Syntheses and Properties of Some Polymethylene-bridged Adenines

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Syntheses of novel 1,2-, 2,*N*(6)-, and 2,9-polymethylene-bridged derivatives of adenine (**7**)—(**9**) are described. Cyclization of the intermediate 2,*N*(4)-bridged 4,6-diamino-5-formamidopyrimidines (**6**) gives a mixture of isomeric, 2,*N*(6)- and 2,9-bridged adenines in a ratio controlled by the number (*n*) of methylene groups in the chain; when *n* = 7, the first type (**8**) predominates, when *n* = 11, the second type (**9**) predominates, and when *n* = 9, both are formed in almost equal amounts. The structures (**8**) are confirmed by independent syntheses from appropriate cyclic iminoethers (**2**) and 5-aminoimidazole-4-carbonitrile (**5**) to give the 1,2-bridged adenine derivatives (**7**), most of which undergo spontaneous Dimroth rearrangement to afford the 2,*N*(6)-bridged adenines (**8**).

We earlier reported a general synthetic method leading to the α-bridged 2,3-polymethylenepyrimidin-4(3*H*)-imines and similar quinazolines which underwent Dimroth rearrangement to afford the isomeric β-bridged 2, *N*(4)-polymethylene-pyrimidin-4-amines and quinazolinamines, respectively.[1,2] This work was later applied to the synthesis of similar 2,*N*(6)-bridged adenosine derivatives which were examined by ^{13}C n.m.r. and u.v. spectroscopy to find their position(s) of protonation.[3] The present paper describes two synthetic routes to analogous 2,*N*(6)-bridged adenines (**8**) as well as the formation of novel

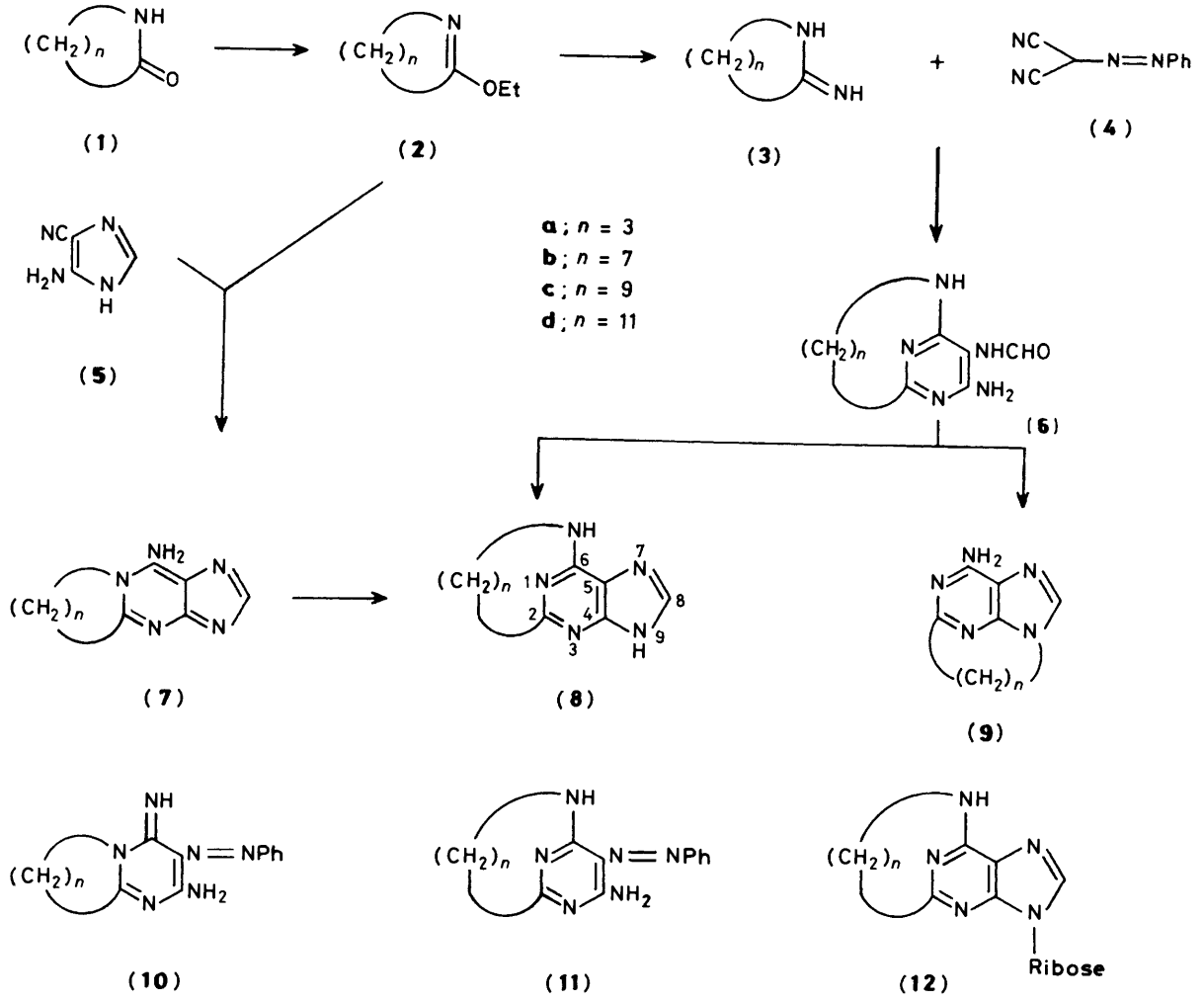

Table 1. ^{1}H N.m.r. data for β-bridged adenines (δ p.p.m.)*

Compd.	*n*	H^a	H^b	H^c	ArH	NH
(8b)	7	3.41 (2 H)	2.71 (2 H)	1.3—1.9 (10 H)	7.95 (1 H)	7.72 (1 H) + 12.60 (1 H)
(8c)	9	3.55 (2 H)	2.70 (2 H)	1.2—1.7 (14 H)	7.92 (1 H)	7.43 (1 H) + 12.57 (1 H)
(8d)	11	3.49 (2 H)	2.66 (2 H)	1.2—1.8 (18 H)	7.98 (1 H)	7.45 (1 H) + 12.60 (1 H)
(9b)	7	4.20 (2 H)	2.71 (2 H)	1.3—1.7 (10 H)	7.93 (1 H)	6.98 (2 H)
(9c)	9	4.20 (2 H)	2.69 (2 H)	0.9—1.8 (14 H)	8.05 (1 H)	7.09 (2 H)
(9d)	11	4.13 (2 H)	2.69 (2 H)	1.0—1.9 (18 H)	7.98 (2 H)	6.99 (2 H)

* H^a = CH_2 adjacent to nitrogen; H^b = CH_2 adjacent to purine–C(2); H^c = Other CH_2 groups.

2,9-bridged isomers (**9**) as competitive products from one of the routes; physical properties of the above products and the only stable 1,2-bridged intermediate (**7a**) are discussed.

Syntheses.—The 2,*N*(6)-polymethylene-bridged adenines (**8b—d**) were each made by two methods: (i) condensation of 5-aminoimidazole-4-carbonitrile (**5**) with cyclic iminoethers (**2**) in boiling butanol; and (ii) cyclodehydration of the corresponding formamidopyrimidines (**6**) in hot formamide. The first method, analogous to that used for 2,*N*(6)-bridged adenosines,[3] afforded the products (**8b—d**) in 63, 77, and 91% yield, respectively. However, under similar conditions, condensation of the aminonitrile (**5**) with the iminoether (**2a**) gave only the 1,2-polymethylene-bridged adenine (**7a**) (85%) because Dimroth rearrangement to its isomer (**8a**) was precluded by the inadequate length of the polymethylene chain (*n* = 3), as observed in other systems.[1,2] The second method (*cf.* ref. 4) resulted in the sterically controlled production of two β-bridged systems (**8**) and (**9**). In simple cases, cyclization of a 6-alkylamino-4-amino-5-formamidopyrimidine in hot formamide usually gives a 9-alkylpurine,[5,6,7] but cyclization of the β-bridged analogues (**6**) occurred in both directions to give products (**8**) and (**9**) in a ratio which depended on the length of the polymethylene chain. When the chain was long enough (*n* = 11), the 2,9-bridged adenine (**9d**) was isolated as the major product (63% yield) while the 2,*N*(6)-bridged adenine (**8d**) was a minor product (3% yield). In contrast, when the chain was short (*n* = 7), cyclization involved the primary rather than the secondary amino group to give the 2,*N*(6)-bridged isomer (**8b**) as the major product (70%) and the 2,9-bridged isomer (**9b**) as a very minor product (5%). When the chain was of medium length (*n* = 9), the products (**8c**) and (**9c**) were formed in 28 and 47% yield, respectively. The structures of 2,*N*(6)-bridged adenines (**8b—d**) were confirmed by comparison with authentic samples prepared by the first method from the iminoethers (**2**) and the imidazole (**5**). The formamidopyrimidines (**6**) were made by condensation of the cyclic amidines (**3b—d**) with phenylazomalononitrile in refluxing butanol to give, not the imines (**10**), but the rearranged intermediates (**11**) which underwent reductive formylation by zinc dust in hot formic acid to afford the products (**6b—d**).

Ionization and Spectra.—The two kinds of β-bridged adenines (**8**) and (**9**) may be distinguished easily by the chemical shifts for those methylene protons adjacent to nitrogen (H^a) (see Table 1); the H^a shifts in the 2,9-bridged adenines (**9**) were 0.8 p.p.m. downfield of those in the 2,*N*(6)-bridged isomer (**8**). In addition, the chemical shift (*ca.* 12.6 p.p.m.) of hydrogens adjacent to ring nitrogen at N(9) in (**8**) was characteristic. The bridged types (**8**) and (**9**) have similar pK_a values (Table 2), all within the range 4—5.3.

Unlike comparable adenosine derivatives,[3] the adenine derivatives were insufficiently soluble in water or dimethyl sulphoxide for definitive ^{13}C n.m.r. spectral determination of their protonation site(s). However, it is clear from models that the polymethylene chain of the 2,*N*(6)-bridged derivative (**8b**) would sterically hinder protonation at N(1), just as it did in the comparable adenosine derivative (**12b**), which has been shown[3] to protonate in consequence at N(3). Although the polymethylene chains of the homologues (**8c**) and (**8d**) are more flexible than that of (**8b**) and might therefore permit protonation at N(1), the u.v. spectra of all three compounds (Table 2) are similar enough (both as neutral molecules and as cations) to preclude any difference in protonation site. Furthermore, all three compounds (**8b—d**) showed a bathochromic shift on cation formation very close to that observed[3] for the adenosine derivative (**12b**), again consistent with N(3) as the protonation site. In contrast, the 2,9-bridged derivatives (**9b—d**) appeared to protonate at N(1) because the u.v. spectra of all three compounds (Table 2) are almost the same (both as neutral molecules and as cations), and showed neither bathochromic nor hypsochromic shift on cation formation. These facts suggest the same protonation site and preclude the N(3) protonation. Their u.v. spectra were similar to those of adenosine itself, which is known to protonate at N(1).[3,8] The steadily decreasing basic strength in the series (**8b—d**) is consistent with steric hindrance to protonation at N(3) by the lengthening flexible polymethylene chain, a phenomenon also evident in comparable pyrimidines.[1] Similarly, the steadily decreasing pK_a value in the series (**9b—d**) can be explained by increasing steric hindrance to protonation at N(1) by the lengthening polymethylene chain.

Table 2. pK_a Values and u.v. spectra of β-bridged adenines

			$\lambda_{max.}$ nm (log ε)[b]	
Compd.	*n*	pK_a[a]	[0]	[+]
(8b)	7	4.96 ± 0.02	271 (4.20)	280 (4.28)
(8c)	9	4.71 ± 0.02	271 (4.22)	280 (4.28)
(8d)	11	3.96 ± 0.03	271 (4.22)	280 (4.27)
(9b)	7	5.32 ± 0.02	267 (4.04)	267 (4.04)
(9c)	9	4.60 ± 0.03	264 (4.10)	264 (4.10)
(9d)	11	4.42 ± 0.02	265 (4.05)	265 (4.05)

[a] Analytical λ = $\lambda_{max.}$ of cation (**8b—d**); 215 nm (**9b—d**). [b] Neutral molecules of (**8b—d**) [0] at pH 7; cations of (**8b—d**) [+] at pH 1.5; Neutral molecules of (**9b—d**) [0] in 10% aqueous ethanol (pH 7.3); cations (**9b—d**) [+] in 10% aqueous ethanol (pH 2.0).

Experimental

M.p.s are uncorrected. U.v. spectra were measured on a Cary-recording-Spectrometer, Model 118. ^{1}H N.m.r. spectra were measured in $(CD_3)_2SO$ on a Bruker AM-400 instrument with tetramethylsilane as internal standard.

9-*Amino*-6,7-*dihydro*-5H-*pyrrolo*[1,2-a]*purine* (**7a**).—5-Aminoimidazole-4-carbonitrile (**5**) (1.08 g) and the cyclic inimoether (**2a**)[1] (1.24 g) in butanol (75 ml) were heated under reflux for 2 days. The reaction mixture was evaporated to dryness and the residue recrystallized from ethanol to give the

1,2-*bridged purine* (**7a**) (85%), m.p. > 330 °C (decomp.) (Found: C, 55.0; H, 5.2; N, 39.9. $C_8H_9N_5$ requires C, 54.8; H, 5.2; N, 40.0%).

6,2-*Epiminoheptanopurine* (**8b**).—(*a*) A solution of the carbonitrile (**5**) (1.08 g) and the iminoether (**2b**)[1] (1.86 g) in butanol was heated under reflux for 4 days to give the crystalline *purine* (**8b**) (63%), m.p. 308—309 °C (from methanol–chloroform) (Found: C, 62.1; H, 7.5; N, 30.3. $C_{12}H_{17}N_5$ requires C, 62.3; H, 7.4; N, 30.3%).

(*b*) The bridged formamidopyrimidine (**6b**) (11.8 g) was heated in formamide (150 ml) containing a trace of water at 165 °C for 1 h. The residue from evaporation was dissolved in chloroform–ethanol (9:1) and submitted to chromatography on a silica gel column (40 × 4.5 cm). The main fraction was evaporated and recrystallized from ethanol to give the same pure product (**8b**) (63%), m.p. 308—309 °C.

6,2-*Epiminononanopurine* (**8c**).—(*a*) The carbonitrile (**5**) (1.08 g) and the iminoether (**2c**)[3] (2.12 g) likewise gave the *purine* (**8c**) (80%), m.p. 311—312 °C (from methanol–chloroform) (Found: C, 64.7; H, 8.1; N, 27.1. $C_{14}H_{21}N_5$ requires C, 64.8; H, 8.2; N, 27.0%).

(*b*) The formamidopyrimidine (**6c**) underwent cyclization in formamide as above. Of the two crystalline products formed, one (28%) proved identical with that described in (*a*).

6,2-*Epiminoundecanopurine* (**8d**).—(*a*) The carbonitrile (**5**) (1.08 g) and the iminoether (**2d**)[9] (2.45 g) gave the *purine* (**8d**) (91%), m.p. 288—289 °C (from methanol–chloroform) (Found: C, 67.1; H, 8.8; N, 24.1. $C_{16}H_{25}N_5$ requires C, 66.9; H, 8.8; N, 24.4%).

(*b*) The filtrate from recrystallization of compound (**9d**) below was evaporated and the residue submitted to silica gel t.l.c. (methanol–chloroform, 1:9). The main band was eluted with methanol–chloroform (1:6) and after evaporation, recrystallization gave (**8d**) (5%) as in (*a*).

6-*Amino*-2,9-*heptanopurine* (**9b**).—The residual liquid from recrystallization of the product (**8b**) [method (*b*)] was evaporated to dryness and submitted to silica gel t.l.c. as in the last paragraph to give the *heptanopurine* (**9b**) (3%), m.p. 237—238 °C (Found: C, 62.1; H, 7.5; N, 30.3. $C_{12}H_{17}N_5$ requires C, 62.3; H, 7.4; N, 30.3%).

6-*Amino*-2,9-*nonanopurine* (**9c**).—The second crystalline product, accompanying product (**8c**) [method (*b*)] above, proved to be the *nonanopurine* (**9c**) (47%), m.p. 222—223 °C (Found: C, 64.8; H, 8.5; N, 26.8. $C_{14}H_{21}N_5$ requires C, 64.8; H, 8.2; N, 27.0%).

6-*Amino*-2,9-*undecanopurine* (**9d**).—The formamidopyrimidine (**6d**) (5.74 g) underwent cyclization in formamide (70 ml) as in the preparation of (**8b**) [method (*b*)] to give the *undecanopurine* (**9d**) (70%), m.p. 216—218 °C (from ethanol) (Found: C, 68.0; H, 8.9; N, 24.2. $C_{16}H_{25}N_5$ requires C, 66.9; H, 8.8; N, 24.4%).

12-*Amino*-13-*formamido*-2,11,14-*triazabicyclo*[8.3.1]*tetradeca*-1(14),10,12-*triene* (**6b**).—2-Ethoxy-3,4,5,6,7,8-hexahydro-2*H*-azonine (**2b**)[1] (16.9 g) and ammonium chloride (5.35 g) in methanol (250 ml) were stirred at room temperature for 2 days. After evaporation and washing with ether, the residue was dried over sulphuric acid *in vacuo*. The white solid (**3b**) was dissolved in butanolic sodium butoxide [sodium (2.76 g) and butanol (150 ml)], the phenylazomalononitrile (**4**) (17 g) was added, and the mixture was refluxed overnight, concentrated to 50 ml and diluted with water (100 ml). Refrigeration gave a solid which was washed with water and dried in a desiccator. The crude yellow solid (**11b**) (30.7 g) was dissolved in formic acid (250 ml), zinc dust (30 g) was added, and the mixture was heated under reflux for 15 min. Insoluble material was removed and the filtrate was evaporated to dryness. The residue was purified by column chromatography (silica gel; ethanol–chloroform, 1:9) and the main fraction recrystallized from ethanol to give the *formamidopyrimidine derivative* (**6b**) (70%), m.p. 226—228 °C (Found: C, 50.2; H, 7.1; N, 24.5. $C_{12}H_{19}N_5O{\cdot}2H_2O$ requires C, 50.1; H, 7.4; N, 24.5%).

14-*Amino*-15-*formamido*-2,13,16-*triazabicyclo*[10.3.1]*hexadeca*-1(16), 12,14-*triene* (**6c**).—When 2-ethoxyazacycloundec-1-ene (**2c**)[3] was used in place of the iminoether (**2b**), the above procedure gave the chromatographically pure *product* (**6c**) (84%), m.p. 295—298 °C (Found: C, 58.2; H, 8.7; N, 23.9. $C_{14}H_{23}N_5O{\cdot}\frac{2}{3}H_2O$ requires C, 58.1; H, 8.5; N, 24.2%).

16-*Amino*-17-*formamido*-2,15,18-*triazabicyclo*[12.3.1]*octadeca*-1(18),14,16-*triene* (**6d**).—Similar treatment of 2-ethoxyazacyclotridec-1-ene (**2d**)[9] gave the chromatographically pure *product* (**6d**) (31%), m.p. 220—221 °C (Found: C, 62.3; H, 9.0; N, 22.2. $C_{16}H_{27}N_5O{\cdot}\frac{1}{4}EtOH$ requires C, 62.5; H, 9.1; N, 2.22%).

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