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Purines. V.[1] The Dimroth Rearrangement of 1-Alkoxyadenines: The Synthesis of N-Alkoxyadenines

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Data presented in the previous papers[4] have demonstrated that the Dimroth rearrangement of 1-alkoxy-9-alkyladenines to N-alkoxy-9-alkyladenines readily proceeds through isolable N′-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidines. The present paper reports a similar rearrangement of 1-alkoxyadenines (I)[5] unsubstituted at the 9-position.

Treatment of 1-methoxyadenine (Ia)[5] with boiling water for 4 hr furnished N-methoxyadenine (Va) in 59% yield. The N-methoxy structure (Va) was confirmed by direct comparison with a sample prepared from 6-chloropurine (VI) and methoxyamine in a manner similar to that reported by Giner-Sorolla, *et al.*[6]

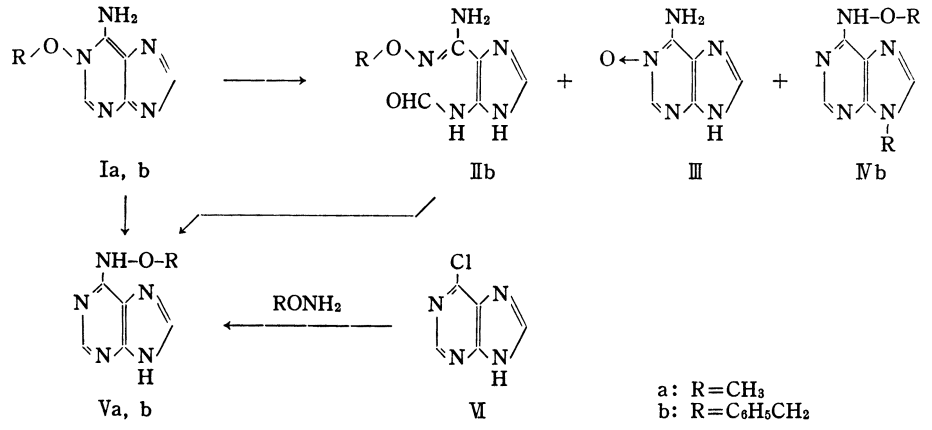

Chart 1

The conversion of 1-benzyloxyadenine (Ib)[5] into N-benzyloxyadenine (Vb) was carried out stepwise *via* N′-benzyloxy-5-formamidoimidazole-4-carboxamidine (IIb) presumed to be an intermediate in the Dimroth rearrangement. Thus, compound Ib was heated at reflux in 50% aqueous N,N-dimethylacetamide (DMAC) for 10 hr to give the ring-opened derivative (IIb) as the major product (39—55%) and adenine 1-oxide (III) (12—14%), Vb (*ca.* 10%), and N-benzyloxy-9-benzyladenine (IVb)[4b] (2.4%) as the minor products. The as-

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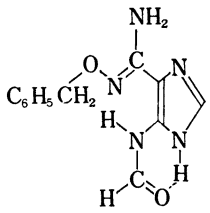
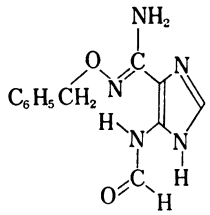
4) *a*) T. Fujii, T. Itaya, C.C. Wu, and S. Yamada, *Chem. Ind.* (London), **1966**, 1967; *b*) T. Fujii, T. Itaya, C.C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971).
5) *a*) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1017 (1965); *b*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971).
6) A. Giner-Sorolla, S.A. O'Bryant, C. Nanos, M.R. Dollinger, A. Bendich, and J.H. Burchenal, *J. Med. Chem.*, **11**, 521 (1968).

signment of structure IIb was based on correct analysis for $C_{12}H_{13}O_2N_5$ and nuclear magnetic resonance (NMR) and infrared (IR) spectra. The NMR spectrum in dimethyl sulfoxide (DMSO) showed two sharp peaks at 4.99 ($C_6H_5CH_2O$ of *trans*-IIb) and 4.93 τ ($C_6H_5CH_2O$ of *cis*-IIb), two fairly sharp signals at 3.97 (NH_2 of *cis*-IIb) and 3.85 τ (NH_2 of *trans*-IIb), a six-proton multiplet in the region of 2.4—2.8 τ (phenyl protons and $C_{(2)}$-H's of *cis*- and *trans*-IIb), a combination of a set of two peaks at 1.65 (HCON, *cis*-IIb) and 0.01 τ (CONH, *cis*-IIb) with a pair of AB type doublets (J=11 cps each) at 1.14 (HCON, *trans*-IIb) and 0.75 τ (CONH, *trans*-IIb), and a dull peak at −2.51 τ ($N_{(1)}$-H's of *cis*- and *trans*- IIb). It is most likely that the appearance of a set of two signals for the respective protons of IIb is, as illustrated in Chart 2, due to *cis-trans* isomerism caused by restricted rotation about the central C—N bond in the formamido group[4,7] at the 5-position. The measurement of the area of the signals for the formyl protons of *cis*- and *trans*-IIb suggests that both isomers exist in the ratio of about 6 to 4 in DMSO at 20°. This ratio makes it possible to assign bands in each



cis-IIb



trans-IIb

Chart 2

of the other sets of two peaks to the respective isomeric protons. The IR spectrum of IIb in a dilute (0.005 M) solution in chloroform revealed absorption bands at 3510 (NH_2), 3390, 3280 (NH_2, $N_{(1)}$-H, and CONH), and 1673 cm^{-1} (CONHAr of *cis*-IIb) with a shoulder at 1696 cm^{-1} (CONHAr of *trans*-IIb). The frequency of the amide I band at 1673 cm^{-1}, attributable to that of *cis*-IIb, is considerably lower than that of the $N_{(1)}$-alkylated derivative (*e.g.*, $\nu_{max}^{CHCl_3}$ 1705 cm^{-1} for N'-ethoxy-1-ethyl-5-formamidoimidazole-4-carboxamidine[4b]). Such a lower shift in frequency would be probably due to intramolecular interaction[8] of the amide carbonyl group with the proximate $N_{(1)}$-H in the *cis*-isomer (see Chart 2).

It may be seen from their pK_a values (*e.g.*, 6.66 for Ia)[5b] that 1-alkoxyadenines are weak bases, and their aqueous solutions are apparently alkaline. Accordingly, the nucleophilic attack of the hydroxide ion at the benzylic carbon atom of Ib would account for the above-mentioned formation of the N-oxide (III) as a by-product,[9] whereas the attack of the hydroxide ion at the 2-position would initiate the breakdown of the pyrimidine moiety of Ib and/or its protonated species, and recyclization of a small portion of the resulting intermediate (IIb) gives the rearranged product (Vb). The formation of the 9-benzylated product (IVb) from Ib is of special interest in view of the recently reported directivity[5] of the 1-alkoxy group in the alkylation of adenine derivatives and alkylating capability[10] of 1-alkoxy-9-alkyladenines. It would be reasonable to assume that intermolecular benzylation of Ib in boiling 50% aqueous DMAC furnishes 1-benzyloxy-9-benzyladenine and III, and the former compound should be readily converted into IVb[4b] under the same reaction conditions.

7) *a*) A.J.R. Bourn, D.G. Gillies, and E.W. Randall, *Tetrahedron*, **20**, 1811 (1964); *b*) W.E. Stewart and T.H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).
8) L.J. Bellamy, "Advances in Infrared Group Frequencies," Methuen & Co., London, 1968, p. 151.
9) For analogous reactions of 1-alkoxy-9-alkyladenine derivatives with nucleophiles, see Ref. 10.
10) *a*) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1452 (1966); *b*) T. Fujii, S. Moro, and T. Itaya, Abstracts of Papers, 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, Hokkaido, July, 1970, p. II-45.

Cyclization of IIb to Vb was accomplished by treating the former with boiling water for 11 hr. The rearranged product (Vb) was identified with a sample synthesized from VI and benzyloxyamine.

It may be noted that N-alkoxyadenines (Va,b) described above are rather unstable in aqueous solutions. Especially under alkaline conditions they have a tendency to form red precipitates, whereas the 9-substituted derivatives[4] are stable. Since 1-alkoxyadenines (Ia,b) are considerably stable in water at room temperature, the first stage (I→II) of the Dimroth rearrangement of I must be much slower than that[4] of the 9-alkylated derivatives.

Experimental[11]

N-Methoxyadenine (Va)——i) Rearrangement of Ia: A mixture of Ia[5] (4.00 g, 24.2 mmoles) in H_2O (200 ml) was refluxed for 4 hr, and the resulting solution was evaporated *in vacuo* to leave a solid. The solid was recrystallized from 0.05M phosphate buffer (pH 7) (600 ml) in the presence of a small amount of $NaHSO_3$ to give pinkish minute crystals (2.37 g, 59%) shown to be homogeneous by paper chromatography. Repeated recrystallizations in a smilar way furnished Va as faintly yellowish needles, dec. point *ca.* 190° (unmelted below 340°) (lit.[6] mp 196°); UV $\lambda_{max}^{95\%aq.EtOH}$: 273 mμ (ε 13100); $\lambda_{max}^{H_2O}$ (pH1) 275 (13000); $\lambda_{max}^{H_2O}$ (pH 7)[13] 271 (12900); $\lambda_{max}^{H_2O}$ (pH 13) *ca.* 276 (unstable); NMR (DMSO)τ: 6.16 (3H, OCH_3), 2.30 and 2.02 (1H each, rather dull, purine protons), −1.30 (1H, dull, NH), −3.05 (1H, broad, NH). *Anal.* Calcd. for $C_6H_7ON_5$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.60; H, 4.31; N, 42.64.

ii) Metathesis of VI with Methoxyamine: A mixture of 6-chloropurine (VI)[14] (1.00 g, 6.47 mmoles), methoxyamine[15] (6.00 g, 127 mmoles), and 1-butanol (100 ml) was heated at 70—80° with stirring for 12 hr. The solution was evaporated *in vacuo* to dryness leaving a solid, which was dissolved in H_2O (180 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (8 ml), and the column was further eluted with H_2O. The effluent was evaporated *in vacuo* to dryness to leave a pale yellow solid (910 mg, 85%). Recrystallization from 0.05M phosphate buffer (pH 7) afforded a pure sample of Va, dec. point *ca.* 190° (unliquefied below 340°), identical with the sample described above [method-(i)] by paper chromatography and comparison of the UV and IR spectra.

N′-Benzyloxy-5-formamidoimidazole-4-carboxamidine (IIb)——A suspension of 1-benzyloxyadenine monohydrate (Ib·H_2O)[5] (7.17 g, 27.7 mmoles) in a mixture of $AcNMe_2$ (310 ml) and H_2O (310 ml) was gently refluxed for 10 hr and then evaporated *in vacuo* to dryness. The partially crystallized residue that resulted was triturated with hot EtOH (120 ml), and the mixture was chilled to give almost colorless precipitates (601 mg, 14%), which were collected by filtration. This sample was identified with authentic anhydrous adenine 1-oxide (III)[16] by paper chromatography and comparison of the IR spectra. The filtrate, which was obtained by removing the above-mentioned precipitates, was concentrated to a volume of *ca.* 100 ml and kept in a refrigerator overnight. The greenish yellow plates of mp 142—145° that formed were filtered and recrystallized from EtOH to afford a first crop (1.46 g) of IIb, mp 145—147°. The filtrates of the crude and the purified crystals were combined and evaporated *in vacuo* to dryness, and the residue was chromatographed on silica gel (115 g). Elution with $CHCl_3$–EtOH (8:1, v/v) yielded 9-benzyl-N-benzyloxyadenine (IVb)[4b] (217 mg, 2.4%), mp 210—211°. Identity was established by melting point, mixture melting point, thin-layer chromatography, UV spectra, IR spectrum, and mass spectrum [*m/e* 331 (M^+)].

Further elution of the column with the same solvent system gave a second fraction. Recrystallization from EtOH produced a second crop (1.31 g; total yield, 2.77 g or 39%) of IIb as colorless plates, mp 145—147°; UV $\lambda_{max}^{95\%aq.EtOH}$ mμ (ε): 237 (18600), 276 (9100); $\lambda_{shoulder}$ (acid)[17] 256 (10100); λ_{max}(neutral)[18] 233 (14300), 262 (shoulder) (9100); λ_{max} (alkaline)[19] 235 (14600), 282 (8400); IR and NMR (see Theoretical Part); Mass Spectrum *m/e* 259 (M^+). *Anal.* Calcd. for $C_{12}H_{13}O_2N_5$: C, 55.59; H, 5.05; N, 27.02. Found: C, 55.83; H, 5.15; N, 26.81.

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11) All melting points are corrected. Paper chromatographies were developed as described previously.[12] See also Ref. 12 for details of instrumentation and measurement. Elemental analyses and measurements of NMR and mass spectra were performed by Mr. Y. Itatani and Misses M. Imai and T. Tsuji at Kanazawa University and by Dr. E. Kimura and his associates at University of Tokyo.

12) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).

13) Measured in 0.005M phosphate buffer (pH 7).

14) *a*) A. Bendich, P.J. Russell, Jr., and J.J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954); *b*) A.G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962).

15) T. Fujii, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 345 (1967).

16) M.A. Stevens, D.I. Magrath, H.W. Smith, and G.B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958).

17) The solvent used was 0.1N HCl (pH 1)—95% aqueous EtOH (95:5, v/v).

18) Measured in 0.005M phosphate buffer (pH 7)–95% aqueous EtOH (95:5, v/v).

19) Determined in 0.1N NaOH (pH 13)–95% aqueous EtOH (95:5, v/v).

Continuation of elution of the column as described above yielded brownish prisms (0.70 g) as a third fraction. Recrystallizations from EtOH afforded N-benzyloxyadenine (Vb) as slightly brownish prisms, mp 86—89° (decomp.)(sintered at *ca.* 70°). The IR spectrum of this sample was virtually identical with that of an authentic specimen prepared as described below. Identification was further established by converting the free base (Vb) into the corresponding hydrochloride and picrate.

N-Benzyloxyadenine (Vb)——i) Cyclization of IIb: A suspension of IIb (2.59 g, 0.01 mole) in H_2O (60 ml) was heated at reflux for 11 hr. The resulting mixture was evaporated *in vacuo* to dryness, and the residue was purified by column chromatography [silica gel (115 g), $CHCl_3$–EtOH (8:1,v/v)]. The eluate which contained Vb was evaporated *in vacuo* to dryness to leave a partially crystallized oil. The oil was triturated with AcOEt (15 ml), and insoluble crystals were filtered, washed with AcOEt (10 ml), and dried to give Vb (2.10 g). Recrystallizations from EtOH furnished a pure sample as almost colorless prisms, mp 87—90° (decomp.) (sintered at *ca.* 70°), which were dried over P_2O_5 at 50° and 2 mmHg for 18 hr. *Anal.* Calcd. for $C_{12}H_{11}ON_5 \cdot C_2H_5OH$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.85; H, 5.91; N, 24.40. This sample was identical (by UV and IR spectra) with the one synthesized by method-(ii). Identity was further confirmed by converting a portion of the free base (Vb) into the corresponding hydrochloride or picrate.

ii) Reaction of VI with Benzyloxyamine: A mixture of VI[14] (2.01 g, 13 mmoles) and benzyloxyamine[15] (29.8 g, 242 mmoles) in 1-butanol (215 ml) was stirred at 65—70° for 15 hr. The resulting solution was evaporated *in vacuo* to dryness to leave an oil. The oil was triturated with ether (200 ml), and the precipitates that resulted were filtered, washed successively with ether (60 ml) and H_2O (50 ml), and dried to yield Vb (2.62 g). Recrystallizations from EtOH and drying over P_2O_5 at 50° and 2 mmHg for 18 hr gave an analytical sample as colorless prisms, mp 87—90° (decomp.) (sintered at *ca.* 70°), which were found to contain EtOH of crystallization; UV $\lambda_{max}^{95\%aq\cdot EtOH}$: 273 mμ (ε 14500); $\lambda_{max}^{H_2O}$ (pH 1) 277 (13600); $\lambda_{max}^{H_2O}$ (pH 7)[13] 272 (14800); $\lambda_{max}^{H_2O}$ (pH 13) 277 (15800); NMR (DMSO-d_6) τ: 8.92 (triplet, CH_3CH_2OH), 6.55 (quartet, CH_3CH_2OH), 5.68 (broad, CH_3CH_2OH), 4.98 (singlet, $C_6H_5CH_2$), 2.67 (multiplet, C_6H_5), 2.44 and 2.26 (purine protons), −1.09 and −2.75 (NH's). *Anal.* Calcd. for $C_{12}H_{11}ON_5 \cdot C_2H_5OH$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.49; H, 5.96; N, 24.37.

The hydrochloride of Vb was prepared from the crude free base (1.00 g) by dissolving it in EtOH (5 ml) and adding 6% (w/v) ethanolic HCl (5 ml). To the mixture was added ether (80 ml) to separate slightly brownish needles (1.10 g). Recrystallizations from EtOH and drying over P_2O_5 at 80° and 2 mmHg for 21 hr furnished an analytical sample as faintly yellowish needles, mp 172—175° (decomp.) (sintered at 168°); UV $\lambda_{max}^{95\%aq\cdot EtOH}$: 273 mμ (ε 14700); $\lambda_{max}^{H_2O}$ (pH 1) 277 (14200); $\lambda_{max}^{H_2O}$ (pH 7)[13] 272 (15000); $\lambda_{max}^{H_2O}$ (pH 13) 277 (15600); NMR (DMSO-d_6) τ: 4.87 (2H, $C_6H_5CH_2$), 2.57 (5H, C_6H_5), 1.94 and 1.07 (1H each, purine protons), −2.88 (3H, NH's and N^+-H). *Anal.* Calcd. for $C_{12}H_{12}ON_5Cl$: C, 51.90; H, 4.36; N, 25.22. Found: C, 51.73; H, 4.48; N, 25.09.

The picrate of Vb was prepared from a portion (200 mg) of the crude free base by dissolving it in EtOH (1 ml) and adding a saturated solution (10 ml) of picric acid in EtOH. Recrystallizations from EtOH produced yellow prisms, mp 209° (decomp.). For analysis they were dried over P_2O_5 at 80° and 2 mmHg for 18 hr. *Anal.* Calcd. for $C_{18}H_{14}O_8N_8 \cdot C_2H_5OH$: C, 46.51; H, 3.90; N, 21.70. Found: C, 46.36; H, 3.94; N, 21.46.

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