Synthesis of Pyrazolo[3,4-*d*]pyrimidines by Intramolecular Cycloaddition of Azahexatrienes

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Treatment of aldehyde pyrimidin-6-ylhydrazones with aromatic aldehydes (or treatment of 6-hydrazinopyrimidines with aromatic aldehydes in excess) in dimethylformamide under reflux gave 2,3-disubstituted pyrazolo[3,4-*d*]-pyrimidines.

PREVIOUS methods for the preparation of pyrazolo-[3,4-*d*]pyrimidines [1] involve (*a*) construction of suitably substituted pyrazole precursors followed by pyrimidine ring closure,[2,3] (*b*) condensation–cyclization of 5-substituted 6-hydrazinopyrimidines,[4,5] and (*c*) oxidative cyclization of 6-benzylidenehydrazinopyrimidine derivatives.[6] We now present the experimental details of a new approach to pyrazolo[3,4-*d*]pyrimidines.[7]

Refluxing aldehyde 1,3-dimethyluracil-6-ylhydrazones (1a—g) [6] with aromatic aldehydes in dimethylformamide gave the corresponding 2,3-disubstituted 5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (2a—k). The structures (2) were confirmed by the benzylic proton signals at δ 5.3—5.5 in the n.m.r. spectra (see Supplementary Publication) and by comparison with authentic samples prepared by benzylation of 3-aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones [6] with benzyl halides and potassium carbonate in dimethylformamide.†

Heating the 6-benzylidenehydrazino-3-methyluracils (3a—c) [6] with aromatic aldehydes in ethanol gave the 5-benzylidene derivatives (4a—d) possessing a diaza-hexatriene-type structure. Refluxing the products (4a—d) in dimethylformamide led to the 3-aryl-2-benzyl-5-methylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (5a—d). Refluxing of compounds (3a—c) with aromatic aldehydes in dimethylformamide gave the pyrazolo-pyrimidines (5a—d) directly; these products were identified by transformation into compounds (2) by methylation with methyl iodide and potassium carbonate in dimethylformamide.

When acetophenone 1,3-dimethyluracil-6-ylhydrazone (6) [8] was treated with benzaldehyde in dimethylformamide, 2-(1-methylbenzyl)-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (7) was obtained.

Heating the 2-amino-6-benzylidenehydrazino-4-hydroxypyrimidines (8a—d) [9] with aromatic aldehydes [or heating 2-amino-6-hydrazino-4-hydroxypyrimidine (10) [9] with an excess of aromatic aldehyde] in dimethylformamide gave the 6-amino-3-aryl-2-benzyl-4-hydroxypyrazolo[3,4-*d*]pyrimidines (9a—d).

EXPERIMENTAL

2,3-Disubstituted 5,7-Dimethylpyrazolo[3,4-d]*pyrimidine-4,6(5H,7H)-diones* (2a—k). *General Procedure.—Method A.* To a solution of an aldehyde 1,3-dimethyluracil-6-ylhydrazone (1) (0.008 mol) in dimethylformamide (50 ml) was added an aromatic aldehyde (0.01 mol). The mixture was refluxed for 7 h, then evaporated to dryness *in vacuo*, and the residue was recrystallized from ethanol to give the corresponding *pyrazolo*[3,4-d]*pyrimidine* (2a—k) (Table 1).‡ M.p.s. and yields are indicated below the formulae.

Method B. A mixture of the pyrazolopyrimidine (5) (see later) (0.002 mol), methyl iodide (0.01 mol), and potassium carbonate (0.01 mol) in dimethylformamide (20 ml) was refluxed for 2 h. Inorganic substances were filtered off, the filtrate was evaporated to dryness *in vacuo*, and the residue was diluted with water. Recrystallization of the resulting crystals from ethanol gave the 5,7-dimethylpyrazolo[3,4-*d*]pyrimidinediones, which were identical with the products from method A. Compounds (2a—c) were obtained in 70, 74, and 64% yield, respectively.

5-Benzylidene-6-benzylidenehydrazino-3-methyluracils (4a—d). *General Procedure.*—A mixture of a 6-benzylidenehydrazino-3-methyluracil (3) (0.008 mol) and an aromatic aldehyde (0.01 mol) in ethanol (100—150 ml) was refluxed for 3 h. After cooling, the crystals which separated were filtered off and recrystallized from ethanol. The following compounds were obtained: *5-benzylidene-6-benzylidenehydrazino-3-methyluracil* (4a) (88%), m.p. 279° (Found: C, 68.45; H, 4.9; N, 16.75. $C_{19}H_{16}N_4O_2$ requires C, 68.65; H, 4.85; N, 16.85%); 5-(p-*chlorobenzylidene*)-6-(p-*chlorobenzylidenehydrazino*)-3-*methyluracil* (4b) (93%), m.p. 298° (Found: C, 56.7; H, 3.7; N, 14.0. $C_{19}H_{14}Cl_2N_4O_2$ requires C, 56.85; H, 3.5; N, 13.95%); 5-(p-*methoxybenzylidene*)-6-(p-*methoxybenzylidenehydrazino*)-3-*methyluracil* (4c), (59%), m.p. 267° (Found: C, 63.7; H, 5.55; N, 14.0. $C_{21}H_{22}N_4O_4$ requires C, 63.95; H, 5.6; N, 14.2%); 5-(p-*chlorobenzylidene*)-6-(p-*methoxybenzylidenehydrazino*)-3-*methyluracil* (4d) (72%), m.p. 258° (Found: C, 60.8; H, 4.3; N, 14.05. $C_{20}H_{17}ClN_4O_3$ requires C, 60.55; H, 4.3; N, 14.1%).

† In the benzylation, the isomeric 1-benzylpyrazolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)-diones were obtained as minor products.

‡ Tables 1—3, containing analytical and n.m.r. data, are available as Supplementary Publication No. SUP 21 975 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

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[3] S. Senda, K. Hirota, and G.-N. Yang, *Chem. and Pharm. Bull.* (*Japan*), 1972, **20**, 391, 399.
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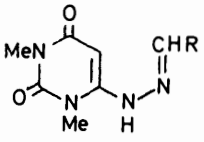
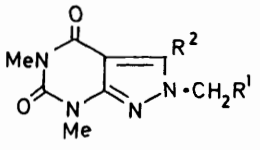
3-Aryl-2-benzyl-5-methylpyrazolo[3,4-d]*pyrimidine*-4,6-(5H,7H)-*diones* (5a—d). *General Procedure.—Method A.* A solution of a hydrazone (4) (0.002 mol) in dimethylformamide (20 ml) was refluxed for 3 h. The mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from ethanol to give the *pyrazolo*[3,4-d]-*pyrimidine* (5) (Table 1). M.p.s and yields are indicated below the formulae.



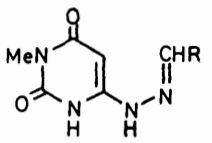
(1)

a ; R = Ph
b ; R = *p*-ClC$_6$H$_4$
c ; R = 3,4-Cl$_2$C$_6$H$_3$
d ; R = *p*-MeO·C$_6$H$_4$
e ; R = *p*-Me$_2$N·C$_6$H$_4$
f ; R = MeCH:CH
g ; R = PhCH:CH



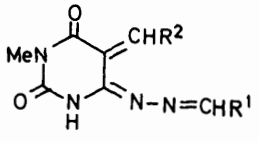
(2)

a ; R^1 = R^2 = Ph (193 °C; 80%)
b ; R^1 = R^2 = *p*-ClC$_6$H$_4$ (181 °C; 87%)
c ; R^1 = R^2 = 3,4-Cl$_2$C$_6$H$_3$ (194 °C; 85%)
d ; R^1 = R^2 = *p*-MeO·C$_6$H$_4$ (160 °C; 84%)
e ; R^1 = R^2 = *p*-Me$_2$N·C$_6$H$_4$ (258 °C; 58%)
f ; R^1 = *p*-MeO·C$_6$H$_4$, R^2 = *p*-ClC$_6$H$_4$ (204 °C; 68%)
g ; R^1 = *p*-Me$_2$N·C$_6$H$_4$, R^2 = Ph (150 °C; 62%)
h ; R^1 = MeCH:CH, R^2 = Ph (126 °C; 32%)
i ; R^1 = MeCH:CH, R^2 = *p*-ClC$_6$H$_4$ (152 °C; 50%)
j ; R^1 = MeCH:CH, R^2 = 3,4-Cl$_2$C$_6$H$_3$ (194 °C; 53%)
k ; R^1 = PhCH:CH, R^2 = Ph (162 °C; 73%)



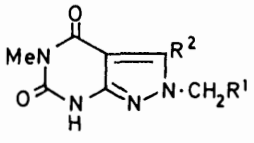
(3)

a ; R = Ph
b ; R = *p*-ClC$_6$H$_4$
c ; R = *p*-MeO·C$_6$H$_4$



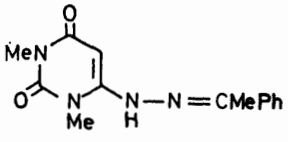
(4)

a ; R^1 = R^2 = Ph
b ; R^1 = R^2 = *p*-ClC$_6$H$_4$
c ; R^1 = R^2 = *p*-MeO·C$_6$H$_4$
d ; R^1 = *p*-MeO·C$_6$H$_4$, R^2 = *p*-ClC$_6$H$_4$

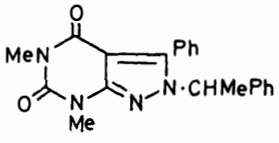


(5)

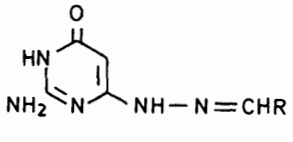
a ; R^1 = R^2 = Ph (231 °C; 68%)
b ; R^1 = R^2 = *p*-ClC$_6$H$_4$ (267 °C; 87%)
c ; R^1 = R^2 = *p*-MeO·C$_6$H$_4$ (247 °C; 78%)
d ; R^1 = *p*-MeO·C$_6$H$_4$, R^2 = *p*-ClC$_6$H$_4$ (200 °C; 65



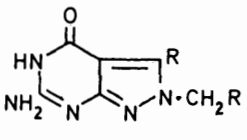
(6)



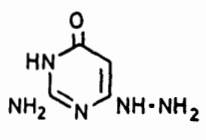
(7)



(8)



(9)



(10)

a ; R = Ph
b ; R = *p*-ClC$_6$H$_4$
c ; R = 3,4-Cl$_2$C$_6$H$_3$
d ; R = *p*-MeO·C$_6$H$_4$

Method B. A mixture of a 6-benzylidenehydrazino-3-methyluracil (3) (0.008 mol) and an aromatic aldehyde (0.01 mol) in dimethylformamide (60—80 ml) was refluxed for 7 h, then evaporated to dryness *in vacuo*, and the residue was recrystallized from ethanol to give (5) in almost the same yields as from method A.

Crotonaldehyde 1,3-*Dimethyluracil*-6-*ylhydrazone* (1f).—To a solution of 1,3-dimethyl-6-hydrazinouracil (6 g, 0.035 mol) in ethanol (180 ml) was added crotonaldehyde (3 g, 0.042 mol), and the mixture was stirred at room temperature for 1 h. The crystals which separated were filtered off, dried, and recrystallized from ethanol to give *prisms* (5.5 g, 70.5%), m.p. 216°, M^+ 222 (Found: C, 54.3; H, 6.45; N, 25.4. $C_{10}H_{14}N_4O_2$ requires C, 54.05; H, 6.35; N, 25.2%).

Cinnamaldehyde 1,3-*Dimethyluracil*-6-*ylhydrazone* (1g).—To a solution of 1,3-dimethyl-6-hydrazinouracil (2 g, 0.012 mol) in ethanol (150 ml) was added cinnamaldehyde (2.1 g, 0.016 mol); treatment as above gave *prisms* (2.84 g, 85%), m.p. 249°, M^+ 312 (Found: C, 63.4; H, 5.55; N, 20.0. $C_{15}H_{16}N_4O_2$ requires C, 63.35; H, 5.65; N, 19.7%).

5,7-*Dimethyl*-2-(1-*methylbenzyl*)-3-*phenylpyrazolo*[3,4-d]-

pyrimidine-4,6(5H,7H)-*dione* (7).—A mixture of acetophenone 1,3-dimethyluracil-6-ylhydrazone (6) (2 g, 0.007 4 mol) and benzaldehyde (1.2 g, 0.01 mol) in dimethylformamide (40 ml) was refluxed for 6 h, then evaporated to dryness, and the residue was recrystallized from ethanol to give *granules* (1.55 g, 59%), m.p. 148°, M^+ 360 (Found: C, 69.9; H, 5.65; N, 15.3. $C_{21}H_{20}N_4O_2$ requires C 70.0; H, 5.6; N, 15.55%).

6-*Amino*-3-*aryl*-2-*benzyl*-4-*hydroxypyrazolo*[3,4-d]-*pyrimidines* (9a—d). *General Procedure.—Method A.* A mixture of 2-amino-6-hydrazino-4-hydroxypyrimidine (10) (0.01 mol) and an aromatic aldehyde (0.024 mol) in dimethylformamide (50 ml) was refluxed for 5 h. After cooling, the crystals precipitated were filtered off and recrystallized from dimethylformamide [yields 60—90% (Table 2)], m.p. $\lessdot 360°$. The structures (9) were confirmed by the benzylic proton n.m.r. signals at δ 5.7—5.5. (Table 3 in Supplementary Publication).

Method B. Compounds (9a—d) were also prepared by the condensation of 2-amino-6-benzylidenehydrazino-4-hydroxypyrimidines (8a—d) and aromatic aldehydes in dimethylformamide in similar yields.

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