Purines, Pyrimidines, and Imidazoles. Part XLIII.[1] Halogenation of *N*-3-Methylbut-2-enylphthalimide; New Syntheses of Zeatin Analogues

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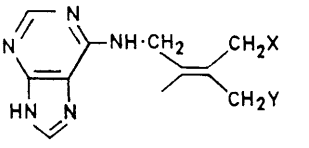
Halogenation of *N*-(3-methylbut-2-enyl)phthalimide with either *N*-bromo- or *N*-chloro-succinimide or with t-butyl hypochlorite in equimolar or greater amounts gives as the major product the *N*-(2-halogeno-3-methylbut-2-enyl)-phthalimide. With an excess of *N*-bromosuccinimide a small amount of *N*-(2,4-dibromo-3-bromomethylbut-2-enyl)phthalimide is obtained. Bromination of (*Z*)- and (*E*)-3-methyl-4-t-butoxybut-2-enylphthalimide with triphenylphosphine dibromide produced (*Z*)-4-bromo-3-methylbut-2-enylphthalimide and the corresponding *E*-isomer, respectively. The bromo-derivatives react readily with nucleophiles and the resulting allylphthalimides may be converted into zeatin analogues by known processes. The structures of the compounds described were confirmed by mass and n.m.r. spectra.

(*E*)-ZEATIN [2] (Ia) appears to be the most effective of all the naturally occurring cytokinins in promoting cell division in plants. Cytokinin activity is common to many 6-alkylaminopurines and in the series of 6-n-alkylaminopurines optimum activity is reached with C_4—C_6 side chains.[3] The difference in activity between (*Z*)- (Ic) and (*E*)-zeatin is striking.[4] In the standard tobacco callus bioassay the *E*-isomer is at least fifty times more active than the *Z*-isomer. As part of a wider structure–activity study we have been especially interested in preparing various analogues of both (*Z*)- and (*E*)-zeatins in which the side-chain hydroxy-group is replaced by other groups.

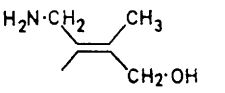
Earlier we described the formation of the allylic chloride (Id) by the reaction of (*E*)-zeatin with methanesulphonyl chloride.[5] Although the chloride might reasonably be regarded as a useful intermediate for the synthesis of other allylic analogues by reaction with appropriate nucleophiles, it has in practice proved difficult to use, not least because of its considerable lability and reactivity.

We have also recorded syntheses of (*E*)-zeatin [2] and various derivatives including the ribonucleoside [2] and ribonucleotide.[6] A key intermediate in all these and subsequent preparations is the aminobutenol (II). One synthesis of this compound [7] involves a preliminary acetoxylation of the isopentenylphthalimide (IIIa) with selenium dioxide in acetic acid and acetic anhydride to produce the acetoxybutenylphthalimide (IIId).

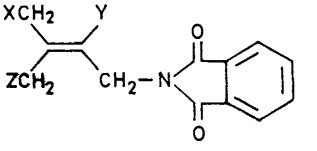
Hydrolysis of the acetate (IIId) produced the aminobutenol (II), which with 6-chloropurine gave (*E*)-zeatin. A later synthesis [8] of the acetate involves the reaction of 3-methyl-4-t-butoxybut-2-enyl chloride with the potassium salt of phthalimide to produce a mixture of the (*Z*)- (IIIj) and (*E*)- (IIIe) 3-methyl-4-t-butoxybut-2-enylphthalimides, which were separable by chromatography on silica gel. The t-butoxy-compounds with acetic toluene-*p*-sulphonic anhydride gave the corresponding (*Z*)- and (*E*)-acetoxy-derivatives (IIIk and d). As an alternative route to the acetates we have, in preliminary experiments, examined the reaction of the dimethylallylphthalimide (IIIa) with *N*-bromosuccinimide in carbon tetrachloride in the hope of obtaining the γ-bromomethyl derivatives (IIIg and h); these could be used at that stage to produce appropriate enylamines by reaction with



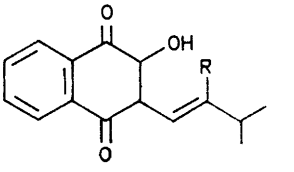
(I) a; X = H, Y = OH
b; X = H, Y = OMe
c; X = OH, Y = H
d; X = H, Y = Cl



(II)



(III) a; X = Y = Z = H
b; X = H, Y = Br, Z = H
c; X = H, Y = Cl, Z = H
d; X = OAc, Y = Z = H
e; X = OBu^t, Y = Z = H
f; X = OMe, Y = Z = H
g; X = Y = H, Z = Br
h; X = Br, Y = Z = H
i; X = Y = Z = Br
j; Z = OBu^t, X = Y = H
k; Z = OAc, X = Y = H



(IV) a; R = Br
b; R = H

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[3] G. Shaw, B. M. Smallwood, and F. C. Steward, *Phytochemistry*, 1971, **10**, 2329.
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[5] G. Shaw, B. M. Smallwood, and D. V. Wilson, *J. Chem. Soc.* (*C*), 1968, 2999.
[6] G. Shaw, B. M. Smallwood, and D. V. Wilson, *J. Chem. Soc.* (*C*), 1968, 1516.
[7] M. Olomucki, A. Desvages, N. Thoai, and J. Roche, *Compt. rend.*, 1965, **260**, 4519.
[8] J. Corse and J. Kuhnle, *Biochem. Biophys. Res. Comm.*, 1972, 618.

nucleophiles, and the latter could be converted into alkenylaminopurines related to (*Z*)- and (*E*)-zeatin.

A crystalline compound was readily obtained containing non-labile bromine but this proved to be the β-bromo-derivative (IIIb). The same compound was obtained when the reaction was carried out in acetonitrile. In addition, use of *N*-chlorosuccinimide or t-butyl hypochlorite gave the analogous monochloro-derivative (IIIc). Such examples of vinylic hydrogen substitution by halogen are reputedly rare, and were claimed as unprecedented by Dudley and Miller,[9] who first recorded a similar product (IVa) from isolapachol (IVb).

When the phthalimide (IIIa) was heated in carbon tetrachloride with an excess of *N*-bromosuccinimide, the monobromo-derivative (IIIb) was again the major product, but a small (*ca.* 1%) amount of the tribromo-compound (IIIi) was also isolated. The monohalogeno-derivative (IIIc) was similarly the major product from use of an excess of *N*-chlorosuccinimide; t.l.c. indicated the presence of a small amount of other (presumably di- or tri-chloro-) derivatives which were not isolated.

The various products were readily identified by elemental analysis, mass spectrometry, and (especially) n.m.r. spectroscopy (Table).* The n.m.r. spectrum of *N*-(3-methylbut-2-enyl)phthalimide (IIIa) shows the expected two methyl singlets, a methylene doublet, a proton triplet and aromatic ring protons. The acetoxy-derivative (IIId) also shows a methylene doublet and olefinic proton triplet, together with an allylic methyl singlet, acetyl methyl singlet, and allylic methylene singlet. After monohalogenation to (IIIb or c) the two methyl signals are unchanged, the methylene doublet collapses to a singlet, and the triplet disappears, showing clearly that the halogen has substituted the olefinic and not either allylic position. The spectrum of the tribromo-product (IIIi) shows only three methylene singlets and aromatic ring protons.

t-Butoxy-derivatives react with triphenylphosphine dibromide to give alkyl halides:[10] ($ROBu^t + Br_2PPh_3 \longrightarrow RBr + Ph_3PO + Bu^tBr$). Treatment of both (*Z*)- and (*E*)-*N*-3-methyl-(4-t-butoxybut-2-enyl)phthalimides (IIIj and e) with bromine and triphenylphosphine in acetonitrile gave excellent yields of the crystalline (*Z*)- and (*E*)-4-bromo-derivatives (IIIg and h), respectively, identified by elemental analysis, mass spectrometry and n.m.r. spectroscopy (Table). In addition, the reaction of the (*E*)-bromo-compound (IIIh) with potassium acetate in ethanol gave the acetoxy-derivative (IIId). Hydrolysis of the bromo-derivative with aqueous alcoholic sodium hydroxide and condensation of the amino-butenol (II) so formed with 6-chloropurine gave (*E*)-zeatin. In a similar manner (*Z*)-zeatin was obtained from the (*Z*)-bromo-derivative (IIIg); this was identical with a sample synthesised by an alternative stereospecific route.[4]

* The Table is available as Supplementary Publication No. SUP 21750 (3 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

The 4-bromo-derivative (IIIh) when similarly condensed with sodium methoxide in methanol gave a high yield of the crystalline methoxy-derivative (IIIf). Hydrolysis of this compound and condensation of the amine produced with 6-chloropurine gave crystalline (*E*)-zeatin methyl ether (Ib). The structures of the compounds followed from elemental analysis and mass and n.m.r. spectra.

EXPERIMENTAL

Evaporations were carried out with a Büchi rotary evaporator, under water-pump vacuum with a flask temperature below 40 °C unless otherwise stated. I.r. spectra were measured with a Perkin-Elmer 157 spectrophotometer, n.m.r. spectra with a JEOL JNM-MH-100 spectrometer (Me_4Si as internal standard), and mass spectra with an A.E.I. MS902 spectrometer. Silica gel $60F_{254}$ 0.25 mm precoated glass plates (Merck) were used for t.l.c., with light petroleum (b.p. 60—80°)–diethyl ether (7 : 3) as solvent.

(E)-N-(4-*Acetoxy*-3-*methylbut*-2-*enyl*)*phthalimide* (IIId) (with B. M. Smallwood).—3-Methylbut-2-enylphthalimide (100 g) was treated with selenium dioxide in acetic acid and acetic anhydride as described elsewhere.[4] The red oil (50 ml) obtained after distillation (b.p. 200—210 °C at 0.4 mmHg) was kept at 5 °C for 2 days; it had then partially crystallised. Ethanol (20 ml) was added and the mixture stirred then set aside at 5 °C overnight. The crystalline mass was collected. The *acetoxy-derivative* (20 g) crystallised from ethanol as needles, m.p. 58—61° (Found: C, 65.6; H, 5.8; N, 5.0. $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.55; N, 5.15%).

N-(2-*Bromo*-3-*methylbut*-2-*enyl*)*phthalimide* (IIIb).—A mixture of 3-methylbut-2-enylphthalimide (2.15 g, 10 mmol) and *N*-bromosuccinimide (1.78 g, 10 mmol) in dry carbon tetrachloride (6 ml) was boiled under reflux for 12 h. The solution was filtered to remove crystalline succinimide, and evaporated to an oil which crystallised from ethanol to give N-(2-*bromo*-3-*methylbut*-2-*enyl*)*phthalimide*, m.p. 116—118°, which crystallised from ethanol as needles (1.8 g, 61%), m.p. 124° (Found: C, 52.95; H, 4.3; N, 4.9%; M^+, 294, $C_{13}H_{12}BrNO_2$ requires C, 53.05; H, 4.1; N, 4.75%; *M*, 294). The same compound was obtained (48%) when the reaction was carried out in acetonitrile.

N-(2,4-*Dibromo*-3-*bromomethylbut*-2-*enyl*)*phthalimide* (IIIi). —*N*-(3-Methylbut-2-enyl)phthalimide with an excess of *N*-bromosuccinimide in carbon tetrachloride as above gave after removal of the monobromo-derivative and evaporation of the mother liquors, a gum which partly crystallised. The *tribromide* (*ca.* 1%) crystallised from ethanol as needles, m.p. 126—128° (Found: C, 34.8; H, 2.45; N, 3.3%; *m/e* 452 and 372. $C_{13}H_{10}Br_3NO_2$ requires C, 34.55; H, 2.25; N, 3.1%; *M*, 452; *M* − Br, 372). T.l.c. of the residual mother liquors showed spots corresponding to the mono- and tri-bromo-derivatives only.

N-(2-*Chloro*-3-*methylbut*-2-*enyl*)*phthalimide* (IIIc).—(*a*) A mixture of 3-methylbut-2-enylphthalimide (2.15 g, 10 mmol) and t-butyl hypochlorite (1.08 g, 10 mmol) was heated on a steam-bath for 5 h then cooled to 5 °C to yield crystals. N-(2-*Chloro*-3-*methylbut*-2-*enyl*)*phthalimide* crystallised from ethanol as spars (0.8 g, 32%), m.p. 113°

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[10] A. G. Anderson and F. J. Freenov, jun., *J. Amer. Chem. Soc.*, 1964, **86**, 5037.

(Found C, 62.7; H, 5.05; N, 5.85%; M^+, 249. $C_{13}H_{12}ClNO_2$ requires C, 62.55; H, 4.85; N, 5.6%; *M*, 249). T.l.c. of the mother liquors showed the presence of the mono-chloro-derivative and some starting material. When the reaction was repeated with an excess of *N*-chlorosuccinimide, t.l.c. then showed the presence of two additional materials but neither was obtained pure.

(*b*) A mixture of *N*-(3-methylbut-2-enyl)phthalimide (1.08 g, 5 mmol) and *N*-chlorosuccinimide (0.67 g, 5 mmol) in dry carbon tetrachloride (10 ml) was boiled under reflux for 10 h and filtered to remove crystalline succinimide, and the filtrate was evaporated to a green oil which crystallised from ethanol (5 ml) to yield needles of the *2-chloro-derivative* (0.31 g, 25%), m.p. 118°, mixed m.p. with the product (m.p. 113°) from the t-butyl hypochlorite reaction 113°, M^+ 249.

(E)-N-(4-*Bromo*-3-*methylbut*-2-*enyl*)*phthalimide* (IIIh).—Bromine (34.6 g, 0.217 mol) was added slowly to a cooled solution of triphenylphosphine (56.7 g, 0.217 mol) in acetonitrile (700 ml) and the mixture was heated on a steam-bath for 5 min. To this solution was added a solution of (*E*)-*N*-(3-methyl-4-t-butoxybut-2-enyl)phthalimide (59.8 g, 0.208 mol) in acetonitrile (150 ml). The mixture was refluxed for 15 min and set aside at 4 °C overnight. The resulting crystalline precipitate was collected and washed with absolute ethanol. The *product* (IIIh) (35 g, 57%) had m.p. 104°. The mother liquor was evaporated to an oil, absolute ethanol (80 ml) was added, and the mixture was set aside at 4 °C overnight to produce a second crop (8 g, 13%) of almost equally pure material, which crystallised from ethanol as plates m.p. 116° (Found: C, 53.30; H, 4.2; Br, 27.4; N, 4.8%; M^+, 294. $C_{13}H_{12}BrNO_2$ requires C, 53.05; H, 4.1; Br, 27.2; N, 4.75%; *M*, 294). The same compound was obtained in lower yield when a commercial sample of triphenylphosphine dibromide was used.

(Z)-N-(4-*Bromo*-3-*methylbut*-2-*enyl*)*phthalimide* (IIIg) was obtained by similar bromination of (*Z*)-*N*-(3-methyl-4-t-butoxybut-2-enyl)phthalimide with triphenylphosphine and bromine, in 59% yield, as plates, m.p. 144° (Found: C, 53.2; H, 4.1; Br, 27.1; N, 4.65%; M^+, 294).

(E)-N-(4-*Acetoxy*-3-*methylbut*-2-*enyl*)*phthalimide* (IIIk).—A solution of (*E*)-*N*-(4-bromo-3-methylbut-2-enyl)phthalimide (0.3 g) and potassium acetate (0.1 g) in ethanol was boiled under reflux for 20 min. T.l.c. suggested that the reaction was still incomplete. More potassium acetate (0.05 g) was added and the solution was boiled for 20 min, then evaporated to dryness; the residue was triturated with water to give the solid acetoxy-derivative (0.067 g), which crystallised from petroleum (b.p. 60—80°) as needles, m.p. and mixed m.p. 64°.

(E)-*Zeatin* (Ia).—A solution of the foregoing (*E*)-4-bromo-derivative (2 g) and sodium hydroxide (27 g) in ethanol (5 ml) was boiled under reflux for 0.5 h. More sodium hydroxide (0.5 g) was added and the solution heated under reflux for 12 h, then evaporated to small volume. The solution was extracted with ether (30 × 10 ml) and the extract evaporated to an oil. This was dissolved in butan-1-ol (15 ml) and triethylamine (0.5 ml), and after addition of 6-chloropurine (0.50 g) the solution was boiled under reflux for 2 h, then evaporated to small volume and cooled. (*E*)-Zeatin (0.25 g) separated and was recrystallised from water; m.p. and mixed m.p. 210°.

(Z)-*Zeatin* (Ic).—A solution of (*Z*)-*N*-(4-bromo-3-methylbut-2-enyl)phthalimide (2.94 g) and sodium hydroxide (3 g) in ethanol (100 ml) and water (10 ml) was boiled under reflux for 12 h, then evaporated to small volume, cooled, and extracted with ether (30 × 10 ml). Evaporation of the extract left an oil (0.5 g). A solution of this with 6-chloropurine (0.65 g) in butan-1-ol (10 ml) and triethylamine (1 ml) was boiled under reflux for 2 h. The solution was evaporated to small volume to afford a yellow precipitate. (*Z*)-Zeatin (0.6 g) crystallised from water as needles, m.p. 209°, identical with an authentic sample prepared from 3,6-dihydro-5-methyl-1,2-oxazine.[4]

(E)-N-(4-*Methoxy*-3-*methylbut*-2-*enyl*)*phthalimide* (IIIf).—Methanolic sodium methoxide (20 ml, from 0.01 mol of sodium) was added to a solution of (*E*)-*N*-(4-bromo-3-methylbut-2-enyl)phthalimide (2.94 g, 0.01 mol) in methanol (80 ml); the mixture was refluxed for 20 min, then evaporated to an oil which when triturated with ice-cold water yielded a white crystalline mass. The product (2 g) was collected, washed with ice-cold water, and dried. The *methoxy-derivative* crystallised from 95% ethanol as plates, m.p. 48° (Found: C, 68.85; H, 6.2; N, 5.85%; M^+, 245. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%; *M*, 245).

(E)-6-(4-*Methoxy*-3-*methylbut*-2-*enylamino*)*purine* (Ib).—A mixture of (*E*)-*N*-(4-methoxy-3-methylbut-2-enyl)phthalimide (1.2 g, 0.005 mol) and 2N-sodium hydroxide (10 ml) was refluxed for 3.5 h, then extracted with chloroform (3 × 20 ml). The organic layers were combined, dried (Na_2SO_4), and evaporated to give a pale yellow gum (100 mg). A solution of the gum (100 mg), 6-chloropurine (15.4 mg, 0.001 mol), and triethylamine (100 mg) in butan-1-ol (10 ml) was refluxed for 1 h. About half the solvent was removed by evaporation and the mixture was cooled to give a crystalline precipitate (12 mg). The *product* (Ib) recrystallised from water as needles, m.p. 191° (Found: C, 56.95; H, 6.7; N, 30.3%; M^+, 233. $C_{11}H_{15}N_5O$ requires C, 56.65; H, 6.45; N, 30.05%; *M*, 233).

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