0 g) in acetic acid (50 ml). The solution deposited a white precipitate of the *bromopyrimidinone* (71%), which crystallised from aqueous ethanol; m.p. 246—248° (Found: C, 45·4; H, 2·9; N, 15·5. $C_{10}H_8BrN_3O$ requires C, 45·4; H, 3·0; N, 15·7%).

2-*Amino*-5-*bromo*-6-p-*nitrophenylpyrimidin*-4(3H)-*one* (20).—Nitration of 2-amino-5-bromo-6-phenylpyrimidin-4(3*H*)-one in 1 : 1 concentrated sulphuric acid–70% nitric acid at 25° (20 min) gave the p-*nitrophenylpyrimidinone* (56%) when the water-quenched mixture was basified with concentrated aqueous ammonia. The product gave cream crystals, m.p. 268—270° (from aqueous ethanol) (Found: C, 38·2; H, 2·7; N, 17·6. $C_{10}H_7BrN_4O_3$ requires C, 38·6; H, 2·8; N, 18·0%).

2-*Amino*-5-*nitro*-6-*phenylpyrimidin*-4(3H)-*one* (18).—2-Nitroamino-6-phenylpyrimidin-4(3*H*)-one (5·0 g) [24] was added slowly to concentrated sulphuric acid (15 ml). The mixture was stirred at 30° (4 h), quenched with water, and neutralised with sodium hydrogen carbonate to precipitate the yellow 5-*nitropyrimidinone* (52%), which crystallised from aqueous ethanol; m.p. 274—276° (Found: C, 51·6; H, 3·5; N, 24·0. $C_{10}H_8N_4O_3$ requires C, 51·7; H, 3·5; N, 24·1%).

5-*Bromo*-2-*nitroamino*-6-*phenylpyrimidin*-4(3H)-*one* (19).—Bromine (3·5 g) in acetic acid (15 ml) was added at 70° to a solution of 2-nitroamino-6-phenylpyrimidin-4(3*H*)-one (4·6 g) in acetic acid (25 ml). The mixture was stirred for 3 h at room temperature and the white *bromonitroaminopyrimidinone* (77%) was collected; m.p. 192—193° (from aqueous ethanol) (Found: C, 38·8; H, 2·3; N, 17·8. $C_{10}H_7BrN_4O_3$ requires C, 38·7; H, 2·3; N, 18·1%). The *ammonium salt* crystallised from aqueous ethanolic ammonia as needles, m.p. 204—206° (Found: C, 37·0; H, 3·0; N, 21·2. $C_{10}H_{10}BrN_5O_3$ requires C, 36·8; H, 3·1; N, 21·4%).

Rearrangement of the bromonitroaminopyrimidinone (19) in concentrated sulphuric acid at 30° for 4 h afforded 2-amino-5-bromo-6-*p*-nitrophenylpyrimidin-4(3*H*)-one (52%) when the solution was poured into ice–water and basified with aqueous ammonia. The product was identical (i.r.) with the sample prepared by nitration of 2-amino-5-bromo-6-phenylpyrimidin-4(3*H*)-one.

2-*Amino*-6-p-*azidophenyl*-5-*bromopyrimidin*-4(3H)-*one* (21).—2-Amino-5-bromo-6-*p*-nitrophenylpyrimidin-4(3*H*)-one (7·0 g) was reduced in ethanol at 70° with Raney nickel (2·0 g) and hydrazine hydrate (20 ml; added in 4 ml portions over 1 h). Removal of catalyst and evaporation of the solution gave crude 2-amino-6-*p*-aminophenyl-5-bromopyrimidin-4(3*H*)-one (3·0 g), which was used without further purification. This diamine (3·0 g) in 2N-hydrochloric acid (50 ml) was diazotised with sodium nitrite (1 mol. equiv.), treated with sodium azide (2·0 g), and stirred at 0° for 2 h. After neutralisation with sodium acetate the *azidophenylpyrimidinone* (68%) was collected and crystallised from aqueous ethanol; m.p. 223—224° (with effervescence) (Found: C, 39·3; H, 2·3; N, 27·4. $C_{10}H_7BrN_6O$ requires C, 39·1; H, 2·3; N, 27·5%); $\nu_{max.}$ 2120 and 2095 cm^{-1} (N_3).

2,4-*Diamino*-5-o-*nitrobenzamidomethylpyrimidine* (23a).—2,4-Diamino-5-aminomethylpyrimidine dihydrochloride (4·0 g) [25] in 2N-sodium hydroxide (60 ml) was treated with *o*-nitrobenzoyl chloride (5·0 g) in benzene (50 ml). The o-*nitrobenzamidomethylpyrimidine* (54%) was collected and crystallised from aqueous ethanol; m.p. 252—253° (Found: C, 50·2; H, 4·2; N, 29·0. $C_{12}H_{12}N_6O_3$ requires C, 50·0; H, 4·2; N, 29·1%).

2,4-*Diamino*-5-p-*nitrobenzamidomethylpyrimidine* (23b), similarly prepared (63%), crystallised from aqueous ethanol; m.p. 267—268° (Found: C, 50·1; H, 4·2; N, 28·9%).

2,4-*Diamino*-5-o-*aminobenzamidomethylpyrimidine* (23c),

[23] J. H. Burckhalter and H. C. Scarborough, *J. Amer. Pharm. Assoc.*, 1955, **44**, 545.

[24] K. Shirakawa, *Yakugaku Zasshi*, 1959, **79**, 1477 (*Chem. Abs.*, 1960, **54**, 11,038).

[25] W. Huber, *J. Amer. Chem. Soc.*, 1943, **65**, 2222.

prepared (74%) by reduction of the corresponding *o*-nitrobenzamide (23a) with Raney nickel and hydrazine hydrate in ethanol at 70°, had m.p. 253—255° (from aqueous ethanol) (Found: C, 53·8; H, 5·3; N, 32·3. $C_{12}H_{14}N_6O$ requires C, 53·7; H, 5·4; N, 32·5%).

2,4-*Diamino*-5-p-*aminobenzamidomethylpyrimidine* (23d), similarly prepared (78%) by reduction of the *p*-nitrobenzamide (23b), had m.p. 282—284° (Found: C, 53·6; H, 5·4; N, 32·4%).

2,4-*Diamino*-5-o-*azidobenzamidomethylpyrimidine* (23e).—A solution of 2,4-diamino-5-*o*-aminobenzamidomethylpyrimidine (2·0 g) in 10N-hydrochloric acid (20 ml) was cooled to 0° and diazotised with sodium nitrite (1 mol. equiv.) in water (5 ml). Sodium azide (2·0 g) was added in portions to the diazonium solution and the mixture was stirred (1 h) at 0°. The o-*azidobenzamidopyrimidine* (85%) was precipitated by addition of an excess of sodium acetate and had m.p. 154—155° (efferv.) (from aqueous ethanol) (Found: C, 51·0; H, 4·4; N, 39·2. $C_{12}H_{12}N_8O$ requires C, 50·7; H, 4·2; N, 39·4%); $\nu_{max.}$ 2140 and 2110 cm^{-1} (N_3).

2,4-*Diamino*-5-p-*azidobenzamidomethylpyrimidine* (23f) was similarly prepared (54%) with 2N-hydrochloric acid as the diazotising medium, and had m.p. 175—176° (efferv.) (Found: C, 50·5; H, 4·5; N, 39·6%); $\nu_{max.}$ 2145 and 2120 cm^{-1} (N_3).

3-(2,4-*Diaminopyrimidin*-5-*ylmethyl*)-1,2,3-*benzotriazin*-4(3H)-*one* (24).—Diazotisation of a solution of 2,4-diamino-5-*o*-aminobenzamidomethylpyrimidine in 2N-hydrochloric acid with sodium nitrite (1 mol. equiv.) gave the *triazinone* (62%) when the mixture was neutralised with sodium acetate; m.p. 124—125° (from aqueous ethanol) (efferv.) (Found: C, 53·2; H, 4·1; N, 36·2. $C_{12}H_{11}N_7O$ requires C, 53·6; H, 4·1; N, 36·4%).

2,4-*Diamino*-5-p-*azidobenzyl*-6-*methylpyrimidine* (25).—A solution of 2,4-diamino-5-*p*-aminobenzyl-6-methylpyrimidine [26] in 2N-hydrochloric acid was diazotised at 0° and treated with an excess of sodium azide as previously described. The p-*azidobenzylpyrimidine* (78%) precipitated when the solution was neutralised with sodium acetate, and crystallised from ethanol as bronze needles, m.p. 197—198° (efferv.) (Found: C, 56·3; H, 5·2; N, 38·7. $C_{12}H_{13}N_7$ requires C, 56·5; H, 5·1; N, 39·0%); $\nu_{max.}$ 2110 cm^{-1} (N_3).

6-*Methyl*-5-o-*nitrobenzamidouracil* (28a).—5-Amino-6-methyluracil (4·0 g) [27] in 2N-sodium hydroxide (60 ml) was shaken with *o*-nitrobenzoyl chloride (7·5 g) in benzene (30 ml) for 1 h. The solid *benzamidouracil* (5·0 g), precipitated when the aqueous layer was acidified with acetic acid, was crystallised from aqueous ethanol (unmelted at 330°) (Found: C, 49·9; H, 3·6; N, 27·9. $C_{12}H_{10}N_4O_5$ requires C, 49·6; H, 3·4; N, 27·6%).

[26] E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3758.

2-*Amino*-6-*methyl*-5-o-*nitrobenzamidopyrimidin*-4(3H)-*one* (29a).—Prepared by *o*-nitrobenzoylation of 2,5-diamino-6-methylpyrimidin-4(3*H*)-one,[28] this *nitrobenzamidopyrimidinone* (73%) had m.p. 322—324° (from aqueous ethanol) (Found: C, 49·6; H, 3·8; N, 24·0. $C_{12}H_{11}N_5O_4$ requires C, 49·8; H, 3·8; N, 24·2%).

2-*Amino*-6-*methyl*-5-p-*nitrobenzamidopyrimidin*-4(3*H*)-*one* (29b), similarly prepared from *p*-nitrobenzoyl chloride and 2,5-diamino-6-methylpyrimidin-4(3*H*)-one, was unmelted at 330° (Found: C, 49·9; H, 3·8; N, 24·1%).

5-o-*Aminobenzamido*-6-*methyluracil* (28c).—Reduction of 6-methyl-5-*o*-nitrobenzamidouracil (4·0 g) with Raney nickel and hydrazine hydrate in ethanol at 70° afforded the *aminobenzamidomethyluracil* (60%), which crystallised from aqueous ethanol as white needles (unmelted at 320°) (Found: C, 55·8; H, 4·6; N, 18·3. $C_{12}H_{12}N_4O_3$ requires C, 55·4; H, 4·7; N, 18·4%).

Similarly prepared were the following: 2-*amino*-5-o-*aminobenzamido*-6-*methylpyrimidin*-4(3H)-*one* (29c) (78%), m.p. 288—289° (from aqueous ethanol) (Found: C, 55·5; H, 5·0; N, 26·9. $C_{12}H_{13}N_5O_2$ requires C, 55·6; H, 5·1; N, 27·0%); 2-*amino*-5-p-*aminobenzamido*-6-*methylpyrimidin*-4(3H)-*one* (29d), m.p. 329—330° (Found: C, 55·7; H, 5·1; N, 26·8%).

5-(3,4-*Dihydro*-4-*oxo*-1,2,3-*benzotriazin*-3-*yl*)-6-*methyluracil* (30).—A solution of 5-*o*-aminobenzamido-6-methyluracil (2·0 g) in 2N-hydrochloric acid (30 ml) was diazotised at 0° with sodium nitrite (0·7 g) in water (5 ml). The precipitated *benzotriazinone* (78%) crystallised from aqueous ethanol; m.p. 293—295° (efferv.) (Found: C, 53·0; H, 3·2; N, 25·5. $C_{12}H_9N_5O_3$ requires C, 53·1; H, 3·3; N, 25·8%).

2-*Amino*-5-(3,4-*dihydro*-4-*oxo*-1,2,3-*benzotriazin*-3-*yl*)-6-*methylpyrimidin*-4(3H)-*one* (31), similarly prepared by diazotisation of 2-amino-5-*o*-aminobenzamido-6-methylpyrimidin-4(3*H*)-one, crystallised from aqueous ethanol; m.p. 229—230° (efferv.) (Found: C, 53·2; H, 3·9; N, 31·1. $C_{12}H_{10}N_6O_2$ requires C, 53·2; H, 3·7; N, 31·1%).

2-*Amino*-5-p-*azidobenzamido*-6-*methylpyrimidin*-4(3H)-*one* (29f).—This p-*azidobenzamidopyrimidine*, prepared (56%) by diazotisation of 2-amino-5-*p*-aminobenzamido-6-methylpyrimidin-4(3*H*)-one in 2N-hydrochloric acid, followed by treatment with an excess of sodium azide, had m.p. 180—181° (from aqueous ethanol) (Found: C, 49·7; H, 4·2; N, 34·3. $C_{12}H_{11}N_7O_2$ requires C, 50·0; H, 3·9; N, 34·0%); $\nu_{max.}$ 2120 and 2090 cm^{-1} (N_3).

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[27] R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 2418.

[28] B. R. Baker and D. V. Santi, *J. Pharm. Sci.*, 1965, **54**, 1252.