# Pyrimidines. Part XVII.[1] Nitration of 5-Acetamido-2-phenylpyrimidine and the Synthesis of Some 5-Nitropyrimidines

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Nitration of 5-acetamido-2-phenylpyrimidine gave 5-acetamido-2-*m*-nitrophenylpyrimidine as the only isolable product. Thus the electron-releasing effect of the 5-acetamido-group is insufficient to overcome the deactivating influence, on the 2-phenyl group, of the pyrimidine ring. The synthesis of several new 5-nitropyrimidines derived from 2-chloro-5-nitropyrimidine is described.

Lythgoe and Rayner [2] showed that, owing to the deactivating influence of the two pyrimidine-ring nitrogen atoms, 2-phenylpyrimidine undergoes nitration only in the *meta*-position of the benzene nucleus. With phenylpyridines, however, as shown by Forsyth and Pyman,[3] the influence of the single nuclear nitrogen atom is insufficient to prevent some *ortho–para*-substitution in the phenyl ring and a mixture of all three isomers is obtained.

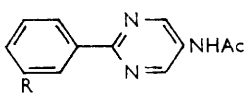
An electron-releasing group in position 5 of the pyrimidine ring would tend to counteract this deactivating effect and we have here examined the nitration of 5-acetamido-2-phenylpyrimidine (I; R = H) in an attempt to find out whether such opposition is powerful

[1] Part XVI, M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, *J. Chem. Soc.* (*C*), 1967, 1204.

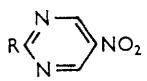
[2] B. Lythgoe and L. S. Rayner, *J. Chem. Soc.*, 1951, 2323.

[3] R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 1926, 2912.

enough to allow *ortho–para*-substitution to take place. The only product isolated, however, was the *meta*-compound (I; R = $NO_2$), the orientation of which was determined by reduction and acetylation to a diacetamido-compound, identical with the product (I; R = NHAc) from similar treatment of 5-nitro-2-*m*-nitrophenylpyrimidine (II; R = *m*-$NO_2 \cdot C_6H_4$).




(I)

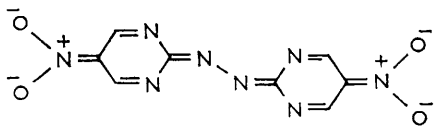



(II)

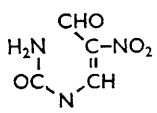
5-Acetamido-2-phenylpyrimidine (I; R = H) has been prepared by Fanta [4] by reduction of the nitro-compound (II; R = Ph) with sodium dithionite, followed by acetylation; we carried out the reduction with hydrazine in the presence of a palladium–charcoal catalyst. An attempt to nitrate compound (I; R = H) directly, in the usual manner, with nitric and sulphuric acids, failed, but the nitrate prepared from (I; R = H) readily underwent nitration when added to concentrated sulphuric acid.

5-Nitro-2-*m*-nitrophenylpyrimidine (II; R = *m*-$NO_2 \cdot C_6H_4$) was prepared by nitration of 5-nitro-2-phenylpyrimidine (I; R = H), and the orientation of the substituents was confirmed by direct comparison with an authentic sample of the dinitro-compound made by condensation of 3-nitrobenzamidine with nitromalonaldehyde.[4]

During attempts to synthesise 5-nitropyrimidine, a number of new derivatives of this compound have been prepared. 2-Chloro-5-nitropyrimidine [5] (II; R = Cl) reacted rapidly with hydrazine hydrate in ethanol to give 2-hydrazino-5-nitropyrimidine (II; R = NH·$NH_2$) or *NN'*-bis-5-nitropyrimidin-2-ylhydrazine, according to the conditions. The latter formed a diacetyl derivative with acetic anhydride and dissolved in 0·1N-sodium hydroxide to give a deep blue solution, presumably by ionisation of the hydrazine protons facilitated by the strong electron-attracting power of the nitropyrimidine rings. The strong colour of the dianion is probably due to delocalisation of the negative charge over the two hydrazine, and, the four ring-nitrogen atoms, and the two nitro-groups, *e.g.*, as in (III). The



(III)




(IV)

bis-compound also formed a deep red monoammonium salt. Attempts to oxidise 2-hydrazino-5-nitropyrimidine to 5-nitropyrimidine with copper sulphate under conditions used for the preparation of pyrimidine [6] from 2-hydrazinopyrimidine were unsuccessful. 2-Chloro-5-nitro- and 2,4-dichloro-5-nitro-pyrimidine with toluene-*p*-sulphonohydrazide gave the corresponding toluene-*p*-sulphonylhydrazinopyrimidines but these did not give 5-nitropyrimidine on treatment with alkali under conditions used for making pyrimidine.[6] Since this work was carried out, D. J. Brown *et al.*[7] have reported the preparation of 5-nitropyrimidine by the oxidation of 4,6-dihydrazino-5-nitropyrimidine with silver oxide.

The preparation of 2-chloro-5-nitropyrimidine proved unexpectedly difficult. Roblin *et al.*[5] made it by chlorination with phosphoryl chloride of 2-hydroxy-5-nitropyrimidine, which itself was made by hydrolysis of 2-amino-5-nitropyrimidine. In our hands, this hydrolysis gave products which either did not undergo chlorination or else gave very low yields of the chloropyrimidine. However, we found that the latter could be made satisfactorily from nitromalonaldehyde monoureide (IV) which underwent ring closure and chlorination in one step when boiled with phosphoryl chloride.

## EXPERIMENTAL

*5-Acetamido-2-phenylpyrimidine* (I; R = H).—5-Nitro-2-phenylpyrimidine [4] (6 g.) was dissolved in hot benzene (150 ml.) and 5% palladium–charcoal (3 g.) was added, followed by 100% hydrazine hydrate (7·5 ml.). The mixture was boiled for 2 hr., then more hydrazine hydrate (7·5 ml.) was added and the whole was boiled for 2 hr. more. The hot mixture was filtered and the filtrate was treated with charcoal and concentrated. The cooled solution gave 5-amino-2-phenylpyrimidine (3·5 g., 67%). A sample, recrystallised from ethanol–benzene and twice sublimed *in vacuo*, had m.p. 94·5—96·5° (lit.,[4] 90—91°).

Acetylation of 5-amino-2-phenylpyrimidine gave 5-acetamido-2-phenylpyrimidine as plates, m.p. 208—209 (from ethanol–water) (lit.,[4] 208—209°) (Found: C, 67·8; H, 4·8; N, 20·0. Calc. for $C_{12}H_{11}N_3O$: C, 67·6; H, 5·2; N, 19·7%).

*Nitration of 5-Acetamido-2-phenylpyrimidine.*—5-Acetamido-2-phenylpyrimidine (1·8 g.) was dissolved in concentrated nitric acid. The solution was set aside for a few min., then added to water, to give 5-acetamido-2-phenylpyrimidine nitrate (2 g., 86%). When recrystallisation from water was attempted, starting material was regenerated; recrystallisation of a sample from benzene–ethanol gave the *nitrate*, m.p. 167° (Found: C, 52·6; H, 4·8; N, 20·7. $C_{12}H_{12}N_4O_4$ requires C, 52·2; H, 4·4; N, 20·3%). The nitrate (0·25 g.) was added in portions to concentrated sulphuric acid (0·37 ml.) with cooling. The mixture was warmed on a water-bath for 4 min., set aside at room temperature for 15 min., then added dropwise, with shaking, to water (5 ml.). The initial yellow precipitate dissolved after a few min. After filtration to remove a small amount of dark tar, the solution was treated dropwise with aqueous ammonia (*d* 0·88) until precipitation

[4] P. E. Fanta and E. A. Hedman, *J. Amer. Chem. Soc.*, 1956, **78**, 1434.
[5] R. O. Roblin, P. S. Winnek, and J. P. English, *J. Amer. Chem. Soc.*, 1942, **64**, 567.
[6] M. P. V. Boarland, J. F. W. McOmie, and R. N. Timms, *J. Chem. Soc.*, 1952, 4691.
[7] M. E. C. Biffin, D. J. Brown, and T. C. Lee, *J. Chem. Soc.* (*C*), 1967, 573.

of the product was just complete. Crude *5-acetamido-2-m-nitrophenylpyrimidine* (70 mg., 30%) was collected; m.p. 235—236° (decomp.) [from ethanol–water (charcoal)] (Found: C, 55·7; H, 4·2; N, 22·0. $C_{12}H_{10}N_4O_3$ requires C, 55·8; H, 3·9; N, 21·7%).

*5-Nitro-2-m-nitrophenylpyrimidine.*— 5-Nitro-2-phenyl pyrimidine [4] (1 g.) in concentrated sulphuric acid (1·7 ml.) was treated with concentrated nitric acid (1 ml.) and warmed over a water-bath for 1 hr. The cooled mixture was added to water (5 ml.) and the 5-nitro-2-*m*-nitrophenylpyrimidine was collected and gave plates (0·6 g., 49%) m.p. 133—134° (from ethanol) (Found: C, 49·1; H, 2·7; N, 23·1. Calc. for $C_{10}H_6N_4O_4$: C, 48·8; H, 2·4; N, 22·8%). Mixed m.p. with a sample (m.p. 135—136°) prepared by Fanta and Hedman,[4] 134—135°.

2-m-*Acetamidophenylpyrimidine.*— 5-Nitro-2-*m*-nitrophenyl pyrimidine (0·4 g.) in benzene (10 ml.) and ethanol (5 ml.) was heated under reflux with 5% palladium–charcoal (0·2 g.) and 100% hydrazine hydrate (0·5 ml.) for 2 hr. More hydrazine hydrate (0·5 ml.) was added, and the refluxing was continued for another 2 hr. The hot solution was filtered and concentrated *in vacuo* to give *5-amino-2-m-aminophenylpyrimidine* (0·2 g., 66%), m.p. 146—147° (from benzene) (Found: C, 64·7; H, 5·4; N, 30·5. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1).

5-Amino-2-*m*-aminophenylpyrimidine (0·16 g.), when boiled with acetic acid (1 ml.) and acetic anhydride (0·5 ml.), gave *5-acetamido-2-m-acetamidophenylpyrimidine* (0·15 g. 65%), m.p. 281° [from ethanol–water (charcoal) and benzene–ethanol] (Found: 62·2; H, 5·3; N, 20·6. $C_{14}H_{14}N_4O_2$ requires C, 62·2; H, 5·2; N, 20·7%).

*Reduction and Acetylation of 5-Acetamido-2-m-nitrophenylpyrimidine.*—Crude 5-acetamido-2-*m*-nitrophenylpyrimidine (75 mg.) in benzene (4 ml.) and ethanol (4 ml.) with 100% hydrazine hydrate (0·2 ml.) and 5% palladium–charcoal (40 mg.) was heated under reflux for 2 hr., additional hydrazine hydrate (0·2 ml.) was added, and the heating was continued for a further 2 hr. The mixture was filtered and evaporated *in vacuo*, and the residue was heated with acetic acid–acetic anhydride. The product gave the acetyl derivative (9 mg.), m.p. 276—278° [from ethanol–water (charcoal)]. Recrystallisation from benzene–ethanol raised the m.p. to 280—281°; the mixed m.p. with 5-acetamido-2-*m*-acetamidophenylpyrimidine was not depressed.

*2-Chloro-5-nitropyrimidine.*—Nitromalonaldehyde monoureide (IV) [8] (5 g.) and phosphoryl chloride (25 ml.) were boiled under reflux for 1 hr. The excess of phosphoryl chloride was removed under reduced pressure and the residue was poured on ice. The product was collected in ether and was washed with aqueous sodium hydrogen carbonate then water alone. Removal of the solvent and recrystallisation from petroleum (b.p. 80—100°) gave 2-chloro-5-nitropyrimidine (0·7 g., 14%), m.p. 108°. It did not depress the m.p. of a sample (m.p. 109—111°) made by the procedure of Roblin *et al.*[5]

*2-Hydrazino-5-nitropyrimidine.*—When 100% hydrazine hydrate (0·21 ml.) was added to 2-chloro-5-nitropyrimidine (0·34 g.) in ethanol (15 ml.), soft matted needles of *2-hydrazino-5-nitropyrimidine* (0·32 g., 97%) separated. A sample gave needles, m.p. 168—169° [from ethanol (charcoal)], which rapidly turned yellow in air (Found: C, 31·5; H, 3·2. $C_4H_5N_5O_2$ requires C, 31·0; H, 3·25%), $\lambda_{max.}$ (ethanol) 335 mμ (log ε 3·90).

*NN'-Bis-5-nitropyrimidin-2-ylhydrazine.*—A mixture of 2-chloro-5-nitropyrimidine (0·2 g.) and 100% hydrazine hydrate (0·04 ml.) in ethanol (10 ml.) was boiled for 1 hr. The *pyrimidinyl hydrazine* separated from the cooled mixture as orange plates (65 mg., 37%), m.p. 257° (from ethanol) (Found: C, 34·7; H, 2·5; N, 40·7. $C_8H_6N_8O_4$ requires C, 34·5; H, 2·2; N, 40·3%), $\lambda_{max.}$ (0·1N-hydrochloric acid) 320 mμ (log ε 4·36), $\lambda_{max.}$ (0·1N-sodium hydroxide) 293 and 592 mμ (log ε 3·91 and 4·61).

When ammonia (*d* 0·88) was added to a solution of the above compound in ethanol the red *mono-ammonium salt* separated (Found: C, 32·9; H, 2·8. $C_8H_9N_9O_4$ requires C, 32·55; H, 3·1%). The *NN'-diacetyl derivative* was prepared by heating the pyrimidinyl hydrazine in acetic anhydride for 0·5 hr.; m.p. 168—169° (from ethanol) (Found: C, 39·4; H, 2·7. $C_{12}H_{10}N_8O_6$ requires C, 39·8; H, 2·8%).

*5-Nitro-2,4-bistoluene-p-sulphonylhydrazinopyrimidine.*—A mixture of 2,4-dichloro-5-nitropyrimidine [9] (3 g.) and toluene-*p*-sulphonohydrazide (8·6 g.) in ethanol (20 ml.) was boiled under reflux for 1·5 hr. The solution was concentrated and, when cooled, yielded the *product* (5·8 g., 76%), m.p. 215—216° (from methanol–benzene) (Found: C, 43·8; H, 4·0; N, 19·6. $C_{18}H_{19}N_7O_6S_2$ requires C, 43·8; H, 3·9; N, 19·9%).

*5-Nitro-2-toluene-p-sulphonylhydrazinopyrimidine.*— This was prepared similarly (69%) from 2-chloro-5-nitropyrimidine. The *compound* had m.p. 243—244° (from methanol) (Found: C, 43·0; H, 3·5. $C_{11}H_{11}N_5O_4S$ requires C, 42·9; H, 3·6%).

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[8] W. J. Hale and H. C. Brill, *J. Amer. Chem. Soc.*, 1912, **34**, 82.

[9] N. Whittaker, *J. Chem. Soc.*, 1951, 1565.