Synthesis, Transformations and Biological Activity of Chloro Enamines and Ynamines Derived from Chloroalkenyl- and Alkynyl-*N*-substituted Purine and Pyrimidine Bases of Nucleic Acids[1]

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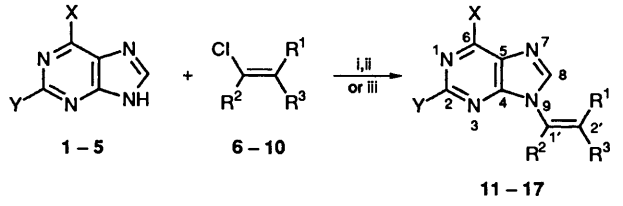
Reactions of nucleic acid bases and related heterocycles **1**-**5**, **18** and **22** with tetra-, tri- and dichloroethylenes **6**–**9** in hexamethylphosphoric triamide gave the corresponding *N*-trichloro-, -dichloro- and -chloro- enamines **11**–**17**, **19**, **20**, **23** and **24** in high regioselectivity (N^9 for purines and N^1 for pyrimidines). Bases **1**, **5**, **18**, **22** and trichloroethylene **7** gave the respective *E*-dichloro enamines **15**, **16**, **20** and **24**. Compounds **16** and **20** were identical with the products obtained by addition of bases **1** and **18** to dichloroacetylene. Thymine **18** and compound **7** gave N^1,N^3-bis-dichloro enamine **21** as the major product. The latter exists at room temperature as a mixture of rotamers **28** and **29** ($\Delta G^{\ddagger} \cong 18$ kcal mol^{-1}). The reaction of adenine **1** with (*Z*)-1,2- or 1,1-dichloroethylene **8** or **9** furnished *Z*-chloro enamine **17** whereas thymine **18** and tetrachloroethylene **6** in dimethyl sulfoxide afforded a reduction product **20**. Benzoylation of N^9-(trichlorovinyl)adenine **11** gave N^6,N^6-dibenzoyl derivative **26**. The reaction of N^1-(dichlorovinyl)cytosine **24** with *N*,*N*-dimethylformamide dimethyl acetal afforded amidine **25**. Interaction of (*E*)-N^9-(dichlorovinyl)-adenine **16** with sodium methoxide gave exclusively *E*-enamine **27**. Trichloro enamines **11**–**14**, **19**, **23** and **26** were transformed to ynamines **30**–**35**. Hydrogenation of compounds **30** and **35** furnished N^9-ethyladenine **36** and N^1-ethylthymine **37**. Alkylation of ynamine **30** with acetone **38** gave only carbinol **41** whereas cyclohexanone **39** gave both compound **42** and cyclic ketal **43**. The reaction of ynamines **30** and **35** with ketone **40** afforded only ketals **44** and **45**. The reaction of compound **30** with *N*,*N*-dimethylformamide dimethyl acetal led to *N*-dimethylaminomethylene derivative **46**. Ynamine **30** is a substrate for adenosine deaminase.

Heterocyclic ynamines containing a terminal acetylene moiety have not been investigated in any detail.[2] Very recently, a single compound of this class, *N*-ethynylpyrrole, was described[3] but it was characterized only by ^{1}H NMR spectroscopy. In connection with our studies of unsaturated nucleoside analogues[4] we became interested in ynamines derived from nucleic acid bases. Such compounds could serve as synthetic intermediates for the preparation of new analogues with a therapeutic potential but they could also exhibit some interesting biological properties *per se*. In addition, they may also become a source of the corresponding polymers (polyacetylenes)[5] containing nucleic acid bases. Similar polymeric materials, polyvinyl analogues of nucleic acids, inhibit RNA polymerase and exhibit other biological effects.[6]

In this communication, we describe the synthesis of chloro enamines **11**–**17**, **19**, **20**, **23**–**27**, ynamines **30**–**35**, and some of their physicochemical and biological properties, as well as alkylation of compounds **30** and **35** with selected ketones. The rotational isomerism of bis-dichloro enamine **21** (rotamers **28** and **29**) will also be discussed.

Synthesis of Chloro Enamines.—The chloro enamines were considered as convenient intermediates for the synthesis of ynamines derived from nucleic acid bases. The base-catalysed reaction of purines **1**–**5** (Scheme 1) and pyrimidines **18** and **22** (Schemes 2 and 3) with chlorinated ethylenes **6**–**9** was selected as a method of choice for synthesis of chloro enamines **11**–**17**, **19**, **20**, **23** and **24**. In the case of dichlorovinyl derivatives **15**, **16**, **20** and **24**, this approach avoided use of the explosive and toxic dichloroacetylene used for the synthesis of (*E*)-*N*-(1,2-dichlorovinyl)imidazole.[7] A similar method was employed in the preparation of *N*-ethynyl derivatives of secondary amines[8,9] and *N*-ethynylpyrrole.[3]

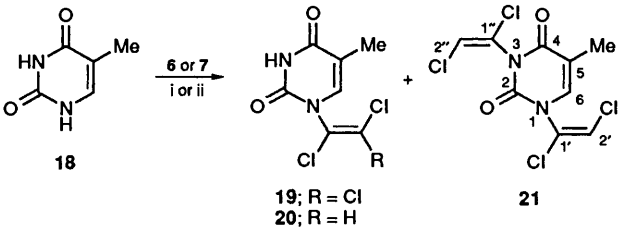
Selection of a suitable solvent was crucial for successful reaction with chlorinated ethylenes **6**–**9**. The appropriate heterocyclic bases **1**–**5**, **18** and **22** were converted into the sodium or potassium salts by using NaH or KH, but only poor yields or side-reactions were observed in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). By contrast, hexamethylphosphoric triamide (HMPA) gave consistent though moderate yields of the desired intermediates **11**–**17**, **19**, **20**, **23** and **24** (20–35%). In the case of reaction of adenine **1** with 1,1-dichloroethylene **9**, a phase-transfer method[10] employing NaOH and NBu_4F (TBAF) in DMF gave better results than reaction in HMPA. 2-Amino-6-chloropurine **5** did not react with tetrachloroethylene **6** but trichloroethylene **7** gave compound **15** in 26% yield. The reaction of adenine **1** and (*Z*)-1,2-dichloroethylene **8** or 1,1-dichloroethylene **9** afforded the



1 – 5 6 – 10 11 – 17

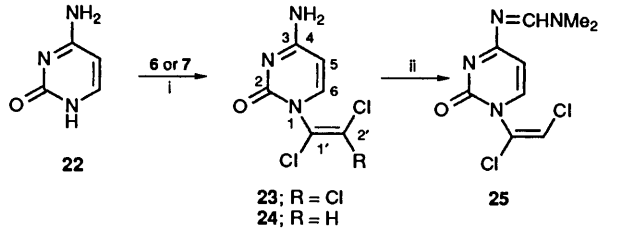
1; X = NH_2, Y = H
2; X = Y = NH_2
3; X = $PhCH_2O$, Y = NH_2
4; X = NHCOPh, Y = H
5; X = Cl, Y = NH_2
6; R^1 = R^2 = R^3 = Cl
7; R^1 = R^3 = Cl, R^2 = H
8; R^1 = Cl, R^2 = R^3 = H
9; R^1 = R^3 = H, R^2 = Cl
10; R^1 = R^2 = H, R^3 = Cl
11; X = NH_2, Y = H, R^1 = R^2 = R^3 = Cl
12; X = Y = NH_2, R^1 = R^2 = R^3 = Cl
13; X = $PhCH_2O$, Y = NH_2, R^1 = R^2 = R^3 = Cl
14; X = NHCOPh, Y = H, R^1 = R^2 = R^3 = Cl
15; X = Cl, Y = NH_2, R^1 = R^2 = Cl, R^3 = H
16; X = NH_2, Y = H, R^1 = R^2 = Cl, R^3 = H
17; X = NH_2, Y = H, R^1 = Cl, R^2 = R^3 = H

Scheme 1 *Reagents and conditions:* i, NaH, HMPA; ii, KH, HMPA; iii, NaOH, NMe_4F, DMF



18 19; R = Cl 20; R = H 21

Scheme 2 *Reagents and conditions:* i, NaH, HMPA; ii, NaH, DMSO



22 23; R = Cl 24; R = H 25

Scheme 3 *Reagents and conditions:* i, NaH, HMPA; ii, $Me_2NCH(OMe)_2$, DMF

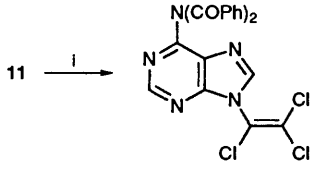
same product, (*Z*)-*N*-(2-chlorovinyl)adenine **17**. The (*E*)-1,2-dichloroethylene **10** did not react. It is of interest that the reaction of thymine **18** with tetrachloroethylene **6** led only to N^1-(trichlorovinyl)thymine **19** but trichloroethylene **7** gave bis-dichloro enamine **21** in 28% yield and only a 6% yield of (*E*)-N^1-(dichlorovinyl)thymine **20**. This is, to the best of our knowledge, the first indication that trichloroethylene **7**, a recognized nephrotoxic compound,[11] mutagen and cancer-suspect agent,[12] is capable of reacting with a functional group present in DNA and involved in Watson–Crick base-pairing. It is then clear that tetrachloroethylene **6** and trichloroethylene **7** differ in reactivity (see also compound **15** discussed above), possibly because of a change in the reaction mechanism (*vide supra*). The reaction of thymine **18** with NaH and tetrachloroethylene **6** in DMSO led to a reductive removal of one chlorine atom to give compound **20**, identical with that obtained by reaction with trichloroethylene **7**. No bis-dichloro enamine was detected.

All these reactions except that of compounds **18** and **7** proceeded with a high degree of regioselectivity with respect to the heterocyclic base. Thus, N^9 is a preferential site of attack for purines and N^1 for pyrimidines. In that respect, the selectivity of alkylation followed the pattern found for reactions of nucleic acid bases with alkylating agents having a leaving group attached to an sp^3-hybridized carbon.[13] This was corroborated by the UV and ^{13}C NMR spectra. Thus, compounds **11**, **16** and **17** exhibit λ_{max} 256–260 nm similar to those of N^9-alkyladenines.[13] A similar pattern was found for purines **12**, **13** and **15**. The ^{13}C NMR spectrum of compound **13** (heterocyclic moiety) has a pattern similar to that found in N^9,6-*O*-dialkylpurines.[14] The UV spectra of pyrimidines **19**, **20**, **23** and **24** are of lesser value for regioisomeric assignments. Thus, both thymine derivatives **19** and **20** have λ_{max} 260 nm, which is similar to that of N^1,N^3-bis-dichloro enamine **21** (λ_{max} 264 nm). Similarly, the UV maximum usually associated with N^1-alkylcytosines at ~275 nm[13] is apparently a part of the broad band at λ_{max} 250 nm in compounds **23** and **24**. Additional evidence for regioisomeric assignments in both purine and pyrimidine chloro enamines will be discussed later. The transformations described herein are stereoselective, giving only a single geometric isomer as seen from the ^1H and ^{13}C NMR spectra. It was shown that reactions of nucleophiles (enolates) with trichloroethylene **7** involved an intermediary formation of dichloroacetylene and, hence, a *trans*-stereochemistry.[15] Therefore, a similar reaction course (elimination–addition) was anticipated with chlorinated ethylenes **8** and **9**. This is also compatible with the finding that, as mentioned earlier, adenine **1** and chloride **8** or **9** gave exclusively the *Z*-isomer **17**. The fact that (*E*)-1,2-dichloroethylene **10**, which cannot form chloroacetylene by a *trans*-elimination, was unable to react with adenine **1** is in accord with such a mechanism.[16] It should be noted that *N*-(1,2-dichlorovinyl)pyrrole, prepared by reflux of the potassium salt of pyrrole in trichloroethylene **7**, was formulated as the *Z*-isomer[3] but no evidence was offered to support this assignment.

These conclusions were further supported by reaction of dichloroacetylene with adenine **1** and thymine **18**. As already mentioned, the former reagent and imidazole gave (*E*)-*N*-(1,2-dichlorovinyl)imidazole as a single product.[7] The reaction of adenine **1** with dichloroacetylene in HMPA was accompanied by extensive formation of coloured by-products and it gave dichloro enamine **16** in only 3% yield and 77% purity. Nevertheless, this compound was identical (TLC, mixed TLC, UV and ^1H NMR) with the product obtained from adenine **1** and trichloroethylene **7** as mentioned above. The reaction of thymine **18** with dichloroacetylene was much cleaner and afforded compound **20** in 12% yield, which was identical with a sample obtained from trichloroethylene **7**. It is noteworthy that the latter reaction was significantly more regioselective than that of thymine **18** with trichloroethylene **7**. Only traces of bis-dichloro enamine **21** were detected in the reaction mixture.

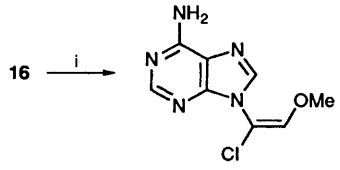
It is obvious that an elimination–addition mechanism *via* the respective acetylenes is precluded in reactions with tetrachloroethylene **6** resulting in the formation of *N*-trichlorovinyl derivatives **11**–**14**, **19** and **22**. The reaction course most likely follows an addition–elimination pattern.[16]

The di- or tri-chlorovinyl moieties of **11** and **24** are stable enough to allow protection by benzoylation or reaction with *N*,*N*-dimethylformamide dimethyl acetal[17] (Schemes 3 and 4). The respective products **26** and **25** were obtained in 56 and 85% yield, respectively. The reaction of (*E*)-N^9-(1,2-dichlorovinyl)-adenine **16** with MeONa in DMF was highly regio- and stereoselective, and afforded a single product in 63% yield (Scheme 5). Since an elimination–addition mechanism can be excluded, four regio- and stereo-isomers, all resulting from an addition–elimination mechanism, are possible. Absence of isomeric



26

Scheme 4 *Reagents and conditions:* i, PhCOCl, pyridine



27

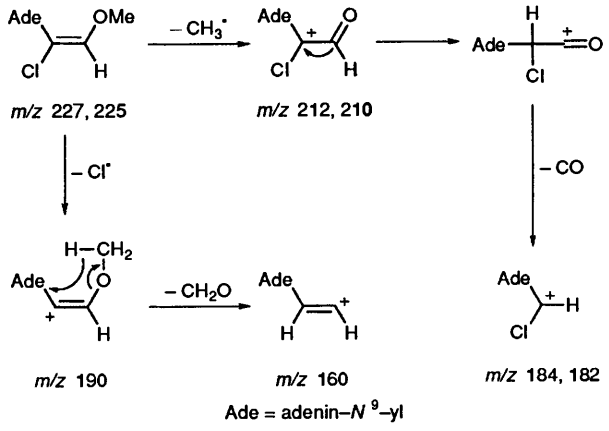
Scheme 5 *Reagents and conditions:* i, MeONa, DMF

products complicated the structural assignment. Nevertheless, similar nucleophilic substitutions are known to proceed with stereoconvergence or retention of the original stereochemistry.[18] Such a reasoning would favour structure **27** for the product.

The 2D ^{1}H and ^{13}C NMR spectrum indicated that the heterocyclic proton signal located at higher field (δ 8.15) belongs to 8-H. Also, the signal at δ_C 147.43 is the hydrogen-carrying vinylic carbon C-2′. The C-1′ signal is then found downfield, at δ 102.33, which is in accord with similar shifts observed in vinyl ethers.[19] The only significant nuclear Overhauser effect (NOE) was observed for the 2′-H and MeO (5.3 and 12%, respectively). This suggested a *cis* or geminal relationship for both functions. It should be noted that the NOE alone could not be used for confirmation of the regio- and stereo-isomeric assignment because of an inherent ambiguity in distinguishing between isomeric olefins related by a 1,2-*trans* interchange of substituents.[20] Smaller NOEs (1–2.8%) were observed between 8-H and 2′-H in compound **27** and dichloro enamine **16**. The distance between both hydrogens is 3.9 and 4.0 Å as determined for the energy-minimized (Chem3D Plus, Version 3.0) structures of compounds **16** and **27**. Similar distances between relevant hydrogen atoms led to NOEs of comparable magnitude as noted for various conformationally restricted nucleosides.[21]

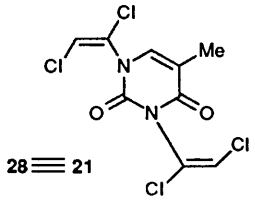
The electron-impact (EI) mass spectrum contains peaks assignable to fragments carrying adenine and a chlorine atom at the same carbon (*m/z* 184, 182; Scheme 6). The latter peak is derived from the molecular ion by a loss of methyl group followed by hydrogen shift and decarbonylation. A similar set of ions originating from the adenine moiety of the respective molecular ions by a consecutive loss of one (*m/z* 155, 157) and two (*m/z* 128, 130) HCN units[22] was also present. This type of fragmentation is fully compatible with structure **27**.

The NMR spectra of (*E,E*)-N^1,N^3-bis(dichlorovinyl)thymine **21** deserve special comment. The 300 MHz ^{1}H NMR spectrum in $CDCl_3$ showed olefinic protons 2′- and 2″-H as singlets but doubling of some signals was observed in the 75 MHz ^{13}C NMR spectrum. The 500 MHz ^{1}H NMR spectrum in $(CD_3)_2SO$ indicated that all proton peaks were doubled (Fig. 1) whereas the corresponding 125 Mz ^{13}C NMR spectrum contained 14 signals, indicating a splitting of all carbons except C-1′, -2′ (or -2″), -5 and Me (Fig. 2). Interestingly, in $CDCl_3$ at 500 MHz none of the proton signals was split but the comparable ^{13}C NMR spectrum exhibited 15 peaks (Fig. 3). Thus, the C-1′ signal, which was observed in $(CD_3)_2SO$ as a single peak, was

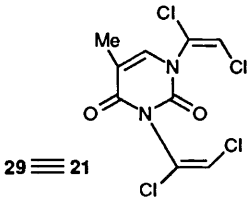


Scheme 6

split in two. Also, the pattern of C-2′ and -2″ signals was rearranged. These results can be readily explained by the presence of two rotational isomers **28** and **29**. It is important to add that the 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra of (*E*)-N^1-(dichlorovinyl)thymine **20** did not show any doubling of signals. The latter observation supports the assignment of structure **20** and, by analogy, trichloro enamine **19** as N^1-regioisomers.



28 ≡ **21**



29 ≡ **21**

The final confirmation came from a temperature-dependence study of ^{1}H and ^{13}C NMR spectra (Figs. 1 and 2). Thus, all proton signals collapsed between 60–80 °C to the respective singlets or doublets. The free-activation energy $\Delta G^{\ddagger}$ of the rotational isomerization is 17.7 kcal mol^{-1} * as calculated from the Eyring equation.[24] The latter value is in excellent agreement with the value $\Delta G^{\ddagger}$ 17.8 kcal mol^{-1} obtained from the ^{13}C NMR spectrum. Although it was possible to determine the ratio of both rotamers as 3:2 from integrated signals of the ^{1}H NMR spectrum, we have been unable to assign the resonances to distinct rotameric forms. It should be noted that the two rotameric (*anti* and *syn*) forms of N^3-(β-D-glucopyranosyl)-6-methyluracil were discernible by ^{1}H NMR spectroscopy in the same ratio.[25] Similar rotamers were also noted in some β-D-glucopyranosylpteridines.[26] In these cases, the rotation of the sugar residue is hindered by two carbonyl groups or a carbonyl function and a heteroaromatic moiety. The obtained $\Delta G^{\ddagger}$-values,[25,26] 18.9 and 18.3 kcal mol^{-1} (the former was calculated from the reported[25] data), indicate a similar rotational barrier in all these compounds. To the best of our knowledge, rotamers **28** and **29** are the first examples of such isomerism in a non-carbohydrate derivative of a nucleic acid base, which is also reflected in the ^{13}C NMR spectrum.

Synthesis and Properties of Ynamines.—The trichlorovinyl derivative **11** was smoothly converted into ynamine **30** in almost 60% yield by using BuLi in tetrahydrofuran (THF) at −70 °C (Scheme 7). A low temperature is essential for the success of

* 1 cal = 4.184 J.

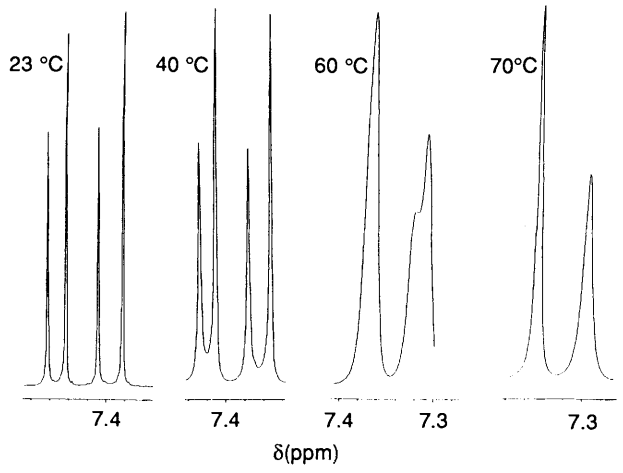
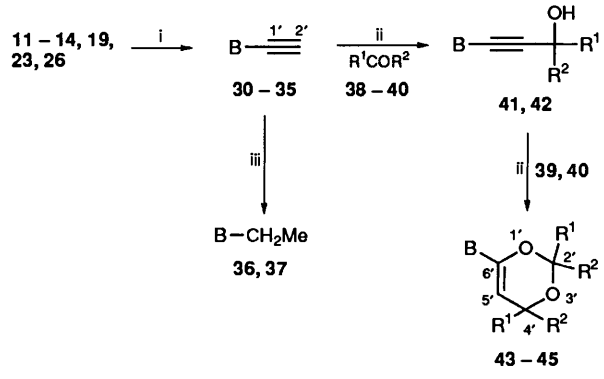


Fig. 1 The temperature dependence of the 500 MHz ^{1}H NMR spectrum of rotamers **28** and **29** in $(CD_3)_2SO$. Only the olefinic region is shown. All values of chemical shifts at 23 °C are listed in the Experimental section. For numbering of signals see formula **21**. Note that all protons of the less abundant rotamer are located downfield from those of the major rotational isomer. The spectra were determined at 23, 40, 60, 70 and 80 °C. At 80 °C all peaks were singlets or, where appropriate, doublets. The $\Delta G^{\ddagger}$-value 17.7 kcal mol^{-1} represents an average of determinations from the 2′- and 2″-H signals.

the reaction; at higher temperatures extensive decomposition occurred. Other chlorinated derivatives such as **16** and **17** did not react, probably because of limited solubility in THF at −70 °C. For these reasons, trichlorovinyl derivatives **12–14**, **19**, **23** and **26** were chosen for generation of the corresponding ynamines **31–35**. The yields were in the range of ~40–50% with the exception of compound **32** which was obtained in only 21% yield. Dichlorovinyl derivative **15** which is soluble in THF did not afford any ynamine. This can be explained by preferential ionization of the C^8–H bond of the heterocyclic moiety[27] which decreases the reactivity at the acetylenic CH function. Attempted debenzylations of compound **32** using boron tri-



30, **36**; B = adenin-N^9-yl
31; B = 2,6-diaminopurin-N^9-yl
32; B = 2-amino-6-benzyloxypurin-N^9-yl
33; B = N^6-benzoyladenin-N^9-yl
34; B = cytosin-N^1-yl
35, **37**; B = thymin-N^1-yl
38; $R^1 = R^2 = Me$
39; $R^1R^2 = [CH_2]_5$
40; $R^1 = R^2 = PhCH_2OCH_2$
41; B = adenin-N^9-yl, $R^1 = R^2 = Me$
42, **43**; B = adenin-N^9-yl, $R^1R^2 = [CH_2]_5$
44; B = adenin-N^9-yl, $R^1 = R^2 = PhCH_2OCH_2$
45; B = thymin-N^1-yl, $R^1 = R^2 = PhCH_2OCH_2$

Scheme 7 *Reagents and conditions:* i, BuLi, THF, −70 °C; ii, $NaNH_2$, THF; iii, H_2, Pd/C, EtOH

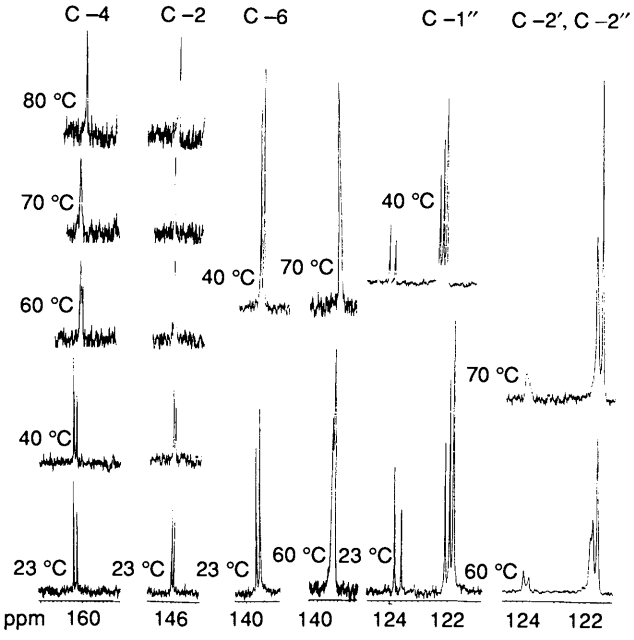


Fig. 2 The temperature dependence of the 125 MHz ^{13}C NMR spectrum of rotamers **28** and **29** in $(CD_3)_2SO$. See Fig. 1. Only the relevant segments of the spectrum are shown. Note that 5 carbons from a possible 9 are doubled. All were single peaks at 80 °C. The $\Delta G^{\ddagger}$-value 17.8 kcal mol^{-1} is an average of determinations from the C-4, C-2, C-6 and C-1″ signals.

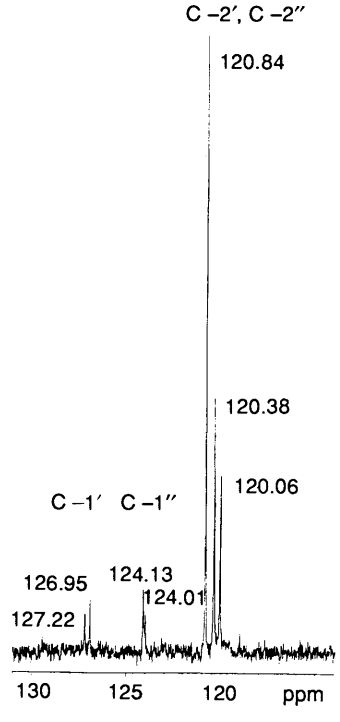
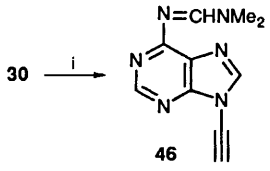


Fig. 3 The 125 MHz ^{13}C NMR spectrum of the olefinic region of rotamers **28** and **29** in $CDCl_3$. See Fig. 1. Note that the signal of the C-1′ carbon is split and the pattern of the C-2′ and -2″ peaks is reversed relative to the spectrum determined in $(CD_3)_2SO$ (Fig. 2). Assignments of the C-1′, -1″ and -2′ (-2″) signals are based on a DEPT experiment.[23]

chloride, trimethylsilyl iodide or sodium in liquid ammonia led only to side-reactions at the ynamine moiety.

The protection of ynamines is of interest in view of the considerable synthetic potential of such derivatives. The N^6-dimethylaminomethylene ynamine **46** was smoothly obtained

from compound **30** by reaction with *N*,*N*-dimethylformamide dimethyl acetal[17] in DMF in 75% yield (Scheme 8). By contrast,



Scheme 8 *Reagents and conditions:* i, $Me_2NCH(OMe)_2$, DMF

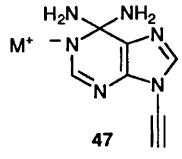
an attempted benzoylation of compound **30** with benzoyl chloride in pyridine led only to products of addition across the triple bond. Nevertheless, the N^6-benzoyl ynamine **33** was obtained from N^6,N^6-dibenzoyl derivative **26** (18%) or, more conveniently, N^6-benzamide **14** (47% yield) by a procedure outlined above. These transformations conclusively showed that reaction of N^6-benzoyladenine **4** with tetrachloroethylene **6** exhibits the same (N^9) regioselectivity as that of adenine **1**.

The obtained ynamines are of sufficient stability to be properly characterized. N^1-Ethynylcytosine **34** is an exception. Solutions of compound **34** in DMSO or DMF turn rapidly brown. The NMR spectra in $(CD_3)_2NCDO$ at −20 °C revealed the presence of signals assignable to olefinic protons which are indicative of a spontaneous polymerization of compound **34**. Hydrogenation of ynamines **30** and **35** afforded the corresponding *N*-ethyl derivatives **36** and **37** (Scheme 7) in 88 and 86% yield, respectively. The latter transformations also showed that reactions of adenine **1** and thymine **18** with tetrachloroethylene **6** were regioselective at N^9 and N^1, respectively. Also, the UV spectrum of compound **34** is similar to that of cytallene,[28] which is in line with the formulation of trichloro enamine **23** as an N^1-substituted cytosine.

The structures of the obtained ynamines were confirmed by spectroscopic methods. The presence of a C≡CH function was apparent from IR and NMR spectra. The C-1′ signals of pyrimidine ynamines are positioned downfield from those of purine derivatives. The trend appears to be the opposite for C-2′. The EI mass spectra of ynamines indicated little cleavage of the C-1′–N bond (peaks of heterocyclic bases are virtually absent). In this respect, the spectra are quite similar to those of other unsaturated derivatives of nucleic acid bases which contain a double bond in conjugation with the heterocyclic moiety.[4]

Reactions of Ynamines **30** *and* **35** *with Ketones.*—Alkylation of alkyl- or aryl-acetylenes with aldehydes or ketones is a general and synthetically useful transformation.[29] By contrast, reaction of ketones with ynamines derived from strong bases (*e.g.*, diethylamine) leads only to rearrangement products of the intermediary carbinols. Less basic ynamines, such as *N*-ethynyl-*N*,*N*-diphenyl- or *N*-ethynyl-*N*-methyl-*N*-phenylamine, can be alkylated with ketones to the corresponding carbinols without difficulty.[30] No such hydroxyalkyl ynamines have been described in the heterocyclic series to the best of our knowledge. We therefore studied the reaction of ynamine **30** with acetone **38**, cyclohexanone **39** and dibenzyloxyacetone[31] **40**. The character of the base catalyst has a profound influence on the success of the alkylation. Thus, experiments using $LiNH_2$ (**38**) or the strongly basic BuLi (**39** or **40**) were fruitless. By contrast, reaction of ynamine **30** with acetone **38** in the presence of $NaNH_2$ in THF gave the corresponding carbinol **41** in 45% yield (Scheme 7). In a similar fashion, cyclohexanone **39** afforded carbinol **42** (70%) accompanied by cyclic unsaturated ketal **43** (29%). Carbinol **42** is an obvious intermediate in the formation of ketal **43**. Thus, reaction of alcohol **42** with a second molecule of ketone **39** leads to the corresponding hemiketal[1b] which then undergoes cyclization to the product ketal **43**. Alkylation of ynamines **30** and **35** with ketone **40** afforded only cyclized products **44** and **45** in 72 and 54% yield, respectively. It should also be noted that carbinols **41** and **42** are stable during chromatography on silica gel and they thus differ from their counterparts derived from *N*-methyl- or *N*-phenyl-aniline.[30]

It is therefore clear that the reactivity of both the ketone (hemiketal formation) and the ynamine play a role in this transformation. Cyclization driven by formation of a hemiketal is generally not observed during alkylation of alkyl- or aryl-acetylenes with aldehydes or ketones but it was described in the case of reactive diacetylene carbinols[32] and formaldehyde. In accord with this trend, interaction of ynamine **30** with acetone **38** gave only carbinol **41**, but reaction of cyclohexanone **39** with ynamine **30** furnished some cyclized product **43**. Neither pyrimidine nor purine ynamines (**30**, **35**) with ketone **40** afforded any carbinol, but gave only cyclic ketals (**44** or **45**). It has to be stressed that changing the reaction conditions, limiting the amount of ketone, and protecting the heterocyclic moiety (ynamines **33** and **46**) did not influence the result. Ketals **44** and **45** were always the major products (after deprotection where appropriate) and the corresponding carbinols were not detected at all. A favourable effect of $NaNH_2$ in these transformations is difficult to explain. However, an interaction of $NaNH_2$ with the heterocyclic moiety, *e.g.* that of ynamine **30**, may lead to transient formation of a base **47** (M = Na) stronger than the starting ynamine and, hence, increase the reactivity of the acetylene CH function. By contrast, BuLi will only decrease such reactivity by ionization of the amino group of ynamine **30**. The less basic $LiNH_2$ is apparently not capable of providing intermediate **47** (M = Li).



Assignments of six-membered β-vinyl ether structures **43**–**45** followed from the NMR spectra. The ^{13}C NMR spectrum of compound **44** showed two olefinic carbons (C-6′ and -5′) at δ_C 146.14 and 92.96, respectively. The spectrum of compound **45** contained similar signals at δ_C 147.54 and 97.30. The signal at higher field was assigned to C-5′ as in other β-vinyl ethers[19] (see also compound **27**). In the case of compound **44**, a distortionless enhancement by polarization transfer (DEPT) experiment[23] confirmed that C-5′ was the hydrogen-carrying carbon. Likewise, the structures of carbinols **41** and **42** were unambiguously established by IR and NMR spectra which confirmed the presence of OH and C≡C functions in both molecules. The UV spectra of carbinols **41** and **42** revealed some important differences in their fine structure (Fig. 4). Thus, compound **42** resembles the parent ynamine **30** more than does the dimethylcarbinol **41**.

Biological Activity.—Compound **30** is a substrate of moderate activity for adenosine deaminase from calf intestine.[1b] Thus, ~90% deamination was observed after incubation for 3 days at room temperature. N^9-(prop-2-ynyl)adenine,[33] a homologue of compound **30**, N^9-vinyladenine and ynamine **31** were inactive. Previous data[1b] indicated that compounds **19**, **30**, **31** and **42** inhibited the growth of murine leukaemia L1210 with IC_{50} 40–150 μmol dm^{-3} as determined by a clonogenic assay.[13] In addition, analogues **11**, **30** and **31** suppressed the growth of mouse and human colon tumours C38, H8 or H116 according to a disk-diffusion assay.[13] Therefore, compounds **11** and **31**

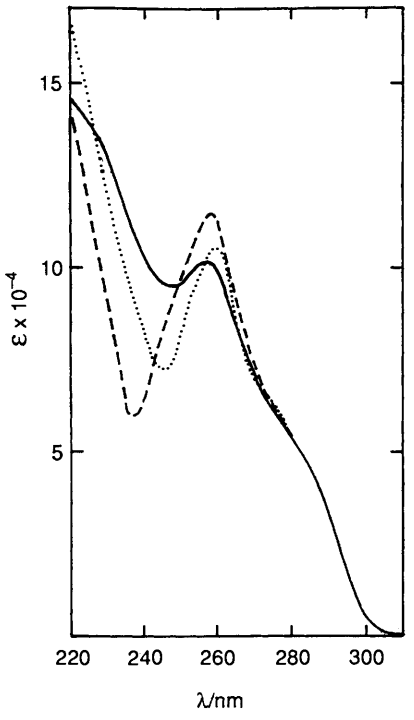


Fig. 4 UV spectra of ynamines **30**, **41** and **42** in ethanol: – – – – compound **30**; —— compound **41**; · · · · compound **42**

were tested *in vivo* against early-stage colon adenocarcinoma C38 in mice. No antitumour activity was observed at a total dose of 1968 and 1100 mg kg^{-1}, respectively.

Analogues **3**, **33**, **16** and **24** were also inactive as antiviral agents against herpes simplex virus (HSV-1) and human cytomegalovirus (HCMV) grown in culture[34,35] at concentrations 100 μmol dm^{-3} or lower. With the exception of compound **3**, they were also not cytotoxic in human foreskin fibroblasts (HFF) or KB cells. Compound **3** inhibited the growth of KB cells with IC_{50} ~ 100 μmol dm^{-3}.

Experimental

For general methods see refs. 28, 36. THF was freshly distilled from sodium benzophenone ketyl. DMF, DMSO, pyridine and HMPA were dried with molecular sieves 3 Å. Column chromatography and TLC were performed in the following solvent systems: S_1, CH_2Cl_2–acetone (1:1); S_2, CH_2Cl_2–MeOH (9:1); S_3, CH_2Cl_2–MeOH (4:1); S_4, CH_2Cl_2–MeOH (95:5); S_5, ethyl acetate–MeOH (95:5); S_6, CH_2Cl_2–acetone (4:1); S_7, CH_2Cl_2–acetone (9:1); S_8, hexane–acetone (7:3). Spots of samples containing high boiling solvents (HMPA) were dried under reduced pressure.[37] The UV and NMR spectra were determined in ethanol and $(CD_3)_2SO$, respectively, unless stated otherwise. *J*-Values are given in Hz. For IR spectra, KBr pellets were used. For chemical ionization (CI) mass spectra, 2-methylpropane was used as the ionization gas.

N^9-(*Trichlorovinyl*)*adenine* **11**. Adenine **1** (2 g, 15 mmol) was dissolved in HMPA (130 cm^3) at 60 °C (bath temperature). The solution was cooled to room temperature and NaH (57% oil suspension; 1.24 g, 30 mmol) was added under N_2. The mixture was stirred till the evolution of H_2 ceased. Tetrachloroethylene **6** (7.36 g, 44.5 mmol) was then added and the mixture was stirred at 60 °C (bath temp.) for 15 h. The progress of reaction was monitored by TLC in solvent S_1. Most of the HMPA was removed under reduced pressure at 90 °C (bath temp.) and the resultant crude product was washed successively with methanol (20 cm^3) and several times with portions (50 cm^3) of solvent system S_2. The combined washings were evaporated and the residue was flash chromatographed on a silica gel column, using solvent system S_1. The appropriate fractions were combined and evaporated to give *compound* **11** (0.84 g, 20%), m.p. 189–190 °C (decomp.). This product was recrystallized from solvent system S_2 (0.1 g/50 cm^3), m.p. 201–202 °C (decomp.) (Found: C, 31.8; H, 1.4; Cl, 40.4; N, 26.2. $C_7H_4Cl_3N_5$ requires C, 31.79; H, 1.52; Cl, 40.21; N, 26.48%); λ_{max}/nm 256 (ε 15 000); δ_H 8.48 and 8.21 (2 H, 2 s, 2- and 8-H) and 7.58 (2 H, s, NH_2); δ_C 156.53, 154.56, 149.56, 140.11 and 118.09 (adenine) and 125.27 and 120.59 (C-1′, -2′); *m/z* (EI) 267, 265 and 263 (M, 5, 15 and 15%), 232, 230 and 228 (M − Cl, 11, 64 and 100) and 205, 203 and 201 (M − HCN − Cl, 2, 17 and 28) (Found: M^+, 262.9528. $C_7H_4{}^{35}Cl_3N_5$ requires M, 262.9532).

(E)-N^9-(1,2-*Dichlorovinyl*)*adenine* **16**.—A. *From adenine* **1** *and trichloroethylene* **7**. The experiment was performed as described for compound **11** but with adenine **1** (0.27 g, 2 mmol), KH (24% oil suspension, 0.68 g, 4 mmol) and trichloroethylene **7** (0.26 g, 2 mmol) in HMPA (total 10 cm^3). The reaction mixture was stirred for 16 h at room temperature. Work-up and chromatography (solvent system S_2) followed similar procedures described for compound **11**, to give *title compound* **16** (0.1 g, 22%), m.p. 229–230 °C after crystallization from solvent system S_3 (Found: C, 36.7; H, 2.4; Cl, 30.6; N, 30.6. $C_7H_5Cl_2N_5$ requires C, 36.55; H, 2.19; Cl, 30.82; N, 30.44%); λ_{max}/nm 258 (ε 15 100); δ_H 8.42 and 8.19 (2 H, 2 s, 2- and 8-H) and 7.52 (3 H, apparent s, NH_2 and 2′-H); δ_C 156.26, 153.81, 149.09, 139.41 and 117.89 (adenine) and 122.05 and 119.55 (C-1′, -2′); *m/z* (EI) 233, 231 and 229 (M, 2, 10 and 16%), 196 and 194 (M − Cl, 32 and 100) and 169 and 167 (M − HCN − Cl, 7 and 21) (Found: M^+, 228.9919. $C_7H_5{}^{35}Cl_2N_5$ requires M, 228.9922).

B. *From adenine* **1** *and dichloroacetylene*. Dichloroacetylene–diethyl ether complex[7] (7.5 cm^3, ~12 mmol) was added dropwise to a solution of adenine **1** (0.27 g, 2 mmol) in HMPA (10 cm^3). The mixture, which gradually became orange, was stirred at room temperature for 1 h before being evaporated, and HMPA was removed at 70 °C (bath-temp.) and 0.025 mmHg pressure. The crude product was chromatographed on a silica gel column in solvent system S_4 to give dichloro enamine **16** (25 mg, 3%), m.p. 220–225 °C, identical (TLC, ^1H NMR) with a sample prepared by method A. Compound **16** was 77% pure as estimated by UV spectroscopy.

(Z)-N^9-(2-*Chlorovinyl*)*adenine* **17**.—A. *From adenine* **1** *and* (Z)-1,2-*dichloroethylene* **8**. A mixture of adenine **1** (0.1 g, 0.74 mmol) and KH (0.25 g, 1.5 mmol) in HMPA (18 cm^3) was stirred at room temperature for 2 h. Reagent **8** (0.14 cm^3, 1.5 mmol) was added and the mixture was stirred at 65 °C (bath temp.) for 7 h. The usual work-up and chromatography in solvent system S_2 gave *product* **17** (50 mg, 35.4%), m.p. 218–219 °C (decomp.) after crystallization from ethanol (Found: C, 43.0; H, 3.0; Cl, 18.4; N, 35.65. $C_7H_6ClN_5$ requires C, 42.98; H, 3.09; Cl, 18.12; N, 35.80%); λ_{max}/nm 260 (ε 12 600); δ_H 8.62 and 8.16 (2 H, 2 s, 2- and 8-H), 7.44 (1 H, d, $J_{1',2'}$ 6.3, 1′-H), 7.41 (2 H, s, NH_2) and 6.61 (1 H, d, $J_{2',1'}$ 6.3); δ_C 156.49, 153.69, 149.37, 138.75 and 117.80 (adenine) and 121.52 and 111.19 (C-1′, -2′); *m/z* (EI) 197 and 195 (M, 17 and 50%), 160 (M − Cl, 100), 133 (M − HCN − Cl, 44), 106 (M − 2 × HCN − Cl, 19) (Found: M^+, 195.0308. $C_7H_6{}^{35}ClN_5$ requires M, 195.0312).

B. *From adenine* **1** *and* 1,1-*dichloroethylene* **9**. Reagent **9** (0.72 cm^3, 9 mmol) was added to a mixture of adenine **1** (0.2 g, 1.5 mmol), NaOH (0.24 g, 6 mmol), 1 mol dm^{-3} TBAF in THF (0.2 cm^3, 0.2 mmol) and 0.5 cm^3 water in DMF (20 cm^3). The mixture was stirred at 60 °C (bath temp.) for 24 h and then was evaporated. Chromatography of the residue in solvent system S_5 gave compound **17** (39 mg, 16%), m.p. 220 °C

(decomp.) which was identical with the product obtained by method A.

2,6-*Diamino*-N^9-(*trichlorovinyl*)*purine* **12**.—The procedure described for compound **11** was followed with 2,6-diaminopurine hemisulfate **2** (2.19 g, 11 mmol), NaH (60%, 1.66 g, 42 mmol) and tetrachloroethylene **6** (5.45 g, 33 mmol) in HMPA (100 cm^3) to give *compound* **12** (1.03 g, 33.1%), m.p. 196–199 °C after crystallization from solvent system S_1 (Found: C, 29.6; H, 2.1; Cl, 37.3; N, 29.4. $C_7H_5Cl_3N_6$·0.25 H_2O requires C, 29.60; H, 1.95; Cl, 37.44; N, 29.59%); λ_{max}/nm 278 (ε 12 400); δ_H 7.95 (1 H, s, 8-H), 6.95 (2 H, s, 6-NH_2) and 6.17 (2 H, s, 2-NH_2); δ_C 161.57, 156.75, 152.05, 135.60 and 112.18 (purine) and 124.27 and 121.66 (C-1′, -2′); *m*/*z* (EI) 284, 282, 280 and 278 (M, 0.1, 4, 13 and 13%), 247, 245 and 243 (M − Cl, 1, 10 and 15) and 205, 203 and 201 (M − HN=C=NH − Cl, 1, 8 and 13) and 49 (100).

2-*Amino*-6-*benzyloxy*-N^9-(*trichlorovinyl*)*purine* **13**.—2-Amino-6-benzyloxypurine[38] **3** (1.20 g, 5.3 mmol), NaH (60%, 0.43 g, 10.6 mmol) and tetrachloroethylene **6** (2.64 g, 16 mmol) in HMPA (100 cm^3) were allowed to react at 60 °C for 15 h. The usual work-up and chromatography in solvent system S_7 afforded *compound* **13** (0.4 g, 20%), m.p. 171–172 °C after crystallization from hexane–acetone (4:1) (Found: C, 45.2; H, 2.9; Cl, 28.5; N, 18.7. $C_{14}H_{10}Cl_3N_5O$ requires C, 45.37; H, 2.72; Cl, 28.70; N, 18.90%); λ_{max}/nm 270 (ε 13 200); δ_H 8.15 (1 H, s, 8-H), 7.47, 7.36 and 7.34 (5 H, d and m, Ph), 6.90 (2 H, s, NH_2) and 5.46 (2 H, s, CH_2); δ_C 161.14, 160.79, 154.22, 137.99 and 112.97 (purine), 136.68, 129.08, 128.84 and 128.59 (Ph), 121.89 and 121.09 (C-1′, -2′) and 67.68 (CH_2); *m*/*z* (EI) 375, 373, 371 and 369 (M, 0.6, 6, 20 and 21%) and 91 ($C_6H_5CH_2$, 100).

N^6-*Benzoyl*-N^9-(*trichlorovinyl*)*adenine* **14**.—A mixture of *N*^{6}-benzoyladenine **4** (0.3 g, 1.25 mmol), NaH (60%, 0.1 g, 2.5 mmol) and tetrachloroethylene **6** (0.62 g, 3.8 mmol) was stirred in HMPA (15 cm^3) for 14 h at 60 °C (bath temp.). After the usual work-up, chromatography in solvent system S_6 gave *compound* **14** (0.1 g, 20%), m.p. 158–160 °C after crystallization from the same solvent mixture (Found: C, 45.65; H, 2.0; Cl, 28.7; N, 19.1. $C_{14}H_8Cl_3N_5O$ requires C, 45.62; H, 2.19; Cl, 28.85; N, 19.00%); ν_{max}/cm^{-1} 3260–3220 (NH) and 1720 (CO); λ_{max}/nm 278 (ε 16 900); δ_H 11.42 (CONH), 8.83 (2 H, s, 2- and 8-H), 8.04 (2 H, d) and 7.62–7.50 (3 H, m) (Ph); *m*/*z* (EI) 371, 369 and 367 (M, 1, 4 and 4%), 344, 342, 340 and 338 (M −29, 1, 10, 30 and 30) and 105 (PhCO, 100).

(E)-2-*Amino*-6-*chloro*-N^9-(1,2-*dichlorovinyl*)*purine* **15**.—2-Amino-6-chloropurine **5** (0.1 g, 0.6 mmol), NaH (60%; 47 mg, 1.2 mmol) and trichloroethylene **7** (0.23 g, 1.7 mmol) were allowed to react in HMPA (10 cm^3) for 15 h at room temperature. The crude product was chromatographed in solvent system S_6 to give *compound* **15** (40 mg, 26%), m.p. 195–196 °C after crystallization from solvent system S_2 (Found: C, 31.9; H, 1.6; Cl, 40.4; N, 26.3. $C_7H_4Cl_3N_5$ requires C, 31.79; H, 1.52; Cl, 40.21; N, 26.48%); λ_{max}/nm 302 (ε 6100) and 247sh (ε 7700); δ_H 7.90 (1 H, s, 8-H), 7.38 (1 H, s, 2′-H) and 6.15 (2 H, s, NH_2); δ_C 161.14, 153.85, 150.93, 141.56 and 122.86 (purine) and 122.16 and 121.15 (C-1′, -2′); *m*/*z* (FAB) 269, 267 and 265 (M + H, 12, 32 and 34%) and 58 (100).

N^1-(*Trichlorovinyl*)*thymine* **19**.—The procedure for compound **11** was followed on a 16 mmol scale of thymine **18**. After evaporation of HMPA the residue was chromatographed in solvent system S_6. The appropriate fractions were evaporated to give, after trituration with solvent system S_8, *solid* **19** (1 g, 25%), m.p. 189–191 °C (softens at 165–170 °C) (Found: C, 32.7; H, 2.05; Cl, 41.8; N, 11.0. $C_7H_5Cl_3N_2O_2$ requires C, 32.91; H, 1.97; Cl, 41.63; N, 10.96%); λ_{max}/nm 259 (ε 10 700); δ_H 11.84 (1 H, s, NH), 7.71 (1 H, d, 6-H) and 1.76 (3 H, apparent s, Me); δ_C 164.16, 148.64, 138.47, 112.66 and 12.43 (thymine), 125.77 and 125.45 (C-1′, -2′); *m*/*z* (EI) 260, 258, 256 and 254 (M, 0.2, 2, 4 and 4%), 223, 221 and 219 (M − Cl, 11, 64 and 100), 217, 215, 213 and 211 (M − HCNO, 1, 10, 31 and 32), 180, 178 and 176 (M − HCNO − Cl, 2, 9 and 14), and 152, 150 and 148 (M − HCNO − CO − Cl, 9, 40 and 54).

(E)-N^1-(1,2-*Dichlorovinyl*)*thymine* **20**.—A. *Reductive alkylation of thymine* **18** *with tetrachloroethylene* **6**.—A mixture of thymine **18** (0.4 g, 3.2 mmol) and NaH (60%; 0.25 g, 6.3 mmol) in DMSO (20 cm^3) was stirred for 1 h at room temperature under N_2. Tetrachloroethylene **6** (1.57 g, 9.5 mmol) was then added and the mixture was stirred for 15 h. TLC in solvent S_7 indicated the presence of title product **20** and a small amount of compound **19**. The volatile components were evaporated off and the residue was chromatographed in solvent S_7 to give *compound* **20** (0.15 g, 20%), m.p. 225–226 °C after crystallization from solvent S_7 (Found: C, 38.25; H, 2.8; Cl, 31.9; N, 12.7. $C_7H_6Cl_2N_2O_2$ requires C, 38.04; H, 2.74; Cl, 32.08; N, 12.67%); λ_{max}/nm 260 (ε 10 300); δ_H 11.75 (1 H, s, NH), 7.60 (1 H, s, 2′-H), 7.31 (1 H, d, 6-H) and 1.77 (3 H, d, Me); δ_C 164.29, 148.58, 138.78, 112.18 and 12.33 (thymine), 127.26 and 120.88 (C-1′, -2′); *m*/*z* (EI) 224, 222 and 220 (M, 0.6, 3 and 3%), 187, 185 (M − Cl, 37 and 100), 181, 179 and 177 (M − HCNO, 2, 12 and 19), 144 and 142 (M − HCNO − Cl, 8, 25) and 116 and 114 (M − HCNO − CO − Cl, 20, 42).

B. *From thymine* **18** *and dichloroacetylene*. Dichloroacetylene–diethyl ether complex[7] (2.5 cm^3, ~4 mmol) was added to a solution of thymine **18** (0.25 g, 2 mmol) in THF–HMPA (2:1; 30 cm^3). The mixture was stirred for 27 h at room temperature whereupon it was evaporated (see compound **16**, method B). Chromatography in solvent S_8 gave dichloro enamine **20** (53 mg, 12%), m.p. 230–231 °C, which was identical (TLC, UV and ^{1}H NMR) with the product obtained by method A.

(E)-N^1-(1,2-*Dichlorovinyl*)*thymine* **20** *and* (E,E)-N^1,N^3-*Bis*-1,2-*dichlorovinyl*)*thymine* **21**.—A mixture of thymine **18** (0.5 g, 4 mmol) and NaH (60%; 0.32 g, 7.9 mmol) in HMPA (10 cm^3) was stirred with trichloroethylene **7** (1.55 g, 11.8 mmol) for 15 h at room temperature. The usual work-up and chromatography in solvent S_8 gave *compound* **21** (0.36 g, 28%), m.p. 155–156 °C after crystallization from solvent S_8 (Found: C, 34.4; H, 2.1; Cl, 45.0; N, 8.8. $C_9H_6Cl_4N_2O_2$ requires C, 34.21; H, 1.91; Cl, 44.88; N, 8.87%); λ_{max}/nm 264 (ε 10 000); δ_H(500 MHz) 7.915 and 7.911 (1 H, 2 d, 6-H), 7.463, 7.443, 7.409 and 7.383 (2 H, 4 s, 1′- and 2″-H), 1.881 and 1.873 (3 H, 2 d, Me); δ_C(125 MHz) 160.425 and 160.263 (C-4), 146.024 and 145.913 (C-2), 139.525 and 139.340 (C-6), 126.371 (C-1′), 123.853 and 123.609 (C-1″), 122.110, 121.995 and 121.829 (C-2′, -2″), 111.508 (C-5) and 12.555 (Me); *m*/*z* (CI) 321, 319, 317 and 315 (M + H, 11, 48, 100 and 76%), 285, 283, 281 and 279 (M − Cl, 2, 21, 63 and 66), 181, 179 and 177 (M − ClCH=CClN=C=O, 0.8, 6, 9%), 144, 142 (M − ClCH=CCl–N=C=O − Cl, 5 and 16) and 116 and 114 (M − ClCH=CCl–N=C=O − CO − Cl, 8 and 17).

Further elution afforded compound **20** (50 mg, 5.7%) which was identical (TLC, IR and ^{1}H NMR) with the product obtained from thymine **18** and tetrachloroethylene **6** in DMSO.

N^1-(*Trichlorovinyl*)*cytosine* **23**.—The procedure for preparation of compound **11** was employed using cytosine **22** (1.11 g, 10 mmol), NaH (57%; 0.84 g, 20 mmol) and tetrachloroethylene **6** (9.94 g, 60 mmol) in HMPA (70 cm^3). The crude product was chromatographed in solvent system S_2 to give *compound* **23** (0.5 g, 20.8%), m.p. 229–230 °C after crystallization from the same solvent (50 mg/25 cm^3) (Found: C, 30.2; H, 1.8; Cl, 44.4; N, 17.3. $C_6H_4Cl_3N_3O$ requires C, 29.97; H, 1.68; Cl, 44.23; N,

17.47%); λ_{max}/nm 250 (ε 9900); δ_H 7.72 (2 H, s, NH_2), 7.65 (1 H, d, 6-H) and 5.87 (1 H, d, 5-H); δ_C 166.79, 152.76, 144.31 and 97.18 (cytosine) and 127.91 and 123.60 (C-1′, -2′): *m/z* (CI) 246, 244, 242 and 240 (M + H, 3, 25, 78 and 82%) and 208, 206 and 204 (M − Cl, 3, 65 and 100).

(E)-N^1-(1,2-*Dichlorovinyl*)*cytosine* **24**.—The procedure for the preparation of compound **16** was followed with cytosine **22** (0.22 g, 2 mmol). The usual work-up and chromatography in solvent system S_2 afforded *compound* **24** (0.1 g, 24.2%), m.p. 219–220 °C after crystallization from solvent system S_3 (Found: C, 34.9; H, 2.4; Cl, 34.6; N, 20.2. $C_6H_5Cl_2N_3O$ requires C, 34.98; H, 2.45; Cl, 34.42; N, 20.40%); λ_{max}/nm 251 (ε 8300); δ_H 7.56 (2 H, s, NH_2), 7.53 (1 H, d, 6-H), 7.10 (1 H, s, 2′-H) and 5.81 (1 H, d, 5-H); δ_C 166.81, 152.78, 144.64 and 96.58 (cytosine), 129.94 and 118.47 (C-1′, -2′); *m/z* (CI) 210, 208 and 206 (M + H, 11, 64 and 100%) and 172 and 170 (M − Cl, 12 and 32).

(E)-N^1-(1,2-*Dichlorovinyl*)-N^4-(*dimethylaminomethylene*)-*cytosine* **25**.—Compound **24** (65 mg, 0.32 mmol) was stirred with *N,N*-dimethylformamide dimethyl acetal (0.11 g, 0.95 mmol) in DMF (2 cm^3) for 15 h at room temperature. The volatile components were removed under reduced pressure (oil-pump) and the residue was triturated with hexane to give *compound* **25** (70 mg, 85%), m.p. 214–215 °C (decomp.) after crystallization from ethyl acetate–acetone (1:1) (Found: C, 41.4; H, 4.0; Cl, 27.1; N, 21.2. $C_9H_{10}Cl_2N_4O$ requires C, 41.40; H, 3.86; Cl, 27.16; N, 21.46%); λ_{max}/nm 318 (ε 29 700); δ_H($CDCl_3$) 8.80 (1 H, s, Me_2NCH=), 7.16 (1 H, d, 6-H), 6.45 (1 H, s, 2′-H), 6.06 (1 H, d, 5-H) and 3.13 and 3.10 (6 H, 2 s, Me_2N); *m/z* (CI) 265, 263 and 261 (M + H, 9, 54 and 82%), and 227 and 225 (M − Cl, 33 and 100).

N^6,N^6-*Dibenzoyl*-N^9-(*trichlorovinyl*)*adenine* **26**.—Pyridine was repeatedly evaporated under reduced pressure from compound **11** (0.3 g, 1.1 mmol). Fresh pyridine (15 cm^3) was added to the residue followed by benzoyl chloride (0.32 g, 2.3 mmol) and the mixture was stirred for 15 h at room temperature. The volatile components were removed under reduced pressure, the last portions by evaporation with toluene (15 cm^3). Chromatography in solvent system S_8 gave *compound* **26** (0.3 g, 56%), m.p. 195–196 °C after crystallization from hexane–acetone (1:1) (Found: C, 53.1; H, 2.4; Cl, 22.4; N, 15.05. $C_{21}H_{12}Cl_3N_5O_2$ requires C, 53.36; H, 2.56; Cl, 22.50; N, 14.82%); λ_{max}/nm 248 (ε 24 400) and 275sh (17 900); δ_H($CDCl_3$) 8.75 and 8.12 (2 H, 2 s, 2- and 8-H) and 7.85 (4 H, d), 7.50 (2 H, t) and 7.37 (4 H, t) (2 × Ph); δ_C 172.11 (CO), 153.54, 152.67, 152.24, 142.90 and 119.20 (adenine), 133.88, 133.20, 129.44 and 128.78 (Ph), and 126.49 and 126.35 (C-1′, -2′); *m/z* (EI) 475, 473 and 471 (M, 1, 4 and 4%).

(E)-N^9-(1-*Chloro*-2-*methoxyvinyl*)*adenine* **27**.—A mixture of compound **16** (34 mg, 0.15 mmol) and MeONa (25% in MeOH; 0.1 cm^3, 0.44 mmol) in DMF (3 cm^3) was stirred for 5.5 h at room temperature whereupon it was evaporated. The residue was washed several times with solvent system S_2 (15 cm^3). The combined washings were evaporated and the crude product was chromatographed in the same solvent mixture to give *compound* **27** (21 mg, 63%), m.p. 162–163 °C after crystallization from solvent system S_1 (Found: C, 42.8; H, 3.7; Cl, 15.6; N, 31.0. $C_8H_8ClN_5O$ requires C, 42.59; H, 3.57; Cl, 15.71; N, 31.04%); λ_{max}/nm 258 (ε 16 000); δ_H 8.21 and 8.15 (2 H, 2 s, 2- and 8-H), 7.39 (2 H, s, NH_2), 7.17 (1 H, s, H-2′) and 3.60 (3 H, s, Me); δ_C 156.15, 153.50, 149.61, 140.91 and 118.04 (adenine), 147.43 (C-2′), 102.33 (C-1′) and 61.04 (Me); *m/z* (EI) 227 and 225 (M, 33 and 100%), 212 and 210 (M − Me, 17 and 56), 190 (M − Cl, 76), 184 and 182 (M − Me − CO, 28 and 89), 160 (63), 157 and 155 (M − HCN − Me − CO, 20 and 65), and 130 and 128 (M − 2 × HCN − Me − CO, 17 and 55) (Found: M$^+$, 225.0414. $C_8H_8{}^{35}ClN_5O$ requires M, 225.0417).

N^9-*Ethynyladenine* **30**.—A solution of compound **11** (0.6 g, 2.3 mmol) in THF (45 cm^3) was cooled to −70 °C. BuLi in pentane (2 mol dm^{-3}; 4.5 cm^3, 9 mmol) was then added dropwise under N_2 to the stirred mixture during 10 min. The mixture was stirred at −70 °C for 1 h. The reaction was quenched with methanol (4 cm^3) and 10% aq. NH_4Cl (9 cm^3) and the mixture was brought to room temperature. The solvents were removed under reduced pressure and methanol was repeatedly evaporated from the residue which was then chromatographed in solvent system S_1. The faster moving dichloroenamine **16** (50 mg, 9.5%) was followed by *ynamine* **30** (206 mg, 57%), m.p. 191–192 °C (decomp.) after crystallization from ethanol (50 mg/50 cm^3) and drying at room temperature. Drying at higher temperature led to decomposition (polymerization) (Found: C, 53.0; H, 3.2; N, 43.9. $C_7H_5N_5$ requires C, 52.81; H, 3.17; N, 44.02%); ν_{max}/cm^{-1} 2140 (C≡C); λ_{max}/nm 258 (ε 11 500); δ_H 8.48 and 8.20 (2 H, 2 s, 2- and 8-H), 7.57 (2 H, s, NH_2) and 4.63 (1 H, s, 2′-H); δ_C 156.34, 154.19, 151.18, 141.49 and 116.75 (adenine), 68.98 (C-1′) and 65.85 (C-2′); *m/z* (EI) 159 (M, 100%), 132 (M − HCN, 24), and 105 (M − 2 × HCN, 8) (Found: M$^+$, 159.0543. $C_7H_5N_5$ requires M, 159.0545).

2,6-*Diamino*-N^9-*ethynylpurine* **31**.—The procedure for ynamine **30** was modified as follows. A solution of compound **12** (1 g, 3.6 mmol) in THF (50 cm^3) was cooled to −70 °C, 2 mol dm^{-3} BuLi in pentane (7.1 cm^3, 14.2 mmol) was added and the reaction mixture was stirred at −70 °C for 3 h. The usual work-up and chromatography (solvent S_2) gave a *tan solid* **31** (0.26 g, 42%), m.p. 198–200 °C (decomp.) after crystallization from methanol (Found: C, 48.5; H, 3.5; N, 48.1. $C_7H_6N_6$ requires C, 48.26; H, 3.47; N, 48.27%); ν_{max}/cm^{-1} 2140 (C≡C); λ_{max}/nm 275 (ε 10 100); δ_H 7.99 (1 H, s, 8-H), 6.96 (2 H, s, 6-NH_2), 6.17 (2 H, s, 2-NH_2) and 4.42 (1 H, s, 2′-H); δ_C 161.89, 156.95, 154.21, 137.75 and 111.33 (purine), 70.40 (C-1′, $J_{1',2'-H}$ 57.9) and 65.39 (C-2′, $J_{2',2'-H}$ 265.5); *m/z* (EI) 174 (M, 100%), 132 (M − HN=C=NH, 16) (Found: M$^+$, 174.0653. $C_7H_6N_6$ requires M, 174.0654).

2-*Amino*-6-*benzyloxy*-N^9-*ethynylpurine* **32**.—The procedure for ynamine **30** was modified using compound **13** (0.2 g, 0.5 mmol) and 2 mol dm^{-3} BuLi (1.1 cm^3, 2.1 mmol) in THF (15 cm^3), and a reaction time 2 h at −78 °C. The crude product was chromatographed in solvent system S_7 to give *ynamine* **32**, which was crystallized twice from hexane–acetone (7:3) (30 mg, 21%), m.p. 200–201 °C (softening from 185 °C) (Found: C, 63.5; H, 4.3; N, 26.2. $C_{14}H_{11}N_5O$ requires C, 63.39; H, 4.18; N, 26.40%); ν_{max}/cm^{-1} 2140 (C≡C); λ_{max}/nm 264 (ε 14 000); δ_H(90% pure) 8.16 (1 H, s, 8-H), 7.49 and 7.37 (5 H, m, Ph), 6.89 (2 H, s, NH_2), 5.46 (2 H, s, CH_2) and 4.56 (1 H, s, 2′-H); *m/z* (EI) 265 (M, 45.6%) and 91 ($C_6H_5CH_2$, 100) (Found: M$^+$, 265.0959. $C_{14}H_{11}N_5O$ requires M, 265.0964).

N^6-*Benzoyl*-N^9-*ethynyladenine* **33**.—A. *From* N^6-*benzoyl derivative* **14**. The procedure for ynamine **30** was followed on a 0.7 mmol scale (THF, 15 cm^3) at −78 °C. After the usual work-up, *compound* **33** was isolated by chromatography in solvent system S_4 (85 mg, 47%), m.p. 175–176 °C after crystallization from the same solvent mixture (Found: C, 63.8; H, 3.3; N, 26.4. $C_{14}H_9N_5O$ requires C, 63.86; H, 3.45; N, 26.61%); ν_{max}/cm^{-1} 2150 (C≡C) and 1680 (CO); λ_{max}/nm 278 (ε 17 700); δ_H 11.38 (1 H, s, NH), 8.82 and 8.81 (2 H, 2 s, 2- and 8-H), 8.02, 7.63 and 7.53 (5 H, d, t and t, Ph) and 4.79 (1 H, s, 2′-H).

B. *From* N^6,N^6-*dibenzoyl derivative* **26**. Method A was employed on a 2.1 mmol scale with dibenzoyl derivative **26**. TLC (S_4) showed the presence of four UV-absorbing spots.

Chromatography in solvent system S_7 afforded the major compound **33** (0.1 g, 18%), identical with the product obtained by method A.

N^1-*Ethynylcytosine* **34**.—The procedure described above was adapted for compound **23** (0.1 g, 0.4 mmol), 2 mol dm^{-3} BuLi (0.8 cm^3, 1.6 mmol) and THF (15 cm^3), reaction time 2 h. Chromatography in solvent S_2 gave a small amount of dichloro enamine **24** followed by *product* **34** (25 mg, 44%), m.p. > 100 °C (decomp.) (Found: C, 53.25; H, 3.5; N, 30.9. $C_6H_5N_3O$ requires C, 53.32; H, 3.73; N, 31.11%); ν_{max}/cm^{-1} 2130 (C≡C); λ_{max}/nm 254 and 282; δ_H[$(CD_3)_2NCDO$, −15 °C] 7.91 (2 H, s, NH_2), 7.71 (1 H, d, 6-H), 6.32 (1 H, d, 5-H) and 4.23 (1 H, s, 2′-H); δ_C 165.66, 154.25, 144.84 and 97.40 (cytosine), 75.43 (C-1′) and 62.23 (C-2′). The olefinic peaks were present in both ^1H and ^{13}C NMR spectra.

N^1-*Ethynylthymine* **35**.—The experiment was performed as in the preceding case. Trichloro enamine **19** (0.4 g, 1.6 mmol), 2 mol dm^{-3} BuLi (3.1 cm^3, 6.2 mmol) and THF (25 cm^3), reaction time 3 h at −70 °C. Chromatography in solvent system S_7 afforded *compound* **35** (0.12 g, 51%), which was crystallized from hexane–acetone (1:1), m.p. 151–152 °C (decomp.) (Found: C, 56.0; H, 4.2; N, 18.45. $C_7H_6N_2O_2$ requires C, 55.98; H, 4.03; N, 18.67%); ν_{max}/cm^{-1} 2140 (C≡C); λ_{max}/nm 269 (ε 7200); δ_H 11.67 (1 H, s, NH), 7.62 (1 H, apparent s, 6-H), 4.22 (1 H, s, 2′-H) and 1.73 (3 H, apparent s, Me); δ_C 164.24, 150.71, 139.68, 112.63 and 12.23 (thymine), 73.46 (C-1′, $J_{1',2'-H}$ 37) and 63.93 (C-2′, $J_{2',2'-H}$ 245); *m/z* (EI) 150 (M, 34%), 107 (M − HCNO, 80), 79 (M − HCNO − CO, 22), 78 (M − HCNO − CO − H, 34) and 52 ($HC{\equiv}C{-}N{=}CH$, 100).

N^9-*Ethyladenine* **36**.—Ynamine **30** (50 mg, 0.3 mmol) was hydrogenated in ethanol (50 cm^3) over Pd/C (10%; 60 mg) at 50 psi in a Parr apparatus for 3 h. The solution was filtered (Celite) and the filtrate was evaporated to give the title solid **36** (45 mg, 88%), m.p. 193–194 °C (lit.,[39] 193 °C) identical with an authentic sample.[36]

N^1-*Ethylthymine* **37**.—Ynamine **35** (50 mg, 0.33 mmol) was hydrogenated for 5 h as described for compound **36** to give the title solid **37** (44 mg, 86%), m.p. 220–221 °C after crystallization from THF–diethyl ether (7:3) (lit.,[40] 220–222 °C); λ_{max}/nm 270 (ε 10 300); the ^1H NMR spectrum was similar to that described.[40]

Reaction of Ynamine **30** *with Acetone* **38**.—A solution of ynamine **30** (50 mg, 0.3 mmol) and $NaNH_2$ (19 mg, 0.5 mmol) in THF (30 cm^3) was stirred at room temperature under N_2 for 25 min. Acetone **38** (70 mm^3, 0.9 mmol) was then added and the mixture was stirred for an additional 5 h. The progress of the reaction was monitored by TLC in solvent system S_2. The mixture was cooled to 0–5 °C and the reaction was quenched with methanol (5 cm^3). The solvents were evaporated off and the crude product was chromatographed using solvent system S_2 as eluent to give *carbinol* **41** (30 mg, 45%), m.p. 225–230 °C (decomp., softening at 209–211 °C) after crystallization from the same solvent mixture (Found: C, 55.1; H, 5.2; N, 32.1. $C_{10}H_{11}N_5O$ requires C, 55.29; H, 5.10; N, 32.24%); ν_{max}/cm^{-1} 2260 (C≡C); λ_{max}/nm 259 (ε 10 200); δ_H 8.40 and 8.20 (2 H, 2 s, 2- and 8-H), 7.50 (2 H, s, NH_2), 5.62 (1 H, s, OH) and 1.47 (6 H, s, Me); δ_C 156.84, 154.56, 151.42, 141.99 and 117.42 (adenine), 80.36 (COH), 68.12 (C-1′), 64.12 (C-2′) and 32.01 (Me); *m/z* (EI) 217 (M, 50%) and 202 (M − Me, 100) (Found: M^+, 217.0959. $C_{10}H_{11}N_5O$ requires M, 217.0964).

Reaction of Ynamine **30** *with Cyclohexanone* **39**.—The reaction was performed as in the preceding experiment, in THF (15 cm^3) with cyclohexanone **39** (61 mg, 0.6 mmol) added. The usual work-up and chromatography in solvent system S_2 afforded *compound* **43** (32 mg, 29%), m.p. 215–217 °C after crystallization from ethanol (Found: C, 64.1; H, 7.2; N, 19.7. $C_{19}H_{25}N_5O_2$ requires C, 64.19; H, 7.09; N, 19.71%); λ_{max}/nm 284sh (ε 6400), 237 (25 000) and 205 (15 400); δ_H 8.32 and 8.14 (2 H, 2 s, 2- and 8-H), 7.32 (2 H, s, NH_2), 6.34 (1 H, s, 5′-H) and 1.58 and 1.38 (20 H, m, cyclohexane); δ_C 156.49, 153.12, 148.77, 139.31 and 118.19 (adenine), 152.28 (C-6′), 113.95 (C-2′), 91.51 (C-5′), 82.84 (C-4′), 38.47, 37.57, 24.68, 24.52, 23.94 and 22.52 (CH_2); *m/z* (FAB) 356 (M + H, 36%), 258 (100) and 136 (adenine + H, 49).

Continued elution gave *carbinol* **42** (56 mg, 70%), m.p. 215–216 °C (Found: C, 60.4; H, 5.8; N, 27.0. $C_{13}H_{15}N_5O$ requires C, 60.67; H, 5.88; N, 27.23%); ν_{max}/cm^{-1} 2260 (C≡C); λ_{max}/nm 259 (ε 10 500); δ_H 8.45 and 8.23 (2 H, 2 s, 2- and 8-H), 7.55 (2 H, s, NH_2), 5.63 (1 H, s, OH) and 1.87, 1.53 and 1.23 (10 H, m, cyclohexane); δ_C 156.30, 154.17, 150.94, 141.38 and 116.90 (adenine), 78.67 (COH), 69.58 (C-1′), 67.03 (C-2′) and 24.84 and 22.73 (CH_2); *m/z* (EI) 257 (M, 49%), 214 (M − 43, 100) and 135 (adenine, 55) (Found: M^+, 257.1280. $C_{13}H_{15}N_5O$ requires M, 257.1277).

Reaction of Ynamine **30** *with* 1,3-*Dibenzyloxyacetone* **40**.—Sodium amide (12 mg, 0.3 mmol) was added to a solution of ynamine **30** (30 mg, 0.2 mmol) in THF (15 cm^3) under N_2 at 0–5 °C. The mixture was stirred at room temperature for 10 min whereupon a solution of 1,3-dibenzyloxyacetone[31] **40** (76 mg, 0.28 mmol) in THF (5 cm^3) was added. The mixture was stirred for 14 h at room temperature. The customary work-up and chromatography in solvent system S_2 gave *compound* **44** (70 mg, 72% based on **40**), m.p. 105–107 °C after crystallization from ethanol (Found: C, 70.2; H, 6.0; N, 10.20. $C_{41}H_{41}N_5O_6$ requires C, 70.36; H, 5.91; N, 10.01%); λ_{max}/nm 288sh (ε 9000), 237 (28 100) and 208 (46 600); δ_H 8.33 and 8.23 (2 H, 2 s, 2- and 8-H), 7.42 (2 H, s, NH_2), 7.25 (20 H, m, Ph), 6.52 (1 H, s, 5′-H), 4.49 (8 H, s, $PhCH_2$) and 3.71 and 3.68 (8 H, 2 s, CH_2); δ_C 156.70, 153.56, 148.80, 139.13 and 118.15 (adenine), 146.14 (C-6′), 138.52, 128.81, 128.07 and 127.99 (Ph), 113.91 (C-2′), 92.96 (C-5′), 86.35 (C-4′) and 73.30, 72.24 and 71.12 (CH_2); *m/z* (FAB) 700 (M + H, 90%) and 176 (100).

Reaction of Ynamine **35** *with* 1,3-*Dibenzyloxyacetone* **40**.—The procedure for compound **44** was followed with $NaNH_2$ (25 mg, 0.6 mmol), ynamine **35** (30 mg, 0.2 mmol) and 1,3-dibenzyloxyacetone[31] **40** (77 mg, 0.3 mmol) in THF (5 cm^3). The crude product was chromatographed in solvent system S_6 to give *compound* **45** (54 mg, 54% based on ketone **40**), m.p. 91–92 °C after crystallization from the same solvent mixture (Found: C, 71.25; H, 6.4; N, 3.9; O, 18.7. $C_{41}H_{42}N_2O_8$ requires C, 71.27; H, 6.13; N, 4.06; O, 18.54%); λ_{max}/nm 284 (ε 7100), 232sh (8500) and 208 (33 900); δ_H 11.44 (1 H, s, NH), 7.34 (1 H, d, 6-H), 7.26 (20 H, m, Ph), 5.89 (1 H, s, 5′-H), 4.47 and 4.45 (8 H, 2 s, $PhCH_2$), 3.65 and 3.61 (8 H, 2 s, CH_2) and 1.65 (3 H, d, Me); δ_C 164.12, 150.21, 140.33, 109.40 and 12.66 (thymine), 147.54 (C-6′), 138.55, 138.43, 128.83, 128.15 and 128.03 (Ph), 113.51 (C-2′), 97.30 (C-5′), 86.17 (C-4′), and 73.30, 72.81, 72.28, 72.21 and 71.11 (CH_2); *m/z* (FAB) 691 (M + H, 10%) and 87 (100).

N^6-*Dimethylaminomethylene*-N^9-*ethynyladenine* **46**.—A solution of ynamine **30** (60 mg, 0.4 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.13 g, 1.1 mmol) in DMF was stirred overnight at room temperature. The volatile components were evaporated off and the residue was chromatographed in solvent system S_2 to give compound **46** (60 mg, 75%), m.p. 162–163 °C (softening from 155 °C) (Found: C, 55.9; H, 4.8; N, 39.1. $C_{10}H_{10}N_6$ requires C, 56.05; H, 4.71; N, 39.24%); ν_{max}/cm^{-1}

2130 (C≡C); λ_{max}/nm 315 (ε 25 000); δ_H 8.88 (1 H, s, Me_2NCH=), 8.58 and 8.46 (2 H, 2 s, 2- and 8-H), 4.69 (1 H, s, 2'-H) and 3.18 and 3.11 (6 H, 2 s, Me_2N); *m/z* (EI) 214 (M, 82%), 199 (M − Me, 79.1), 158 (M − HCN − NMe, 100) and 144 (M − N=CH–NMe_2 + H, 57).

Adenosine Deaminase Assay.—Compound **30** (3 μmol) was dissolved in warm 0.05 mol dm^{-3} Na_2HPO_4 (pH 7.5; 0.2 cm^3). After cooling of the mixture to room temperature, a solution of adenosine deaminase (Type VIII, Sigma Chemical Co., St. Louis, Missouri, USA, 0.4 unit) in the same buffer (0.4 cm^3) was added. The incubation was continued for 3 days and the progress of reaction was followed periodically by TLC in solvent system S_2) and by UV spectroscopy. A large amount (~90%) of compound **30** was deaminated.

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