Pyrimidine Derivatives and Related Compounds. XXV.[1] The Synthesis of 6-Cyanouracil Derivatives and the Conversion of 6-Cyano-1,3-dimethyluracil to 5-Cyano Compound[2]

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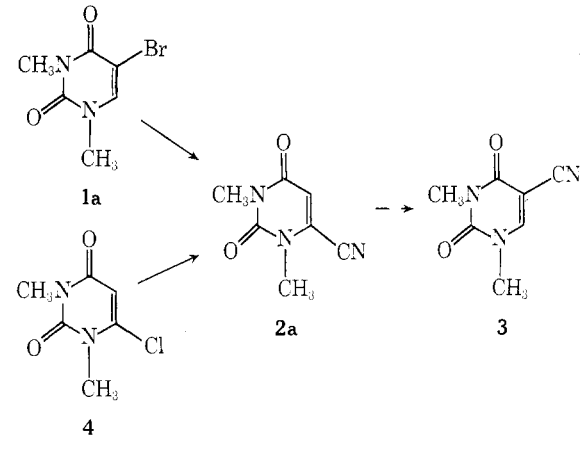
5-Bromo-1,3-dimethyluracil (**1a**) reacted with equimolar sodium cyanide in dimethylformamide (DMF) to give 6-cyano-1,3-dimethyluracil (**2a**), which was also obtained from 6-chloro-1,3-dimethyluracil (**4**) by the same treatment as above. Compound **2a** was readily converted to 5-cyano-1,3-dimethyluracil (**3**) when heated with a catalytic amount of sodium cyanide in DMF. The mechanism for these cine substitutions was shown by deuterium-exchange experiments to involve an addition–elimination process. Furthermore, a variety of N-substituted 6-cyanouracils (**2b,c** and **14a,c**) and N-substituted 6-carbamoyluracils (**12a–c**) were prepared by the reaction of 5-bromouracils (**1a–c** and **13a,c**) with sodium cyanide in DMF or 50% aqueous ethanol.

The chemistry of 5-substituted uracils[3] bearing an electron-withdrawing group at the 5 position, *e.g.*, 5-nitro-,[4] 5-formyl-,[5] and 5-carboxyuracils,[6] has been already studied by many investigators. We previously reported the synthesis of 5-cyanouracil derivatives[7] and the hydrolysis[8] and reduction[9] of their cyano group. Meanwhile, 6-cyanouracil derivatives are very interesting in potential biological activity as orotic analogs. However, synthesis of such 6-cyanouracils has not been widely done yet. Only Ueda, *et al.*,[10] reported the formation of the 6-cyanouridine derivative together with the 5-cyano relative by treatment of the 5-bromouridine derivative with 5 equiv of sodium cyanide. In this paper, we report that treatment of 5-bromouracils and 6-cyanouracils with sodium cyanide causes cine substitution to give 6-cyanouracils and 5-cyanouracils, respectively.

5-Bromo-1,3-dimethyluracil (**1a**) was selected as a model compound for examining of the mode of reaction of 5-bromouracil derivatives with sodium cyanide. At first, **1a** was treated with a large excess of sodium cyanide in dimethylformamide (DMF) at 80° for 2 hr to afford the known[11] 5-cyano-1,3-dimethyluracil (**3**) in 68% yield. When **1a** was, however, allowed to react with an equimolar sodium cyanide in DMF at room temperature for 2 hr, the sole product which we could isolate in high yield was not **3**, but 6-cyano-1,3-dimethyluracil (**2a**). The structure of **2a** was fully supported by its spectral and elemental analyses. The proton magnetic resonance (pmr) spectrum of this compound in deuteriochloroform ($CDCl_3$) showed a sharp singlet (1 H) at δ 6.30, corresponding to the absorption for the C-5 proton (δ 5.73) of 1,3-dimethyluracil but did not show an absorption for the C-6 proton (δ 7.98) as observed in **3**. The infrared (ir) spectrum indicated a weak CN peak at 2240 cm^{-1}, unlike a strong CN peak of **3** at 2220 cm^{-1}. The optimum condition for the synthesis of **2a** from **1a** was the use of equimolar sodium cyanide with **1a** at room temperature in DMF as a solvent.

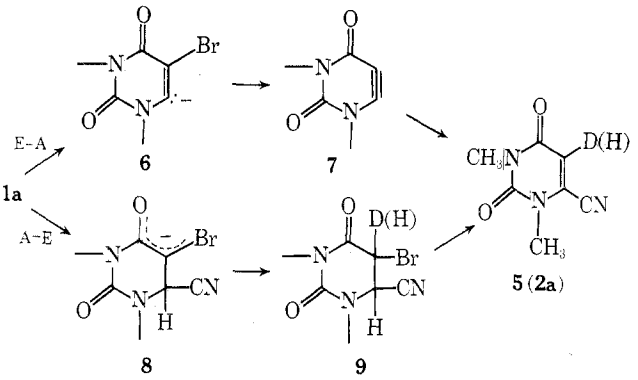
By the way, Liebenow, *et al.*,[12] obtained **3** in 73% yield by treating 6-chloro-1,3-dimethyluracil (**4**) with excess potassium cyanide in dimethyl sulfoxide (DMSO) at 90–110°. In our laboratory, however, compound **4** gave **2a** in high yield when the reaction was carried out with equimolar sodium cyanide in dry DMF at room temperature for 2 hr. Although **2a** was not converted to **3** in the absence of sodium cyanide, the desired **3** was obtained by treating **2a** in DMF at 80° with a catalytic amount of sodium cyanide. On the contrary, the conversion of **3** to **2a** was unsuccessful under the same conditions as above. Furthermore, it was found that occurrence of the reaction was greatly dependent on the reaction medium; in an aprotic polar solvent such as DMF and DMSO, the conversion proceeded, but in a protic polar solvent such as water and ethanol, alternative reactions occurred to give 6-carbamoyl-1,3-dimethyluracil (**12a**) and ethyl imidate (**15a**),[13] respectively. From these results, it appeared that the reaction of **1a** and **4** with sodium cyanide proceeds by the following steps: (**1a** and **4**) → **2a** → **3a** (Scheme I).

Scheme I

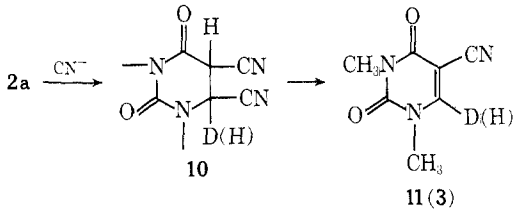


Because of the low reactivity of the 5-bromine atom, 5-bromouracils undergo substitution with amines[14] or base-catalyzed hydrolysis[15] under drastic conditions only. However, recent studies have revealed that 5-bromouracils can be easily debrominated with sulfur-containing reagents such as NaSH,[16] Na_2SO_3,[17] $NaHSO_3$,[18] and cysteine.[19] The mechanism of the above reaction most likely involves an addition–elimination mechanism, initiated by nucleophilic attack of an anion at the C-6 position, followed by formation of the 5,6-dihydrouracil intermediate, and then removal of the bromine.[16,19a] In this connection, two possible mechanisms for the cine substitution of **1a** to **2a** are suggested:[20,21] one is an addition–elimination (A–E) mechanism, as described above, and another is an elimination–addition (E–A) mechanism *via* deprotonation at the C-6 proton of the uracil ring and formation of a hetaryne. Hetaryne formation has been well investigated in halogenoheterocyclic aromatic compounds by Kauffmann[21] and van der Plas.[22] In order to elucidate the mechanism, **1a** was treated with sodium cyanide using DMF–D_2O (10 equiv of D_2O to **1a**) as a solvent. Although an intermediate addition product could not be detected, the final product was 6-

Scheme II



Scheme III

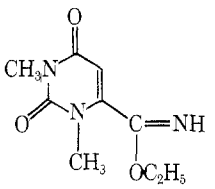


cyano-5-deuterio-1,3-dimethyluracil (**5**) in which 85% of the hydrogen was exchanged with deuterium at the C-5 position, as indicated by integration of its diminished C-5 hydrogen peak in the pmr spectrum. The participation of D_2O in this reaction reasonably supports the A–E mechanism rather than the E–A mechanism. That is, if the E–A mechanism were involved, the addition of D_2O (H_2O), a good protonating agent for the carbanion precursor **6** of pyrimidyne (**7**), would inhibit the reaction.[23] Actually D_2O had no influence on the reaction and a deuterium atom was incorporated into the C-5 position. Thus, the mechanism would be as follows: the initial nucleophilic attack by cyanide occurs at C-6 to give a carbanion **8**, which forms the 5,6-dihydro intermediate **9** by abstraction of a deuterium (proton) from D_2O (H_2O), and, at last, dehydrobromination of **9** gives **5** (**2a**) (Scheme II).

The mechanism for conversion of **2a** to **3** was then studied. Thus **2a** was allowed to react with a catalytic amount of sodium cyanide in the presence of 10 equiv of D_2O to yield 5-cyano-6-deuterio-1,3-dimethyluracil (**11**), in which 84% of C-6 hydrogen was exchanged with deuterium. D_2O (H_2O) was also concerned in this conversion as well as in the reaction of **1a** to **2a.** In view of the above, we presumed that the most likely mechanism for this reaction might involve a 1,2 addition, initiated by a nucleophilic attack of cyanide at C-5, followed by abstraction of a deuterium (proton) from D_2O (H_2O) at C-6. Then, hydrogen cyanide would be removed from the resulting 5,6-dihydrouracil intermediate **10** to give **11** (**3**) (Scheme III).

Fox, *et al.*, once proposed[24] such a mechanism involving an initial "C-5 attack" to account for the exchange of H-6 for deuterium in 5-halogenouracils, but they have withdrawn it recently.[25] The present case involving "C-5 attack" is therefore the first example of an A–E mechanism and is rather unusual in uracil derivatives compared with that caused by "C-6 attack."

We have investigated the reaction of N-substituted 5-bromouracil derivatives with sodium cyanide in more detail and the results are summarized in Table I. The reactions are classified into three types according to the presence or absence of a substituent at N-1 or/and N-3. In the case of type I, 1,3-disubstituted 5-bromouracils **1,** alkylated in both 1 and 3 positions, gave good yields of 1,3-disubstituted 6-cyanouracils **2** when allowed to react with equimolar sodium cyanide in DMF at room temperature (method A). When the reaction was carried out in refluxing 50% ethanol instead of DMF, 1,3-disubstituted 6-carbamoyluracils **12,** where the cyano group was further hydrolyzed, were obtained (method B). It is reasonable to assume that the reaction proceeds by way of **2** and an imidate **15,** because of the fact that **2a** readily formed an imidate **15a** when **1a** in ethanol solution was subjected to the action of a catalytic amount of an alkali; the resulting **15a** underwent base-catalyzed hydrolysis to afford **12a.** 1-Substituted 5-bromouracils **13** having no substituent at the N-3 position were then subjected to the reactions of methods A and B to give 1-substituted 6-cyanouracils **14** only (type II). Compound **14** failed to give an imidate under the same conditions as described in the formation of **15a,** and this would be the reason why **14** was no longer hydrolyzed to 6-carbamoyl compounds. As to 3-substituted 5-bromouracils (example, 3-substituent; H, CH_3, and C_4H_9) which are not alkylated at N-1, the desired 6-cyano compound was not obtained but only salt formation between these acidic N(1)-H and sodium cyanide was observed (type III).



15a

As described above, the reaction between N-substituted 5-bromouracils and sodium cyanide is greatly influenced by the presence of substituents at N-1 and N-3; properties of substituents such as steric hindrance and electron attractivity have no marked influence on the reaction.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. Pmr spectra were determined on a 60-Mc Hitachi Perkin-Elmer R-20B spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. Ir spectra were obtained with a Hitachi 215 instrument as KBr pellets.

Formation of 6-Cyano- (or Carbamoyl-) uracils. General Procedure. Method A. To a stirred suspension of the 5-bromouracil derivative (0.005 mol) in 10–15 ml of DMF was added a solution of NaCN (0.29 g, 0.006 mol) in 0.5 ml of water and the mixture was stirred at room temperature . After the reaction was complete, the mixture was poured into *ca.* 100 ml of chilled water. Depending on the solubility of the product in the solvent, the 6-cyano compound was either isolated by filtration or extracted with $CHCl_3$, dried, and evaporated *in vacuo.* The resulting crude product was recrystallized (see Table I).

Method B. A mixture of the 5-bromouracil derivative (0.005 mol) and NaCN (0.29 g, 0.006 mol) was refluxed in 20 ml of 50% aqueous ethanol. After the reactants were dissolved, refluxing was continued for a further 1–2 hr. The solution was evaporated to dryness *in vacuo* and the residue was triturated with 50 ml of cold water and acidified with HCl. The precipitate was collected by filtration and recrystallized (see Table I).

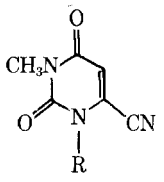
5-Cyano-1,3-dimethyluracil (3). (a) A mixture of 1.1 g (0.005 mol) of 5-bromo-1,3-dimethyluracil (**1a**) and 0.58 g (0.012 mol) of NaCN in 1 ml of DMF was heated at 80–90° for 2 hr. The solvent was evaporated *in vacuo.* To the residue was added 5 ml of water and the precipitate was collected by filtration, giving 0.76 g (92%) of the crude product, mp 162–164°. Recrystallization from ethanol afforded colorless needles: mp 165° (lit.[11] mp 165°); ir ν max 2220 (CN), 1720, and 1650 cm^{-1} (C=O); pmr ($CDCl_3$) δ 3.54 (3 H, s, NCH_3), 3.40 (3 H, s, NCH_3), and 7.98 ppm (1 H, s, 6-CH).

Anal. Calcd for $C_7H_7O_2N_3$: C 50.91; H, 4.27; N, 25.45. Found: C, 50.93; H, 4.28; N, 25.54.

Table I

Formation of N-Substituted 6-Cyano- (or Carbamoyl-) uracils from 5-Bromouracils with Sodium Cyanide

Type I



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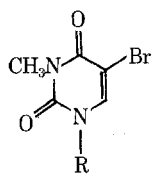
method A



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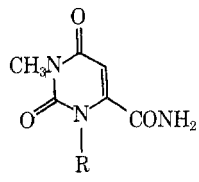
method B



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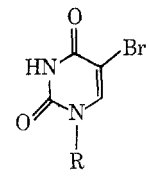
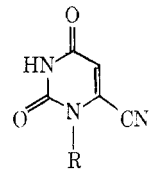
Type II



13

method A
method B



14

Starting material	R	Method[a]	Time, hr	Product	Yield, %	Mp, °C (solvent of recrystn)	Spectral data: Pmr,[b] δ, ppm (5-CH)	Spectral data: Ir, cm^{-1} (C≡N)	Formula	Calcd (found): C	H	N
1a	CH_3	A	2	**2a**	95	168–170 (EtOH)	6.34	2240	$C_7H_7O_2N_3$	50.91 (51.05)	4.27 (4.30)	25.45 (25.72)
1a	CH_3	B	2	**12a**[c]	86	238–239 (MeOH)[d]	5.81		$C_7H_9O_3N_3$	45.90 (46.10)	4.95 (5.14)	22.94 (22.76)
1b	C_6H_{11}	A	24	**2b**	94	209–211 (EtOH)	6.27	2235	$C_{12}H_{15}O_2N_3$	61.78 (61.49)	6.48 (6.44)	18.02 (17.50)
1b	C_6H_{11}	B	3	**12b**	93	179–180 (H_2O)	5.65		$C_{12}H_{17}O_3N_3$	57.35 (57.29)	6.81 (6.84)	16.72 (16.90)
1c	C_6H_5	A	1	**2c**	86	205 (EtOH)	6.38	2250	$C_{12}H_9O_2N_3$	63.43 (63.25)	3.99 (4.11)	18.49 (18.39)
1c	C_6H_5	B	2	**12c**	90	274–275 (MeOH)	5.92		$C_{12}H_{11}O_3N_3$	58.77 (58.98)	4.52 (4.56)	17.14 (16.83)
13a	CH_3	A	5	**14a**	53	228–229	6.36	2240	$C_6H_5O_2N_3$	47.68 (47.54)	3.34 (3.32)	27.81 (27.94)
		B	2		93	(H_2O)						
13c	C_6H_5	A	6	**14c**	69	242–245 (EtOH)	6.42	2250	$C_{11}H_7O_2N_3$	61.97 (61.90)	3.31 (3.32)	19.71 (19.58)

[a] See Experimental Section. [b] Solvents: **2a–c**, $CDCl_3$; **12a–c** and **14a, c**, DMSO-d_6. [c] Alternate synthesis reported: K. A. Chkhivadze, N. E. Britikova, and O. Y. Magidson, *Biol. Akt. Soedin.*, 22 (1965) [*Chem. Abstr.*, **63**,18081*a* (1960)]. [d] Lit. mp 239° (H_2O).

(**b**) To a solution of 0.83 g (0.005 mol) of 6-cyano-1,3-dimethyluracil (**2a**) in 5 ml of DMF was added 30 mg (0.6 mmol) of NaCN. The mixture was heated at 80–85° for 5 hr and the solvent was removed by evaporation. To the residue was added 50 ml of cold water and the precipitate was filtered, washed with water, and recrystallized from ethanol to give 0.5 g (67.5%) of colorless needles of **3**.

6-Cyano-1,3-dimethyluracil (2a) from 6-Chloro-1,3-dimethyluracil (4). To a stirred solution of 0.87 g (0.005 mol) of **4** in 10 ml of DMF[26] was added 0.29 g (0.006 mol) of NaCN. The reaction mixture was maintained at room temperature for 2 hr and poured into *ca.* 100 ml of ice–water. The precipitate was filtered, washed with cold water, and recrystallized to give 0.7 g (88%) of the product **2a**, which was identified by ir and pmr spectra and mixture melting point with an authentic sample prepared from 5-bromo-1,3-dimethyluracil.

6-Cyano-5-deuterio-1,3-dimethyluracil (5). To a solution of 1.1 g (0.005 mol) of 5-bromo-1,3-dimethyluracil (**1a**) in 15 ml of DMF[26] was added 0.9 ml (0.5 mol) of D_2O and 0.29 g (0.006 mol) of NaCN with stirring at room temperature. The reaction mixture was treated as described above for the preparation of **2a** to give 0.83 g of **5**; the pmr spectrum ($CDCl_3$) showed that 85% of H-5 exchanged with deuterium; the remainder of the spectrum was identical with that of **2a**; ir ν max 2290 cm^{-1} (C–D).

5-Cyano-6-deuterio-1,3-dimethyluracil (11). To a solution of 0.83 g (0.005 mol) of 6-cyano-1,3-dimethyluracil (**2a**) in 10 ml of DMF[26] were added 0.9 ml (0.05 mol) of D_2O and 30 mg (0.0006 mol) of NaCN. Work-up of the reaction product was the same as in the reaction of **2a** to **3**, to give 0.80 g of **11**; pmr ($CDCl_3$) showed that 84% of H-6 exchanged with deuterium; the remainder of the spectrum was identical with that of **3**; ir ν max 2290 cm^{-1} (C–D).

Ethyl 6-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro)pyrimidylimidate (15a). (**a**) A mixture of 0.83 g (0.005 mol) of **2a** and 0.028 g (0.0005 mol) of potassium hydroxide in 10 ml of ethanol was refluxed for 1 hr. After neutralization with hydrochloric acid, the solution was evaporated *in vacuo* and the residue was triturated with 1 ml of cold water. Filtration then gave 0.90 g (85%) of **15a**. An analytical sample was recrystallized from ligroine: mp 98–100°; ir ν max 3330 cm^{-1} (NH); pmr ($CDCl_3$) δ 1.39 (3 H, t, J = 8 Hz, CH_2CH_3), 3.38 (6 H, s, $2NCH_3$), 4.35 (2 H, q, J = 8 Hz, OCH_2), and 5.81 ppm (1 H, s, 5-CH).

Anal. Calcd for $C_9H_{13}O_3N_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 50.89; H, 6.00; N, 20.06.

(**b**) Compound **2a** was treated with 0.1 equiv of sodium cyanide instead of potassium hydroxide by the same procedure as described above to give **15a** in 63% yield, identical with a sample prepared in method a.

6-Carbamoyl-1,3-dimethyluracil (12a). (**a**) A suspension of 0.49 g (0.0025 mol) of **15a** in 5 ml of a 5% aqueous solution of sodium hydroxide was refluxed for 10 min. The soluton was neutralized with hydrochloric acid and concentrated *in vacuo*. The residual solid was washed with cold water to give 0.48 g (52%) of the crude product. Recrystallization from methanol gave the colorless needles of **12a**.

(**b**) A mixture of 0.83 g (0.005 mol) of **2a** and 0.025 g (0.0005 mol) of sodium cyanide in 10 ml of water was refluxed for 1 hr. After neutralization with hydrochloric acid, the solution was evaporated *in vacuo* and the residue was triturated with cold water. Filtration then gave the crude product of **12a** in 71% yield, identical with a sample prepared in method a.

Registry No.—**1a**, 7033-39-8; **1b**, 53293-08-6; **1c**, 53369-64-5; **2a**, 49846-86-8; **2b**, 53293-09-7; **2c**, 53293-10-0; **3**, 36980-91-3; **4**, 6972-27-6; **5**, 53293-11-1; **11**, 53293-12-2; **12a**, 2019-20-7; **12b**, 53293-13-3; **12c**, 53369-65-6; **13a**, 6327-97-5; **13c**, 53369-66-7; **14a**, 53293-14-4; **14c**, 53293-15-5; **15a**, 53293-16-6; NaCN, 143-33-9.

References and Notes

(1) For part XXIV, see S. Senda and K. Hirota, *Chem. Pharm. Bull.*, **22**, 2921 (1974).
(2) A part of this work was presented as a communication: S. Senda, K. Hirota, and T. Asao, *Tetrahedron Lett.*, 2647 (1973).
(3) (a) For recent reviews on the chemistry of uracils, see D. J. Brown,

Chem. Heterocycl. Compounds, 16, 227 (1962); (b) Chem. Heterocycl. Compounds, Suppl. 1, 166 (1970).
(4) (a) W. Pfleiderer and H. Mosthof, Chem. Ber., 90, 728 (1957); (b) H. U. Blank, I. Wempen, and J. J. Fox, J. Org. Chem., 35, 1131 (1970); (c) I. H. Pitman, M. J. Cho, and G. S. Rork, J. Amer. Chem. Soc., 96, 1840 (1974).
(5) (a) R. Brossmer and D. Ziegler, Tetrahedron Lett., 5253 (1966); (b) K. Y. Zee-Cheng and C. C. Cheng, J. Org. Chem., 33, 892 (1968).
(6) K. Isono, S. Suzuki, M. Tanaka, T. Nanbata, and K. Sibuya, Tetrahedron Lett., 425 (1970).
(7) S. Senda, K. Hirota, and J. Notani, Chem. Pharm. Bull., 20, 1380 (1972).
(8) S. Senda, K. Hirota, and J. Notani, Chem. Pharm. Bull., 20, 1389 (1972).
(9) S. Senda, K. Hirota, and J. Notani, Chem. Pharm. Bull., 22, 1179 (1974).
(10) H. Inoue and T. Ueda, Chem. Pharm. Bull., 19, 1743 (1971).
(11) M. R. Atkinson, G. Shaw, and R. N. Warrener, J. Chem. Soc., 4118 (1956).
(12) W. Liebenow and H. Liedtke, Chem. Ber., 105, 2095 (1972).
(13) Cyano groups substituted at the α position of heteroatoms were observed to form the corresponding stable imidate: H. Watanabe, Y. Kikugawa, and S. Yamada, Chem. Pharm. Bull., 21, 465 (1973).
(14) (a) F. R. Gerns, A. Perrtta, and G. H. Hitching, J. Med. Chem., 9, 108 (1966); (b) S. Senda, K. Hirota, and K. Banno, ibid., 15, 471 (1972).
(15) (a) S. Y. Wang, J. Amer. Chem. Soc., 81, 3786 (1959); (b) E. R. Garrett, H. J. Nestler, and A. Somidi, J. Org. Chem., 33, 3460 (1968); (c) B. A. Otter, E. A. Falco, and J. J. Fox, ibid., 34, 2636 (1969).
(16) L. Szabo, T. I. Kalman, and T. J. Bardos, J. Org. Chem., 35, 1434 (1970).
(17) E. G. Sander and C. A. Deyrup, Arch. Biochem. Biophys., 150 (1972).
(18) J. L. Fourrey, Bull. Soc. Chim. Fr., 4580 (1972).
(19) (a) F. A. Sedor and E. G. Sander, Biochem. Biophys. Res. Commun., 50, 328 (1973); (b) Y. Wataya, K. Negishi, and H. Hayatsu, Biochemistry, 12, 3992 (1973).
(20) F. Pietra, Quart. Rev., Chem. Soc., 23, 504 (1969).
(21) T. Kauffmann and R. Wintwein, Angew. Chem., Int. Ed. Engl., 10, 20 (1971).
(22) H. J. den Hertog and H. C. van der Plas, Advan. Heterocycl. Chem., 4, 121 (1965).
(23) T. Kauffmann, R. Nurnberg, and K. Udluft, Chem. Ber., 102, 1177 (1969).
(24) R. J. Cushley, S. R. Lipsky, and J. J. Fox, Tetrahedron Lett., 5393 (1968).
(25) J. A. Rabi and J. J. Fox, J. Amer. Chem. Soc., 95, 1628 (1973).
(26) DMF used was purified by distillation and dried over calcium hydride.

Linear Benzoadenine. A Stretched-Out Analog of Adenine

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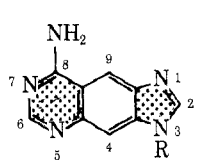
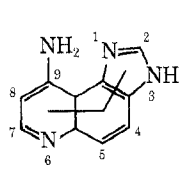
The synthesis of 8-aminoimidazo[4,5-*g*]quinazoline (**1**), an extended or "stretched-out" version of adenine which is given the descriptive name *lin*-benzoadenine, is reported. The synthesis involves the elaboration of 7-chloro-4-quinazolone (**6**) to imidazo[4,5-*g*]quinazolin-8-one (**11**) in four steps, followed by thiation to 8-mercaptoimidazo[4,5-*g*]quinazoline (**12**) and subsequent replacement of the thiol function by ammonia to yield the *lin*-benzoadenine isomer **1**. The aralkyl derivatives of **1**, *e.g.*, 8-amino-1- and 3-benzylimidazo[4,5-*g*]quinazoline (**17** and **16**), which are necessary to serve as uv models in assigning the structure of nucleoside and nucleotide targets and to direct further substitution, were obtained indirectly *via* benzylation of 8-methylthioimidazo[4,5-*g*]quinazoline (**13**). The structure assignment of the 3-benzyl isomer was checked by an unambiguous synthesis, and its value as a uv model was confirmed by spectral comparison with 8-amino-3-cyclohexylaminoimidazo[4,5-*g*]quinazoline (**30**). A general comparison of the uv spectra of various 8-methylthio- and 8-aminoimidazo[4,5-*g*]quinazoline derivatives in neutral, acidic, and basic solution indicates that first protonation occurs mainly on the imidazole ring of the methylthio compounds and on the quinazoline ring of the amino compounds.

There has been considerable interest in the synthesis of analogs of the naturally occurring nucleic acid bases and their corresponding nucleosides, nucleotides, and coenzymes.[1] In the course of our continuing study of the role of purines and pyrimidines in nature, we questioned what properties might be associated with compounds in which the pyrimidine ring and the imidazole ring of the purine system are separated by a benzene ring to form an extended or "stretched-out" purine model. Compounds such as **1** and **1a** would be expected to have 1,N^6 binding sites similar to those in adenine and adenosine, stronger π-bonding characteristics, and larger spatial requirements. The physical and biological properties of compounds **1** and **1a** and their congeners hold considerable interest since they are previously unknown and since differences in their behavior in relation to the corresponding naturally occurring adenine compounds might be relatable to defined geometrical changes.

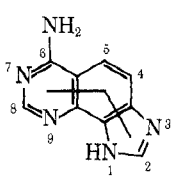
In this paper we describe the synthesis, structure proof, and properties of the linear benzolog of adenine, 8-aminoimidazo[4,5-*g*]quinazoline (**1**), for which we suggest the descriptive name *lin*-benzoadenine.[2] This name is capable of easy adaptation to derivatives related to adenosine, adenylic acid, adenosine 5′-diphosphate, and the like. In the following paper we discuss the preparation of the structural isomers of **1**, 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), which are the proximal and distal isomers of benzoadenine, respectively.[2] We feel justified in using the term "benzo" in the trivial names of these three compounds because *only when the additional ring is central* does it contain no nitrogens and is accordingly "benzo."



1, R = H
1a, R = β-D-ribofuranosyl

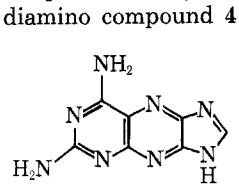


2

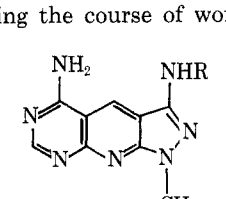


3

A review of the literature reveals only several cases where tricyclic heterocyclic systems related to **1** have been described. For none of the compounds was their preparation based on the criterion that they might be biologically active as purine surrogates. Taylor and Sherman synthesized diamino compound **4** during the course of work on



4



5, R = H, CHO, $COCH_3$