Unconventional Nucleotide Analogues. Part X.[1] Synthesis of *N*-Substituted 3-(Adenin-9-yl)pyrrolidin-2-ones

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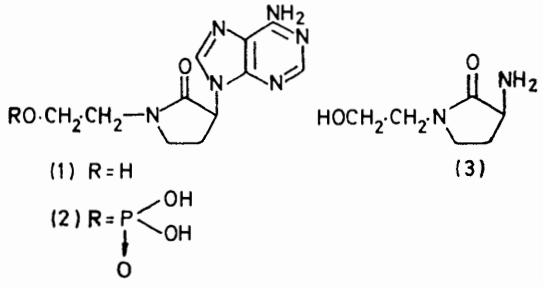
3-(Adenin-9-yl)-*N*-2-hydroxyethylpyrrolidin-2-one (1) was synthesized by constructing the purine base on the amino-group of 3-amino-*N*-2-hydroxyethylpyrrolidin-2-one (3), itself obtained from 2-dibenzylaminobutyrolactone by aminolysis, followed by chlorination of the product and recyclization. Attempts to obtain compound (3) from acylated 2-aminobutyrolactones (4a and b) led to side reactions, the mechanisms of which are discussed. 3-(6-Chloropurin-9-yl)-*N*-2-hydroxyethylpyrrolidin-2-one (18b) was converted into the AMP analogue (2) by a phosphorylation–amination–debenzylation sequence. Iodination of compound (1), followed by dehydrohalogenation of the product led to the *N*-vinyl derivative (21), a monomer for a poly-A model.

THE synthesis and polymerization of a non-glycosidic pyrimidine nucleoside analogue, in which a pyrrolidin-2-one system replaces the carbohydrate unit, is described in the preceding paper.[1] We now report the synthesis of the corresponding adenosine analogue (1) and its phosphate derivative (2).



The synthesis of compound (1) was approached *via* a *de novo* construction of the purine system, since direct alkylations of adenine [2,3] or 6-chloropurine [4,5] are known to lead to mixtures of isomeric purinyl derivatives. We therefore synthesized the intermediate (3), for appropriate elaboration.[6]

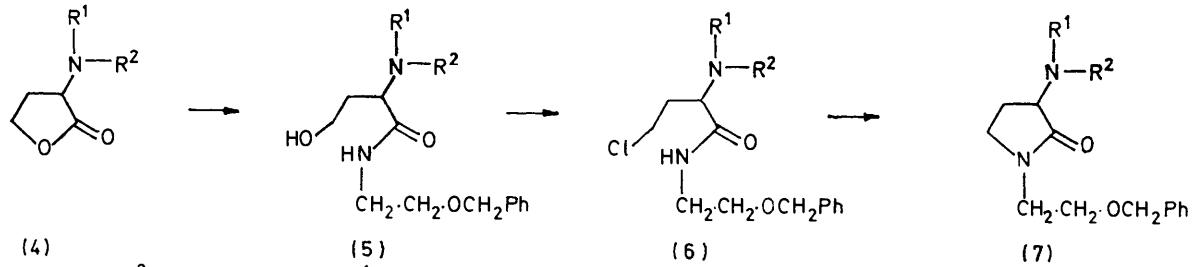
Synthesis of 3-*Amino*-N-(2-*hydroxyethyl*)*pyrrolidin*-2-*one* (3) (*Scheme* 1).—The synthesis involved aminolysis of a suitably protected α-amino-lactone with 2-benzyloxyethylamine, ring closure of the corresponding chloride (6), and removal of protecting groups. Several amine-protecting groups were studied; the results while not always leading to the desired lactam (7), provided results of chemical interest which are discussed.

The 2-aminobutyrolactone hydrobromide [7] was readily converted into its *N*-benzoyl derivative (4a). Aminolysis of the latter with 2-benzyloxyethylamine [8] and chlorination ($SOCl_2$) of the resulting hydroxy-amide (5a) afforded the chloride (6a). Treatment of compound (6a) with sodium methoxide in methanol [9] gave a mixture from which two products were isolated in 75% overall yield. One of these (60%) was the expected lactam (7a); the other (40%) has been assigned the oxazine structure (10) on the basis of its i.r., n.m.r., and (especially) u.v. spectra. The u.v. spectrum exhibited maxima at 238 (ε 12,700) and 248 nm (14,700) in ethanol and in ethanolic hydrogen chloride, respectively [*cf.* 233 (11,500) and 244 nm (13,800) for 5,6-dihydro-2-phenyl-1,3-oxazine]. The oxazine (10) must be formed by cyclization of the anion (9) which may be in equilibrium with (8a).

The mass spectrum of the oxazine (10) shows a fragmentation pattern which is, however, not apparently in accord with the proposed structure; in particular, a peak at *m/e* 105 ($PhCO^+$) and other ions suggest the azetidine structure (11). Since a thermal rearrangement [(10) ⟶ (11)] appears unlikely [10,11] in view of the strain associated with the formation of the four-membered ring, it appears that an electron-impact-induced Chapman rearrangement [12] may occur. This problem is under investigation.

We next studied the benzyloxycarbonylamino-lactone (4b). We expected that, in this case, the protecting acyl group would be conveniently removable at the lactam stage (7b). The lactone (4b) [13] was converted into the chloride (6b) *via* the alcohol (5b) as before. Attempts to cyclize the chloride under basic conditions gave a single product in 90% yield. This, however, was the diazaspiro[2.4]heptane (13), whose formation, in the presence of an excess of base, can be rationalized in terms of two base-catalysed ring-closure steps described (Scheme 2). Although the sequence (8b) ⟶ (12) ⟶ (13) has not been established (*i.e.* cyclopropane ring closure may precede hydantoin formation) this transformation of (8b) is the most likely chain of events; an analogous ion (8a) from the chloride (6a) has never

[1] Part IX, G. J. Koomen and U. K. Pandit, preceding paper.
[2] J. A. Montgomery and H. J. Thomas, *J. Heterocyclic Chem.*, 1964, **1**, 115.
[3] N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, 1962, **84**, 2148.
[4] J. A. Montgomery and C. Temple, *J. Amer. Chem. Soc.*, 1961, **83**, 630.
[5] H. J. Schaeffer and R. Vince, *J. Medicin. Chem.*, 1965, **8**, 33, 710.
[6] (*a*) R. Vince and J. Donovan, *J. Medicin. Chem.*, 1969, **12**, 175; (*b*) H. J. Schaeffer and R. Vince, *ibid.*, 1968, **11**, 15; (*c*) Y. F. Shealy and J. D. Clayton, *J. Amer. Chem. Soc.*, 1969, **91**, 3075.
[7] T. Sheradsky, Y. Knobler, and M. Frankel, *J. Org. Chem.*, 1961, **26**, 1482.
[8] L. C. Lappas and G. L. Jenkins, *J. Amer. Pharm. Assoc. Sci. Edn.*, 1952, **41**, 257.
[9] C. J. M. Stirling, *J. Chem. Soc.*, 1960, 255.
[10] W. Seeliger and W. Thier, *Annalen*, 1966, **698**, 158.
[11] W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellmann, *Angew. Chemie*, 1966, **78**, 913.
[12] R. Rogier and D. Neilson, *Chem. Rev.*, 1961, **61**, 190.
[13] Y. Knobler and M. Frankel, *J. Chem. Soc.*, 1958, 1629.



(4)

R^1	R^2
a; Bz	H
b; $PhCH_2 \cdot OCO$	H
c; Ph_3C	H
d; H	H
e; $PhCH_2$	$PhCH_2$

(5)

R^1	R^2
a; Bz	H
b; $PhCH_2 \cdot OCO$	H
c; $PhCH_2$	$PhCH_2$

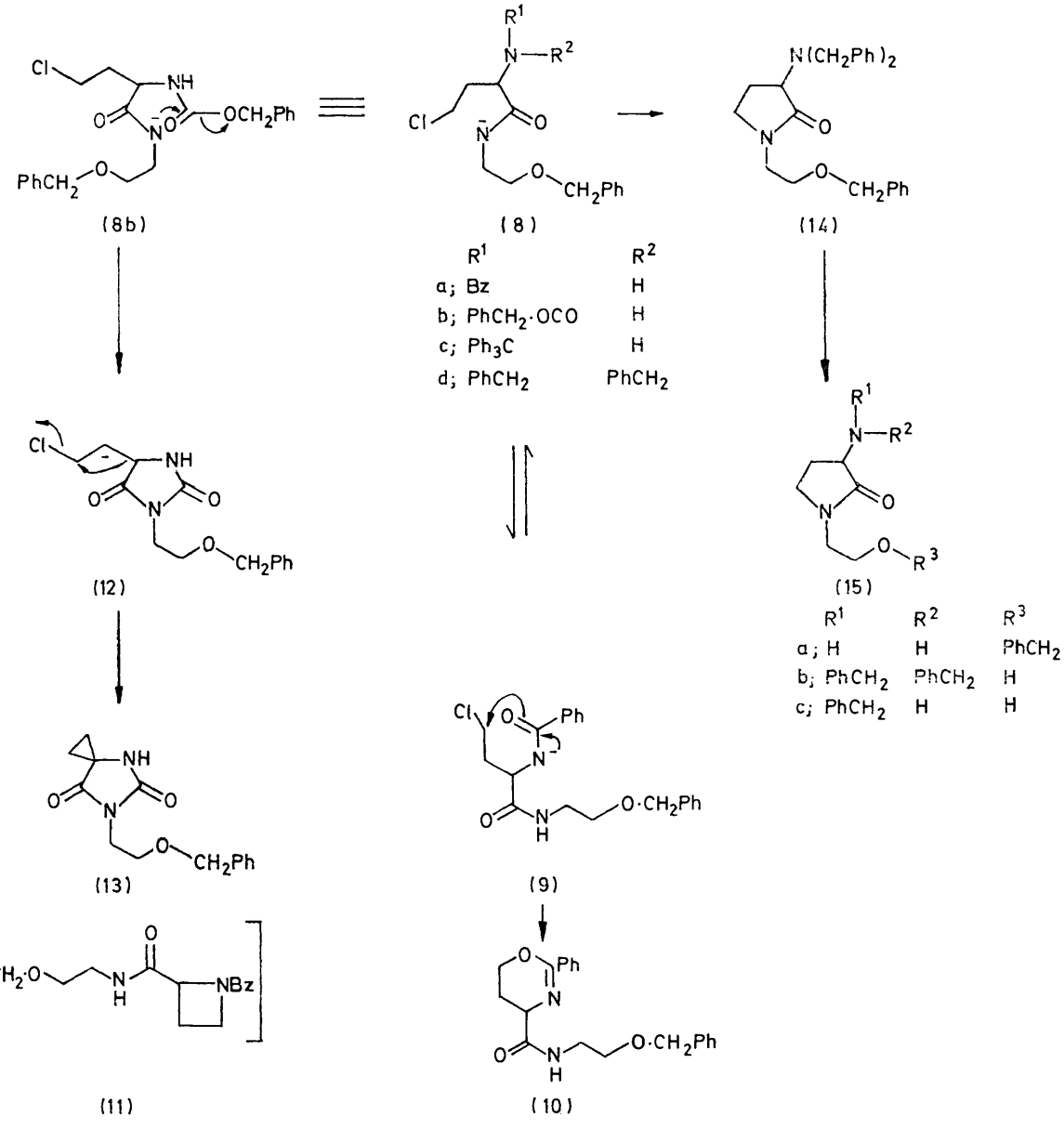
(6)

R^1	R^2
a; Bz	H
b; $PhCH_2 \cdot OCO$	H
c; $PhCH_2$	$PhCH_2$

(7)

R^1	R^2
a; Bz	H
b; $PhCH_2 \cdot OCO$	H

SCHEME 1



(8b)

(8)

R^1	R^2
a; Bz	H
b; $PhCH_2 \cdot OCO$	H
c; Ph_3C	H
d; $PhCH_2$	$PhCH_2$

(14)

(12)

(15)

R^1	R^2	R^3
a; H	H	$PhCH_2$
b; $PhCH_2$	$PhCH_2$	H
c; $PhCH_2$	H	H

(13)

(9)

(11)

(10)

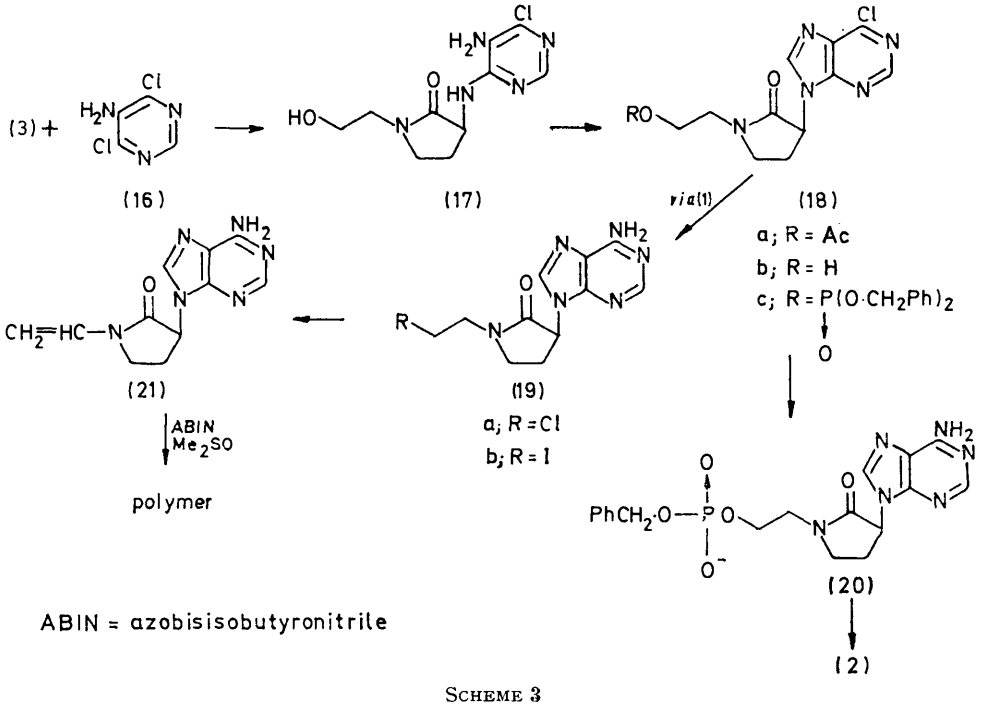
SCHEME 2

been observed to undergo a corresponding formation of a three-membered ring. Once cyclization [of (8b)] to the hydantoin, with ready displacement of a benzyloxy-group, has taken place, the excess of base can abstract a proton to yield the ion (12), which would be expected to undergo ring closure to (13). Removal of the proton from the nitrogen atom in protonated (12) would result in a non-productive anion.

The use of the triphenylmethyl group for amine protection [lactone (4c)] was then investigated. However this group proved too sensitive to the reaction conditions required for the various steps. Satisfactory protection was eventually achieved by replacement of both amine hydrogen atoms with benzyl groups.

rently the lactone (4e) is stable at these reaction temperatures. Hydrogenation of (15b) under mild neutral conditions resulted in monodebenzylation to compound (15c). The latter could be further hydrogenated to the the amine (3). Upon catalytic reduction (60°; 20 atm), compound (15b) was smoothly converted into crystalline (3) in 80% yields.

Synthesis of 3-(*Adenin-9-yl*)-N-(2-*hydroxyethyl*)*pyrrolidin-2-one* (1) *and its Phosphate* (2).—Condensation of the pyrrolidinone (3) with 5-amino-4,6-dichloropyrimidine [15] (16) in butanol–triethylamine yielded a mixture in which the desired product (17) (Scheme 3) was spectrally identified as the major component. Without isolation in the pure state compound (17) was treated with triethyl



SCHEME 3

2-Dibenzylaminobutyrolactone (4e) was obtained by treatment of 2-bromobutyrolactone with dibenzylamine.[14] Stepwise reaction with 2-benzyloxyethylamine and thionyl chloride led to compounds (5c) and (6c), and the latter cyclized smoothly to the pyrrolidinone (14) on treatment with methanolic methoxide. The ring closure was monitored by observing the disappearance of the amide II band at 1560 cm^{-1}. Compound (14), obtained as an oil, was readily debenzylated (H_2–Pd; HCl) to the crystalline amine (3). Hydrogenolysis of (14) under mild conditions (acetic acid or dilute hydrochloric acid as solvent) led to partial debenzylation to compound (15a).

Aminolyses of the lactone (4e) with 2-aminoethanol (215°) and 2-benzyloxyethylamine (230°) led directly to the pyrrolidinones (15b) and (14), respectively. Apparently the lactone (4e) is stable at these reaction temperatures. Hydrogenation of (15b) under mild neutral conditions resulted in monodebenzylation to compound (15c). The latter could be further hydrogenated to the the amine (3). Upon catalytic reduction (60°; 20 atm), compound (15b) was smoothly converted into crystalline (3) in 80% yields.

Synthesis of 3-(*Adenin-9-yl*)-N-(2-*hydroxyethyl*)*pyrrolidin-2-one* (1) *and its Phosphate* (2).—Condensation of the pyrrolidinone (3) with 5-amino-4,6-dichloropyrimidine [15] (16) in butanol–triethylamine yielded a mixture in which the desired product (17) (Scheme 3) was spectrally identified as the major component. Without isolation in the pure state compound (17) was treated with triethyl orthoformate and acetic anhydride to give the chloropurinyl derivative (18a); alternatively, treatment with triethyl orthoformate in the presence of hydrochloric acid [16] gave compound (18b) in good yield. The formation of the purine nucleus was attested in each case by observation of n.m.r. signals for the C-2 and C-8 protons. Treatment of either product with ethanolic ammonia at 110° gave compound (1), as a crystalline product.

The phosphate (2) was synthesized *via* the chloropurinyl derivative (18b). Reaction of this alcohol with dibenzyl phosphorochloridate [17] in pyridine–carbon tetrachloride [18] yielded the protected phosphate (18c), readily recognized by the typical long-range coupling pattern (*J* 10 Hz) of the phosphorus with the benzyl and the ethylene side-chain methylene protons. Am-

[14] M. Frankel, Y. Knobler, and T. Sheradsky, *J. Chem. Soc.*, 1959, 3642.

[15] W. W. Zorbach and R. S. Tipson, 'Synthetic Procedures in Nucleic Acid Chemistry,' Interscience, New York, 1968, p. 75.

[16] Ref. 15, pp. 6, 48.

[17] (*a*) F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 1945, 382; (*b*) F. R. Atherton, *Biochemical Preparations*, 1957, **5**, 1.

[18] A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 1954, 34.

monolysis of (18c) led to the adeninyl system with simultaneous removal of one of the protecting benzyl groups. The monobenzyl phosphate (20) so obtained, could be converted into compound (2) by hydrogenation over palladium. The AMP analogue (2) was isolated as its lithium salt.

Polymerization of 3-(*Adenin-9-yl*)-N-*vinylpyrrolidin-2-one*.—The alcohol (1) could be converted conveniently into its chloride (19a) or its iodide (19b) by treatment with thionyl chloride or triphenoxymethylphosphonium iodide,[19] respectively. Dehydrohalogenation of (19b) yielded the vinyl derivative (21), recognized from the characteristic pattern[1] for the vinylic protons in its n.m.r. spectrum. Without isolation of the product in a completely purified state, it was subjected to ABIN-(*NN'*-azobisisobutyronitrile) catalysed polymerization. The progress of the reaction was followed by examining the disappearance of the vinylic proton signals in the n.m.r. spectrum. The resulting polymer was obtained as a colourless solid. Attempts to investigate its spectral properties were frustrated owing to its extreme insolubility in suitable solvents.

The AMP analogue (2) showed no activity in (*a*) adenylate-kinase-catalysed phosphate exchange (AMP + ATP $\rightleftharpoons$ 2ADP) and in (*b*) oxidative phosphorylation in rat-liver mitochondria. No significant biological activity was shown by compounds (1) and (18a) in the L-1210 murine leukaemia test system.

EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP 200 instrument and u.v. spectra on a Cary-14 recording spectrophotometer. N.m.r. spectra were obtained with a Varian A60 or HA100 spectrometer (tetramethylsilane as an internal standard). Mass spectra were recorded with an A.E.I. MS-902 spectrometer.

2-Benzamido-N-(2-benzyloxyethyl)-4-hydroxybutyramide (5a).—A solution of 2-benzamidobutyrolactone (4a)[13] (2·1 g, 0·01 mol) and 2-benzyloxyethylamine[8] (1·8 g, 0·012 mol) in methanol was kept at room temperature for 24 h, then evaporated. The residue was taken up in chloroform and washed repeatedly with water. Drying ($MgSO_4$) and evaporation yielded an *oil*, which slowly crystallized (yield 2·65 g, 75%), m.p. 101—103°, $\nu_{max.}$ ($CHCl_3$) 3500 (NH, OH), 1680—1620 (2 C=O), 1520 (NH def.), 1100 (C–O–C), and 1060 cm^{-1} (OH), δ ($CDCl_3$) 4·45 (s, PhCH_2 + OH) and 7·2—7·9 (m, Ph + 2 NH) (Found: C, 67·5; H, 6·9; N, 7·8; O, 18·0. $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·8; N, 7·85; O, 17·95%).

2-Benzamido-N-(2-benzyloxyethyl)-4-chlorobutyramide (6a).—To an ice-cold solution of the hydroxy-amide (5a) (5 g) in chloroform (35 ml), purified thionyl chloride (12 ml) was added dropwise. After one night at room temperature, solvent and excess of reagent were removed *in vacuo*. The residual oil was refluxed with ether; the resulting white *solid*, crystallized from cyclohexane (yield 3·5 g, 67%), had m.p. 106—108°, $\nu_{max.}$ ($CHCl_3$) 3400 (N–H), 1640—1680 (2 C=O), 1520 (NH def.), and 1100 cm^{-1} (C–O–C) (Found: C, 64·1; H, 6·3; Cl, 9·6; N, 7·6. $C_{20}H_{23}ClN_2O_3$ requires C, 64·1; H, 6·15; Cl, 9·5; N, 7·5%).

Reaction of the Chloride (6a) *with Sodium Methoxide*.—The chloride (6a) (1·05 g) was refluxed in methanolic N-sodium methoxide (30 ml) for 4 h. The precipitate (NaCl) was filtered off, the solvent was removed, and the residue was taken up in water. Extraction with chloroform (×3), drying (Na_2SO_4), and evaporation gave an oil (0·85 g), which, according to t.l.c. (alumina; chloroform–ethyl acetate, 1 : 1) was a mixture of two compounds (R_F 0·2 and 0·7). The mixture, dissolved in a small quantity of ethyl acetate, was placed on a Florisil column and eluted with ethyl acetate (30 ml fractions). Fractions 5—11 contained the oxazine (10) (0·2 g, 21%), and the pyrrolidine (7a) (0·7 g, 53%) was obtained from fractions 14—21. *N-(2-Benzyloxyethyl)-5,6-dihydro-2-phenyl-4H-1,3-oxazine-4-carboxamide* (10) had m.p. 75—77°, $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1660 (C=O, C=N), 1530 (NH def.), and 1100 cm^{-1} (C–O–C), δ ($CDCl_3$) 1·6—2·6 (m, 5-H), 3·4—3·7 (m, O·CH_2·CH_2·N), 4·0—4·2 (m, 6-H_2), 4·3—4·6 (m, 4-H), and 4·5 (s, PhCH_2), *m/e* 338 (11%, M^+), 247 (28%, M^+ – CH_2Ph), 232 (33%, M^+ – PhCHO), 217 (22%, M^+ – CH_2·O·CH_2Ph), 161 (77%, M^+ – PhCH_2·O·CH_2·CH_2·NCO, 160 (100%, 161 – H), 130 (12%), 105 (45%, $PhCO^+$), 91 (25%, $C_7H_7^+$), and 77 (18%, $C_6H_5^+$) (Found: C, 70·6; H, 6·7; N, 8·4. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·55; N, 8·3%). *3-Benzamido-1-(2-benzyloxyethyl)pyrrolidin-2-one* (7a), an oil, had $\nu_{max.}$ ($CHCl_3$) 3400—3500 (NH), 1690, 1660 (2 C=O), 1520 (NH def.), and 1100 cm^{-1} (C–O–C), δ ($CDCl_3$) 1·6—2·1 (m) and 2·5—3·0 (m) (4-H_2), 3·3—3·8 (m, 5-H_2, 1'-H_2), 4·4—4·7 (m, 3-H_2), and 4·5 (s, PhCH_2), *m/e* 338 (3%, M^+), 247 (20%, M^+ – CH_2O), 232 (22%, M^+ – PhCHO), 217 (5%, M^+ – CH_2·O·CH_2Ph), 160 (4%), 105 (100%, $PhCO^+$), 91 (40%, $C_7H_7^+$), and 77 (33%, $C_6H_6^+$).

2-Benzyloxycarbonylamino-N-(2-benzyloxyethyl)-4-hydroxybutyramide (5b).—A solution of 2-benzyloxycarbonylaminobutyrolactone (4b)[13] (11·8 g, 0·05 mol) and 2-benzyloxyethylamine[8] (8·7 g, 0·057 mol) in methanol (100 ml) was refluxed for 3 h, then evaporated. The residue was taken up in chloroform. Addition of hexane and cooling gave the amide (5b) (18·7 g, 97%), m.p. 72—80°, $\nu_{max.}$ ($CHCl_3$) 3500 (N–H), 1700 (C=O ester), 1660 (C=O amide), and 1520 cm^{-1} (NH def.), δ ($CDCl_3$) 4·4 (s, ether PhCH_2), 5·1 (s, ester PhCH_2) 6·3 (d, NH), and 7·25 (s, Ph + NH).

2-Benzyloxycarbonylamino-N-(2-benzyloxyethyl)-4-chlorobutyramide (6b).—To an ice-cold solution of the hydroxy-amide (5b) (0·97 g, 0·025 mol) in chloroform, thionyl chloride (2·5 ml) was added during 1 h. After an additional 3 h at room temperature, the solvent and excess of reagent were removed *in vacuo*. The residue was dissolved in ether. Cooling yielded the chloride (6b) as white *crystals* (0·65 g, 65%), m.p. 83—86°, $\nu_{max.}$ ($CHCl_3$) 3500 (N–H), 1710 (C=O ester), 1660 (C=O amide), and 1520 cm^{-1} (NH def.), δ ($CDCl_3$) 4·45 (s, ether PhCH_2), 5·1 (s, ester PhCH_2), and 5·9 (d, *J* 8 Hz, NH) (Found: C, 62·2; H, 6·3; Cl, 8·7; N, 7·1. $C_{21}H_{25}ClN_2O_4$ requires C, 62·3; H, 6·2; Cl, 8·75; N, 6·9%).

6-(2-Benzyloxyethyl)-4,6-diazaspiro[2.4]heptane-5,7-dione (13).—To a solution of sodium (0·58 g, 25 mmol) in methanol (20 ml), the amide (6b) (1·0 g, 2·5 mmol) dissolved in methanol (5 ml) was added. The mixture was refluxed for 3 h. The precipitate (NaCl) was filtered off and the solvent removed. The residue was taken up in water and the (alkaline) solution was extracted with chloroform. Concentration of the dried ($MgSO_4$) organic layer yielded compound (13) (0·67 g, 90%) as an oil. Treatment with

[19] J. P. H. Verheyden and J. G. Moffatt, 'Synthetic Procedures in Nucleic Acid Chemistry,' eds. W. W. Zorbach and R. S. Tipson, Interscience, New York, 1968, pp. 383, 415.

tetrahydrofuran–hexane gave a white *solid*, m.p. 81—82° ether–hexane), $\nu_{max.}$ ($CHCl_3$) 3300 (N–H), 1760, 1700) (2 C=O), and 1100 cm^{-1} (C–O–C), δ ($CDCl_3$) 1·5 and 1·7 (m, cyclopropyl AA'BB' system), 3·75 (m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}N$), 4·5 (s, $PhCH_2$), 7·2 (s, Ph), and 7·95 (s, NH) (Found: C, 64·3; H, 6·3; N, 10·5. $C_{14}H_{16}N_2O_3$ requires C, 64·6; H, 6·2; N, 10·75%).

2-(*Triphenylmethylamino*)*butyrolactone* (4d).—A solution of triphenylmethyl bromide (32·3 g, 0·1 mol) in dry chloroform (300 ml) was added to an ice-cold suspension of 2-aminobutyrolactone hydrobromide [7] (18·2 g, 0·1 mol) in dry chloroform (150 ml). During 5 h, triethylamine (30 ml) in dry ether (200 ml) was slowly added to the cooled mixture. After 5 h stirring at 0°, followed by 3 days at room temperature, the mixture was poured into water. The organic layer was separated and washed with water. After drying ($MgSO_4$) the solvents were removed and the *residue* was recrystallized from methanol (57% yield); m.p. 160—162°, $\nu_{max.}$ ($CHCl_3$) 3050 (C–H), 1760 (C=O), 1600, and 1500 cm^{-1} (Ph), δ ($CDCl_3$) 0·9—1·8 (m, 3-H_2), 2·9 (s, NH), 3·2—4·2 (m, 4-H_2, 2-H), and 7·0—7·7 (m, Ph) (Found: C, 80·4; H, 6·3; N, 4·3; O, 9·4. $C_{23}H_{21}NO_2$ requires: C, 80·45; H, 6·15; N, 4·1; O, 9·3%).

N-(2-*Benzyloxyethyl*)-2-*dibenzylamino*-4-*hydroxybutyramide* (5c).—2-Dibenzylaminobutyrolactone (4e) [14] (3·4 g, 0·03 mol) was heated at 120°, overnight, with 2-benzyloxyethylamine [8] (9·1 g, 0·06 mol). The mixture was dissolved in ether and the ether layer washed with water (×6) in order to remove the excess of 2-benzyloxyethylamine. Evaporation of solvent after drying (Na_2SO_4) gave (5c) as an oil. The product was sufficiently pure for further reactions. Crystallization from ether gave *material* of m.p. 57—62°, $\nu_{max.}$ ($CHCl_3$) 3300—3500 (OH, NH), 1650 (C=O), 1530 (NH def.), and 1100 cm^{-1} (C–O–C) (Found: C, 75·0; H, 7·6; N, 6·5; O, 11·1. $C_{27}H_{32}N_2O_3$ requires C, 74·95; H, 7·45; N, 6·5; O, 11·1%).

N-(2-*Benzyloxyethyl*)-4-*chloro*-2-*dibenzylaminobutyramide* (6c).—Purified thionyl chloride (75 ml, *ca.* 1 mol) was slowly added to an ice-cold solution of the amide (5c) (4·5 g) in dry chloroform (200 ml). After stirring overnight at room temperature, the solvent and excess of reagent were removed *in vacuo*. The residue was taken up in chloroform and washed with water (twice), saturated aqueous sodium hydrogen carbonate, and water. The solution was dried and filtered through a small (5 × 10 cm) silica column. The eluate was concentrated *in vacuo* and the residual oil extracted with boiling petroleum (b.p. 60—80°). The product was isolated by decantation and cooling of the clear solution. Repeating the procedure gave the *chloride* (6c) as pale yellow crystals (20 g, 43%), m.p. 58—61°, $\nu_{max.}$ ($CHCl_3$) 3460 (NH), 1670 (C=O), 1520 (NH def.), and 1100 cm^{-1} (C–O–C) (Found: C, 71·9; H, 7·0; Cl, 7·8; N, 6·1; O, 7·3. $C_{27}H_{31}ClN_2O_2$ requires C, 71·9; H, 6·95; Cl, 7·85; N, 6·2; O, 7·1%).

N-(2-*Benzyloxyethyl*)-3-*dibenzylaminopyrrolidin*-2-*one* (14).—(*A*) A solution of the chloride (6c) (22·5 g, 0·05 mol) in dry methanol (50 ml) was added to a stirred solution of sodium (11·5 g, 0·5 mol) in dry methanol (200 ml). After 3 h under reflux, the solvent was removed *in vacuo* and the residue was taken up in water. The alkaline water layer was extracted with ether and the combined extracts were dried (Na_2SO_4). Evaporation gave (14) as a brown oil (16·3 g, 80%).

(*B*) A mixture of 2-dibenzylaminobutyrolactone (4e) (3·0 g, 0·11 mol) and 2-benzyloxyethylamine (1·8 g, 0·012 mol) was heated at 230° under nitrogen for 5 h. After cooling, the mixture was dissolved in ether and washed with water. Drying ($MgSO_4$) and evaporation gave (14) as a brownish-yellow oil (92—98%), $\nu_{max.}$ ($CHCl_3$) 1680 (C=O), 1600, 1500 (aromatic rings), and 1100 cm^{-1} (C–O–C), δ ($CDCl_3$) 3·9 and 3·6 (AB system, *J* 14 Hz, $PhCH_2{\cdot}N$), 4·45 (s, $PhCH_2{\cdot}O$), and 7—7·5 (m, Ph).

3-*Dibenzylamino*-N-(2-*hydroxyethyl*)*pyrrolidin*-2-*one* (15b).—A mixture of the lactone (4e) and 2-aminoethanol (1·5 equiv.) was heated in a distillation apparatus at 215°. Water, formed during the reaction, was distilled off. Losses of 2-aminoethanol were replaced by addition of more amine in portions (total 10 equiv.). After 6 h, excess of 2-aminoethanol was removed under reduced pressure. The residue was a yellow viscous oil (15b) (80—90%), $\nu_{max.}$ ($CHCl_3$) 3400 (OH) and 1660 cm^{-1} (C=O) (amide II band absent).

3-*Amino*-N-(2-*benzyloxyethyl*)*pyrrolidin*-2-*one* (15a).—The pyrrolidinone (14) (4·1 g, 0·01 mol) was hydrogenated over palladium–charcoal (10%; 0·5 g) in ethanol (20 ml) and acetic acid (20 ml) (initial pressure 4 atm) for 24 h at room temperature. After filtration and evaporation the product was taken up in chloroform and washed with saturated sodium carbonate solution. Drying ($MgSO_4$) and evaporation gave an oil (2·0 g, 80%), $\nu_{max.}$ ($CHCl_3$) 3450 (NH), 1680 (C=O), and 1100 cm^{-1} (C–O–C), δ ($CDCl_3$) 1·8—2·6 (m, 4-H_2, NH_2) and 4·5 (s, $PhCH_2$).

3-*Amino*-N-(2-*hydroxyethyl*)*pyrrolidin*-2-*one* (3).—(*A*) Compound (14) (24 g) in ethanol (200 ml) and conc. hydrochloric acid (6 ml) was hydrogenated over palladium–charcoal (10%; 3·0 g) for 18 h at room temperature (initial pressure 4 atm). After filtration and evaporation 5% potassium hydroxide (100 ml) was slowly added. The solution was evaporated to dryness and the residue extracted with chloroform. The extracts contained the pure product (60%).

(*B*) Compound (15b) (162 g) in ethanol (1·5 l) was hydrogenated over palladium–charcoal (10%; 50 g) at 60° and 20 atm in a steel bomb. Filtration and evaporation gave the pure *product*, which was crystallized from tetrahydrofuran (yield 57·0 g, 72%), m.p. 77—80°, $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1670 (C=O), 1580 (NH_2), and 1070 cm^{-1} (OH), δ 1·8 (2q, 4-H), 2·4 (m, 4-H), 2·8 (s, NH_2 + OH), 3·3—3·6 (m, 3-H, 5-H_2), and 3·6—3·8 (2t, 1'-H_2, 2-H_2) (Found: C, 49·9; H, 8·4; N, 19·6; O, 22·4. $C_6H_{12}N_2O_2$ requires C, 50·0; H, 8·4; N, 19·45; O, 22·2%).

N-(2-*Acetoxyethyl*)-3-(6-*chloropurin*-9-*yl*)*pyrrolidin*-2-*one* (18a).—A solution of compound (3) (7·2 g) and 5-amino-4,6-dichloropyrimidine (16) [15] (6·3 g) in a mixture of n-butanol (100 ml) and triethylamine (23 ml) was refluxed under nitrogen for 2 days. Crystals of triethylammonium chloride, formed upon cooling to 0°, were filtered off and the filtrate was treated with activated carbon and evaporated to dryness (oil pump; 30°). The brownish oil (17) was dissolved in a mixture of acetic anhydride (75 ml) and triethyl orthoformate (75 ml) and refluxed for 2 h. After cooling and evaporation the product was dissolved in ethyl acetate and placed on a silica column. Elution with ethyl acetate–propan-2-ol (2 : 1) gave the product (18a) in pure state [t.l.c. on silica in ethyl acetate–propan-2-ol (2 : 1), R_F 0·3]; it could be recrystallized from ethanol; yield 2·4 g (17%), m.p. 109—111°, $\nu_{max.}$ ($CHCl_3$) 1730 (ester C=O), 1700 (lactam C=O), 1590, 1560, and 940 cm^{-1}, $\lambda_{max.}$ (EtOH) 265 nm (ε 9500), δ ($CDCl_3$) 2·1 (s, Me), 3·6—3·9 (m, 5-H_2, $CH_2{\cdot}CH_2{\cdot}OAc$), 4·33 (t, $CH_2{\cdot}OAc$), 5·35 (t, 3-H), and 8·25 (s) and 8·72 (s) (purine 2-H, 8-H) (Found: C, 48·3; H, 4·5;

Cl, 10·9; N, 21·7; O, 14·9. $C_{13}H_{14}ClN_5O_3$ requires C, 48·2; H, 4·35; Cl, 10·95; N, 21·65; O, 14·85%).

3-(6-*Chloropurin*-9-*yl*)-N-(2-*hydroxyethyl*)*pyrrolidin*-2-*one* (18b).—The crude coupling product (17) (10 g) was dissolved in triethyl orthoformate (100 ml) containing concentrated hydrochloric acid (5 ml). The solution was stirred at room temperature for 2 days. After addition of ether (600 ml) the mixture was refluxed for 2 h. Upon cooling to room temperature a red oil separated. The ether solution was decanted and cooled to −20°, whereupon the *product* (18b) crystallized; yield 2—3 g (30—40%), m.p. 132—133° (chloroform–carbon tetrachloride), $\nu_{max.}$ ($CHCl_3$) 3400 (OH), 1690 (C=O), 1580, 1560, and 940 cm^{-1}, $\lambda_{max.}$ (EtOH) 265 nm (ε 9500), δ [$(CD_3)_2SO$] 3·3—3·9 (m, 5-H_2, [CH_2]OH), 5·6 (t, 3-H), and 8·75 (s, purine 2-H, 8-H) (Found: C, 46·8; H, 4·1; Cl, 12·8; N, 24·8. $C_{11}H_{12}ClN_5O_2$ requires C, 46·9; H, 4·3; Cl, 12·6; N, 24·85%).

3-(*Adenin*-9-*yl*)-N-(2-*hydroxyethyl*)*pyrrolidin*-2-*one* (1).—In a Carius tube ethanol (30 ml) was saturated with dry ammonia (gas) at −10°. After addition of the chloropurine derivative (18a) [or (18b)] (2·0 g) the sealed tube was heated at 100° for 3 h. Cooling to room temperature gave a white *precipitate*, which was washed with water; yield 1·6 g (80%), m.p. 272—278°, $\nu_{max.}$ (KBr) 3400, 3150 (OH, NH_2), 1690 (C=O), 1660, 1600, 1570 (adenine), and 1060 cm^{-1} (OH), $\lambda_{max.}$ (EtOH) 261 (ε 14,700), δ [$(CD_3)_2SO$] 4·8 (t, OH), 5·5 (t, 3-H), 7·15 (s, NH_2), and 8·1 and 8·15 (2s, purine 2-H, 8-H) (Found: C, 50·2; H, 5·5; N, 31·8; O, 12·3. $C_{11}H_{14}N_6O_2$ requires C, 50·35; H, 5·4; N, 32·05; O, 12·2%).

Reaction of 3-(6-*Chloropurin*-9-*yl*)-N-(2-*hydroxyethyl*)*pyrrolidin*-2-*one* (18b) *with Dibenzyl Phosphorochloridate*.—To a solution of dibenzyl phosphonate [20] (0·75 g) in dry carbon tetrachloride (6 ml), cooled to −15°, was added, dropwise, a saturated solution of chlorine in carbon tetrachloride until the colour persisted. After 15 min stirring, excess of chlorine and hydrogen chloride formed were removed by passing dry nitrogen through the solution at room temperature. To the cooled solution (−15°) were added, successively, dry pyridine (2 ml) and compound (18b) (0·42 g, 0·0015 mol), and the mixture was stirred at −15° for 1 h. The solution was filtered, washed with water (3 × 5 ml), and dried ($MgSO_4$). The organic layer was concentrated *in vacuo* and placed on a silica column [eluant propan-2-ol–ethyl acetate (1 : 1); t.l.c. on silica R_F 0·25]. The pure *protected phosphate* (18c) was isolated as an oil (40—60%), $\nu_{max.}$ ($CHCl_3$) 1700 (C=O), 1590, 1560 (phenyl + purine), 1260, and 1020 cm^{-1} (phosphate), δ ($CDCl_3$) 2·2—2·8 (m, 4-H_2), 3·4—3·7 (m, 5-H_2, CH_2·CH_2·O), 4·15 (2q, CH_2·O), 5·05 (d, *J* 10 Hz, PhCH_2), 5·2 (t, 3-H), and 8·25 (s) and 8·7 (s) (purine 2-H, 8-H) (Found: C, 55·4; H, 4·6; Cl, 6·4; N, 12·9; P, 5·7. $C_{25}H_{25}ClN_5O_5P$ requires C, 55·4; H, 4·65; Cl, 6·55; N, 12·9; P, 5·7%).

2-[3-(*Adenin*-9-*yl*)-2-*oxopyrrolidin*-1-*yl*]*ethyl Dibenzyl Phosphate* (20).—In a Carius tube ethanol (10 ml) (at −15°) was saturated with ammonia (gas). The chloride (18c) (0·3 g) was added and the mixture was heated to 110° during 3 h. Evaporation left a mixture of compound (20) as its ammonium salt and ammonium chloride. Pure product was obtained by preparative t.l.c. [cellulose F_{254}; propan-2-ol–water–25% ammonia (7 : 2 : 1) R_F 0·7]; yield 50%, δ (CD_3OD) 4·9 (d, *J* 13 Hz, PhCH_2), 5·4 (t, 3-H), and 8·2 and 8·1 (2s, purine 2-H, 8-H).

2-[3-(*Adenin*-9-*yl*)-2-*oxopyrrolidin*-1-*yl*]*ethyl Dihydrogen Phosphate* (2).—A solution of the ammonium salt of (20) (1·4 g) in ethanol–water (9 : 1; 30 ml) was added to a pre-hydrogenated suspension of palladium–charcoal (10%; 0·2 g) in ethanol–water (9 : 1; 30 ml) and the mixture was reduced at room temperature overnight. After filtration the solution was concentrated *in vacuo* and placed on a cellulose column [eluant propan-2-ol–water–ammonia (25%) (7 : 2 : 1, gradient to 7 : 2 : 6)]. Fractions containing pure (2) [t.l.c. on cellulose F_{254}; eluant propan-2-ol–water–ammonia (5 : 2 : 3), R_F 0·5] were evaporated to dryness (yield 0·26 g). The compound was isolated as its lithium salt by treatment with Dowex 50 resin (H^+), followed by careful neutralization with lithium hydroxide; m.p. >325° (decomp.), $\nu_{max.}$ (KBr) 1690 (C=O), 1600—1580 (adenine), and 1080 cm^{-1} (phosphate) δ (D_2O) 5·65 (t, 3-H) and 8·2 (2s, purine 2-H, 8-H).

3-(*Adenin*-9-*yl*)-N-(2-*chloroethyl*)*pyrrolidin*-2-*one* (19a).—To refluxing thionyl chloride (10 ml) was added, in portions, compound (1) (0·4 g). After 1 h under reflux the excess of reagent was removed *in vacuo* and the residue was taken up in refluxing ethanol. Cooling the solution gave compound (19a) as its hydrochloride (0·3 g, 62%), m.p. 218—223°. The salt was dissolved in water and neutralized to pH 7—8 with 10% sodium carbonate solution. Cooling the solution and recrystallization of the precipitate from ethanol gave pure *product* (19a) (40%), m.p. 205—207°, $\nu_{max.}$ (KBr) 3400, 3200 (NH_2), 1700 (C=O), 1670, and 1600 cm^{-1} (adenine), δ [$(CD_3)_2SO$] 5·4 (t, 3-H), 7·25 (s, NH_2), and 8·15 (s, purine 2-H, 8-H) (Found: C, 47·1; H, 4·7; Cl, 12·7; N, 29·9. $C_{11}H_{13}ClN_6O$ requires C, 47·05; H, 4·65; Cl, 12·65; N, 29·95%).

3-(*Adenin*-9-*yl*)-N-(2-*iodoethyl*)*pyrrolidin*-2-*one* (19b).—To a suspension of compound (1) (0·5 g) in dry dimethylformamide (50 ml) was added freshly prepared triphenoxymethylphosphonium iodide [19] (1·0 g, 1·15 equiv.). The mixture was stirred at room temperature until all starting material had dissolved (*ca.* 18 h), then concentrated *in vacuo*. The residue was taken up in chloroform and washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to dryness. Addition of ether gave a white *solid* which was recrystallized from propan-2-ol; yield 70%, m.p. 285° (decomp.), $\nu_{max.}$ (KBr) 3400, 3200 (NH_2), 1690 (C=O), 1640, and 1600 cm^{-1} (adenine), δ [$(CD_3)_2SO$] 5·4 (t, 3-H), 7·3 (s, NH_2), and 8·2 (s, adenine 2-H, 8-H) (Found: C, 35·6; H, 3·7; I, 34·2; N, 22·4. $C_{11}H_{13}IN_6O$ requires C, 35·5; H, 3·5; I, 34·1; N, 22·6%).

3-(*Adenin*-9-*yl*)-N-*vinylpyrrolidin*-2-*one* (21).—A solution of potassium t-butoxide (0·1 g, 1·1 equiv.; freshly sublimed) in dimethoxyethane was added to the iodide (19b) (0·3 g) in dimethoxyethane (50 ml) and the mixture was stirred at room temperature for 3 h. The suspension was concentrated *in vacuo* and the residue extracted with chloroform. The organic layer was washed with water. Drying and evaporation gave the vinyl compound (21) (containing small amounts of starting material) in 80% yield; $\nu_{max.}$ (KBr) 3400, 3200 (NH_2), 1700 (C=O), and 1630 cm^{-1} (C=C), δ [$(CD_3)_2SO$] 4·6 (d, *J* 9 Hz), 4·65 (d, *J* 16 Hz) (=CH_2), 5·6 (t, 3-H), 7·0 (2d, *J* 16 and 9 Hz, N–CH=), 7·3 (s, NH_2), and 8·2 (2s, purine 2-H, 8-H).

Poly-[3-(*adenin*-9-*yl*)-N-*vinylpyrrolidin*-2-*one*].—A solution of compound (21) (60 mg) and azobisisobutyronitrile (ABIN) (2 mg) was heated to 60° in an n.m.r. tube in a nitrogen atmosphere. After one night the n.m.r. spectrum

[20] J. Sowden, *Ann. Rev. Biochem.*, 1957, **26**, 645.

of the solution did not exhibit any vinyl signals. The polymer, however, could not be further purified, because of its insolubility in water and organic solvents.

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