Diazo Coupling Reactions of Some Methylpyrimidines

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The coupling of diazotised *p*-chloroaniline with 4-methyl- and 4,6-dimethyl-2-pyrimidone has been shown to occur not at the 5-position as previously reported, but at the 4-methyl group to give the *p*-chlorophenylhydrazones of the corresponding pyrimidine-4-carbaldehydes. 2,6-Dimethyl-4-pyrimidone and 1,4,6-trimethyl-2-pyrimidone undergo the same reaction at the 6-methyl group. *p*-Chlorobenzenediazonium chloride has been shown to react with 5-methylcytosine to give a *p*-chlorophenylazoaminopyrimidine which also has another *p*-chlorophenyl azo-group, probably at N-1.

THE 5-position of pyrimidine is the least electron-deficient and, if vacant, the most likely to be attacked by electrophilic reagents. However, the presence of at least one electron-releasing group, such as NH_2 or OH, preferably in the 2-position, is required for successful diazo coupling reactions, and the reaction takes place much more readily if two electron-releasing groups are present.[1,2]

Although diazo coupling is useful for introducing a 5-amino-group into pyrimidines, since the coupling and subsequent reduction can frequently be carried out under mild conditions, little systematic work seems to have been carried out on this reaction.

The conditions under which pyrimidines couple with diazo compounds have been reviewed [1-5] and many examples of coupling in the 5-position are known (see refs. 1 and 2 for examples). Among the compounds reported to give 5-arylazopyrimidines in good yield are 6-methylpyrimidine-2,4-dione (1a) [3] and 4-methyl- (2a) [4] and 4,6-dimethyl-2-pyrimidone (2b).[4,6]

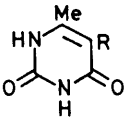
The site of coupling with (1a) has been shown [3] to be the 5-position by reduction of the arylazo-product to the known 5-aminopyrimidine (1b). However, the reported formation of the 5-arylazo-derivatives of (2a and b) has been assumed without confirmation.

We have coupled diazotised *p*-chloroaniline with compounds (2a and b) under the conditions described by Polonovski and Pesson,[4] and have shown that the products, obtained in high yield, are the *p*-chlorophenylhydrazones (2c and d), respectively, resulting from attack at the 4-methyl group.

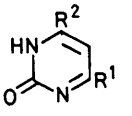
The n.m.r. spectrum of (2c) in trifluoroacetic acid shows doublets for the 5- and 6-protons at τ 2.5 and 1.4, respectively; the methine singlet appears at τ 2.2 and the A_2B_2 system of the *para*-disubstituted benzene ring at τ 1.6—2.1. The mass spectrum shows the molecular ion at *m/e* 248 (for ^{35}Cl), the base peak being at *m/e* 91 ($C_6H_5N^{+\cdot}$).

The n.m.r. spectrum of (2d) shows the signals for the benzene ring protons together with the methine proton at τ 1.6—1.9, the 5-proton signal at τ 2.5 and the 6-methyl signal at τ 6.7. The mass spectrum shows the molecular ion at *m/e* 262 (for ^{35}Cl), the base peak being at *m/e* 127 ($^{35}ClC_6H_4NH_2$).

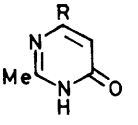
Thus it seems that if the only strongly electron-releasing group in the pyrimidine ring is a 2-' hydroxy '-group, coupling does not occur at the 5-position, but attack at a 4-methyl group can occur. 2-Pyrimidone itself is known not to undergo diazo coupling.[1]



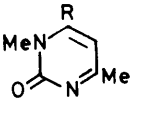
(1) a; R = H
b; R = NH_2



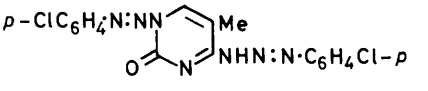
(2) a; R^1 = Me, R^2 = H
b; R^1 = R^2 = Me
c; R^2 = H, R^1 = CH:N·NH·C_6H_4Cl-*p*
d; R^2 = Me, R^1 = CH:N·NH·C_6H_4Cl-*p*



(3) a; R = Me
b; R = CH:N·NH·C_6H_4Cl-*p*



(4) a; R = Me
b; R = CH:N·NH·C_6H_4Cl-*p*



(5)

Diazo coupling reactions with 2,6-dimethyl-4-pyrimidone (3a) and 1,4,6-trimethyl-2-pyrimidone (4a) gave the products (3b) and (4b), respectively, resulting from attack at the 6-methyl group, further establishing that with only one strongly electron-releasing group 5-diazo coupling is not favoured and 4(6)-methyl attack is preferred.

The diazo coupling of (4a) is thought to occur at the 6- rather than the 4-methyl group since the former methyl group has been shown to be the more reactive to deuterium exchange [7] and the 6-methyl group of 1,4,5,6-tetramethyl-2-pyrimidone has been shown [8] to be

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[2] D. J. Brown, ' The Pyrimidines, Supplement I,' Wiley-Interscience, New York and London, 1970.
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[5] M. Israel, H. Schlein, C. Maddock, S. Farber, and E. Modest, *J. Pharm. Sci.*, 1966, **55**, 568.
[6] P. N. Evans, *J. Prakt. Chem.*, 1893, **48**, 489.
[7] T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171.
[8] D. T. Hurst, S. G. Jonas, J. Outram, and R. A. Patterson, *J.C.S. Perkin I*, 1977, 1688.

the more reactive to nitrosation. However we have not as yet been able to obtain conclusive proof of this by unambiguous synthesis.

The existence of each of the above products in the methine (CH:N·NHAr) rather than the methylene (CH_2·N:NAr) form is indicated by the n.m.r. spectra, which do not show CH_2 signals but do show in the low field region either a one-proton methine singlet or a signal corresponding to the benzene ring protons plus one.

The site of reaction for the diazo coupling of pyrimidines is thus analogous in many cases to that for the nitrosation. Nitrosation of 4(6)-methylpyrimidines to form the oximes of the corresponding pyrimidinecarbaldehydes has been observed in a number of cases.[8-10] Also, whereas some pyrimidinethiones react with nitrous acid to form disulphides,[8] some react with diazotised amines to give arylthiopyrimidines.[11]

The use of diazo coupling reactions to introduce nitrogen functionality at the 5-position of the pyrimidine ring is thus seen to be less widely applicable than has been previously inferred.

Several groups of workers[3,12,13] have noted that diazotised sulphanilic acid gives a red colour with thymine and some other 5-substituted pyrimidines, this method (the ' Hunter ' method) having been used for the determination of thymine.[14,15] However, these workers were all unsuccessful in attempting to isolate and identify the products of these reactions. We also have so far not identified the products of diazo coupling reactions of thymine. However, we have coupled diazotised *p*-chloroaniline with 5-methylcytosine to obtain a deep red product in high yield. This product has two diazo groups attached to one pyrimidine ring and we propose the structure (5). The n.m.r. spectrum (trifluoroacetic acid) shows the A_2B_2 pattern for the benzene ring protons at τ 2.1—2.6, the 6-proton signal at τ 3.4, and that of the 5-methyl protons at τ 7.4 (integral ratios 8 : 1 : 3). The mass spectrum shows the molecular ion at *m/e* 401 ($C_{17}H_{13}{}^{35}Cl_2N_7O$), the base peak being at *m/e* 127 ($^{35}ClC_6H_4NH_2$). Other major fragment ions include *m/e* 290 [M − 111($C_6H_4{}^{35}Cl$)], 262 [M − 139($C_6H_4{}^{35}ClN_2$)], and others indicative of dual coupling of the diazo compound with 5-methylcytosine.

A theory for coupling of diazotised amines with thymine has been proposed,[16] although no positive evidence was offered. The above result seems to provide such evidence in the case of 5-methylcytosine. Our results on thymine also tend to support the coupling of two molecules of diazotised amine with one of thymine.[17]

EXPERIMENTAL

N.m.r. spectra were recorded with a Perkin-Elmer R10 60 MHz spectrometer and mass spectra with an A.E.I. MS9 spectrometer; elemental analyses were carried out by the Butterworth Microanalytical Consultancy.

Diazotisation of p-*Chloroaniline.*[4]—Typically *p*-chloroaniline (8.7 g) was dissolved in 50% hydrochloric acid (67 ml) with warming and the solution was cooled in ice–salt to below 10 °C. Sodium nitrite (4.7 g) in water (*ca.* 20 ml) was added dropwise with stirring, the temperature being kept at about 5 °C. The resulting clear solution was used immediately.

Coupling of 4-*Methyl*-2-*pyrimidone.*[4]—4-Methyl-2-pyrimidone hydrochloride (10 g) was dissolved in water (200 ml) containing sodium acetate (50 g) with warming. The solution was then cooled to below 3 °C in ice–salt and the diazotised *p*-chloroaniline was added dropwise with stirring. Stirring was continued for 6 h, then the precipitate was collected, washed with water, and dried under vacuum. The solid produced (2c) was extracted with toluene (Soxhlet) and the red crystalline 1,2-*dihydro*-2-*oxopyrimidine*-4-*carbaldehyde* p-*chlorophenylhydrazone* (100%) was dried *in vacuo*; m.p. 300—303° (decomp.), τ (CF_3·CO_2H) 2.2 (s), 1.6—2.1 (q), 2.5 (d), and 1.4 (d) (1 : 4 : 1 : 1), $M^{+\cdot}$ (^{35}Cl) 248 (Found: C, 52.8; H, 4.0; N, 22.4. $C_{11}H_9ClN_4O$ requires C, 53.0; H, 3.6; N, 22.5%).

Coupling of 4,6-dimethyl-2-pyrimidone in a similar manner gave the *hydrazone* (2d) (100%), m.p. >350° (decomp.), τ (CF_3·CO_2H) 1.6—1.9 (m), 2.5 (s), and 6.7 (s) (5 : 1 : 3), $M^{+\cdot}$ (^{35}Cl) 262 (Found: C, 54.6; H, 4.3; N, 21.4. $C_{12}H_{11}ClN_4O$ requires C, 54.75; H, 4.2; N, 21.3%).

Similar coupling of 1,4,6-trimethyl-2-pyrimidone gave the *hydrazone* (4b) (98%) as a red powder, m.p. 290—294° (decomp.), τ (CF_3·CO_2H) 1.7 (s), 1.9—2.3 (m), 5.9 (s), and 7.0 (s) (1 : 5 : 3 : 3), $M^{+\cdot}$ (^{35}Cl) 276 (Found: C, 55.85; H, 4.75; N, 20.55. $C_{13}H_{13}ClN_4O$ requires C, 56.3; H, 4.7; N, 20.2%).

Similar coupling of 2,6-dimethyl-4-pyrimidone gave the *hydrazone* (3b) as a bright red powder (25%), m.p. 248—252°, τ (CF_2·CO_2H) 2.2—2.7 (q + s), 3.5 (s), and 7.5 (s) (5 : 1 : 3), $M^{+\cdot}$ (^{35}Cl) 262 (Found: C, 54.6; H, 4.0; N, 20.8. $C_{12}H_{11}ClN_4O$ requires C, 54.75; H, 4.2; N, 21.3%).

Coupling of 5-*Methylcytosine with Diazotised* p-*Chloroaniline.*—*p*-Chloroaniline (0.48 g) dissolved in 4M-hydrochloric acid (4 ml) was diazotised with sodium nitrite (0.22 g) in water (2 ml) at 5 °C. 5-Methylcytosine hydrochloride (0.5 g) was dissolved in a solution of sodium acetate (5 g) in water (10 ml) and sodium hydroxide (4M; 5 ml), and the solution was cooled to below 3 °C. Addition of the diazotised amine gave a deep red precipitate. The crystalline product (*ca.* 100%), m.p. >250°, was collected, washed with water, and dried; τ (CF_3·CO_2H) 2.0—2.6 (q), 3.4 (s), and 7.3 (s) (*ca.* 8 : 1 : 3), $M^{+\cdot}$ (^{35}Cl) 401.

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