A Novel Synthesis of Eritadenine:† Reactions of Some Purines with γ-Lactones

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Summary Reactions of several purines with 2,3-*O*-protected D-erythronolactone provide a simple route to the synthesis of eritadenine (VI).

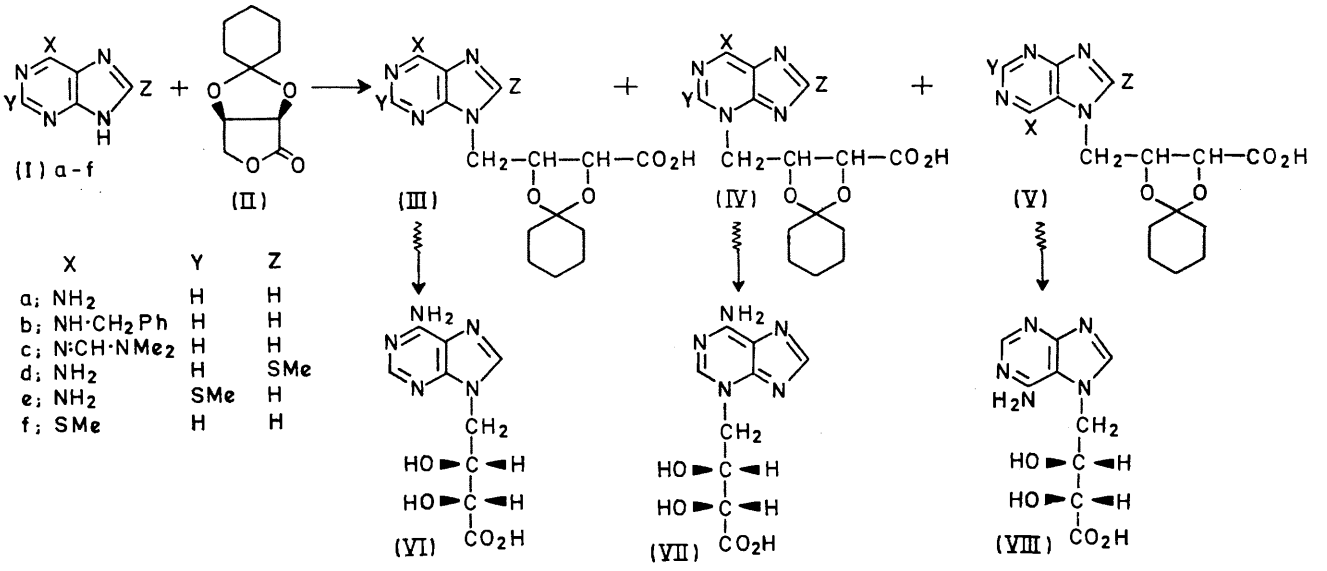
RECENT papers[1-3] have reported the isolation, structural elucidation, and total synthesis of a new hypocholesterolaemic substance, eritadenine (VI), isolated from *Lentinus edodes* Sing.

The need for a convenient preparation of (VI) prompted us to develop our synthetic work further. The reaction of the sodium salt of adenine (Ia) with the lactone (II) at 140—145° in dimethylformamide afforded (IIIa),‡ m.p. 231—232° (dec.), λ_{max} (pH 12·35) 262 (ε 15,700), λ_{max} (pH 1·52) 259·5 nm (ε 15,300), $[\alpha]_D^{25}$ +97·8° (*c* 1, 0·1N-NaOH), as a major product, and a minor product, "3-isoeritadenine" (VII), m.p. 297—299° (dec.), λ_{max} (pH 12·30) 276 (ε 14,000),

† The two trivial names "lentinacin"[1] and "lentysine"[2] have been abandoned; both groups of workers have agreed to use the name "eritadenine" for this compound.

‡ Satisfactory elemental analyses were obtained for each new compound and the spectral data for all compounds were in accord with the structural assignments made.

λ_{max} (pH 1·36) 276 nm (ϵ 19,700), $[\alpha]_D^{25}$ +86·7° (*c* 1, 0·1N-NaOH), was also obtained from the acid hydrolysate of the crude product. This result encouraged us to investigate further the reactions of the lactone (II) with other substituted purines (Ib—f) that would be convertible into adenine. These reactions were carried out under similar conditions to those described above and the results are shown in the Table.



Product composition in the reactions of the purines (Ia—f) *with the lactone* (II)

Expt. No.	Purine	Product ratio 9-Isomer	3-Isomer	7-Isomer	Total yield %
1.	(Ia)	100	9[a]	—	44·2
2.	(Ib)	100	34	—	31·2
3.	(Ic)	100[b]	—	184	36·5
4.	(Id)[c]	100	103	—	26·8
5.	(Ie)	100	trace[a]	—	52·0
6.	(If)[c]	100	—	9	67·3

[a] Determined by u.v.-spectrometric analysis of the mixture obtained from the hydrolysate of the crude product.
[b] As the intermediate (IIIc) could not be isolated owing to the instability of the N^6-protecting group, the value was estimated from the amount of the final product (VI).
[c] Determined by n.m.r.-spectrometric analysis of the mixture.

The 9-substituted compound is not always obtained as the predominant product from the direct alkylation[4-8] of adenine in the presence of alkali. However, in the case of (Ia) and (Ib) substitution at N^9 of the purine was the preferred reaction. The 7-substituted product (Vc), m.p. 211—213° (dec.), λ_{max} (pH 12·30) 316 (ϵ 28,100), λ_{max} (pH 1·36) 332 nm (ϵ 38,100) $[\alpha]_D^{25}$ +150·1° (*c* 1, 0·1N-NaOH), was a major product in experiment 3. On hydrolysis, it gave "7-isoeritadenine" (VIII), m.p. 278—279° (dec.), λ_{max} (pH 12·30) 272·5 (ϵ 10,400), λ_{max} (pH 1·36) 274 nm (ϵ 13,400), $[\alpha]_D^{20}$ +59·1° (*c* 1, 0·1N-NaOH), in high yield.

It would be interesting to utilize the purine (Ic), m.p. 252—255°, λ_{max} (pH 12·63) 308 (ϵ 23,900), λ_{max} (pH 1·65) 324 nm (ϵ 21,700), as a starting material in the preparation of 7-glycosyladenine.

The high yield of the 3-substituted product (IVd), m.p. 215—218° (dec.), λ_{max} (pH 12·30) 308 (ϵ 25,800), λ_{max} (pH 1·36) 303 nm (ϵ 25,800), $[\alpha]_D^{25}$ +145·0° (*c* 1, 0·1N-NaOH), in experiment 4 and the low yield of the corresponding product (IVe) in experiment 5 are attributable to steric hindrance by the SMe groups at C-2 or C-8 of the purine (Id or Ie). Each product obtained in the reaction was converted into the corresponding isomeric eritadenine by reduction or reductive desulphurization or aminolysis, and by subsequent hydrolysis.

The protecting group of the lactone (II) was replaced by cyclopentylidene- and isopropylidene-acetal groups in the expectation that the reactivity on the γ-carbon would be enhanced. As expected, the reactivity of 2,3-*O*-cyclopentylidene-D-erythronolactone was the highest of those studied in the reaction with adenine under mild conditions (100°).

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[1] I. Chibata, K. Okumura, S. Takeyama, and K. Kotera, *Experientia*, 1969, **25**, 1237.
[2] T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Tetrahedron Letters*, 1969, 4729.
[3] M. Hashimoto, Y. Saito, H. Seki, and T. Kamiya, *Tetrahedron Letters*, 1970, 1359.
[4] N. J. Leonard and T. Fujii, *J. Amer. Chem. Soc.*, 1963, **85**, 3719.
[5] N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, 1962, **84**, 2148.
[6] L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, 1964, **86**, 5320.
[7] B. C. Pal, *Biochemistry*, 1962, **1**, 558.
[8] J. A. Montgomery and H. J. Thomas, *J. Heterocyclic Chem.*, 1964, **1**, 115.