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A NOVEL METHOD FOR THE SYNTHESIS OF PURINE α-RIBONUCLEOSIDES

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Syntheses of purine nucleosides have generally been carried out by the coupling of purine bases with sugars whose hydroxyl groups are substituted with suitable protecting groups (1). Recently a direct synthesis of nucleosides have been published and have attracted attention in which D-ribose or D-deoxyribose was heated as such with adenine in the presence of polyphosphoric ester (2,3). The method, however, has disadvantages that the yields are generally low and that the formation of isomeric nucleosides is inevitable (3,4). For the improvement of the direct method we tried to apply Bonner and coworkers' method of O-glucosylation (5) for the synthesis of purine nucleosides by the use of the boron trichloride complex of methyl D-ribofuranoside (I).

The complex (2 mmoles), prepared according to the Bonner and coworkers' procedure, was refluxed with N^6-octanoyladenine (1.6 mmoles) (6) in chloroform (20 ml) for 3 hr, and the product deacylated with sodium methoxide. Paper electrophoresis (PE, 0.05 M borate, pH 9.2) of the reaction mixture showed that a nucleosidic product having a similar mobility to that of adenosine was formed in 36% yield. The nucleoside showed a positive test for the periodate-benzidine reagent. The UV absorption spectra were identical with those of adenosine.

Addition of pyridine (3.7 mmoles), an acid acceptor, to the reaction raised the yield of the nucleoside to 55% as determined by PE. The reaction product was applied on a column of Dowex-1 (OH^-). Elution with 0.01 M

ammonium chloride-ammonium hydroxide (pH 10.5) and subsequent desalting with charcoal gave a crude nucleoside, whose NMR spectrum indicated that the nucleoside was virtually pure α-adenosine and free from other possible isomers. For further purification the product was precipitated from a methanol solution by the addition of ethyl ether to afford α-adenosine* (II) as an amorphous powder (49% yield). Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot 2H_2O$: C, 39.65; H, 5.65; N, 23.10. Found: C, 39.44; H, 5.86; N, 23.20. UV mμ: $\lambda_{max}^{pH\ 2}$ 257, $\lambda_{max}^{pH\ 6}$ 259. $[\alpha]_D^{24}$ +17.8° (c=0.65, H_2O) [lit. (7) $[\alpha]_D$ +24° (c=0.65, H_2O)]. NMR (D_2O) δ: 6.30 (doublet, J=4.5 cps, $H_{1'}$) [lit. (8) δ 6.38, J=4.5 cps]. Picrate: mp 195-200° (decomp.). [lit. (7) mp 190° (decomp.)]. Anal. Calcd. for $C_{16}H_{16}N_8O_{11}$: C, 38.72; H, 3.25; N, 22.58. Found: C, 38.46; H, 3.24; N, 22.44.

N^2-Palmitoylguanine (5 mmoles) (6) was allowed to react with the boron trichloride complex of I (10 mmoles) under the conditions as described above. PE of the reaction mixture showed two UV absorbing spots having M_{GR}** = 1.0 (22% yield) and 1.3*** (5% yield). These two spots were detected by periodate-benzidine reagent. The former spot (M_{GR} = 1.0) possessed the same UV absorption spectra as those of guanosine. The reaction mixture, after removal of guanine by precipitation, was applied on a column of Dowex-1 (borate). The column was eluted with 0.06 M potassium chloride-0.04 M sodium borate and the eluate desalted by charcoal treatment to afford α-guanosine* (III) as an amorphous powder (15% yield). M_{GR} = 1.0. Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.88; H, 5.05; N, 23.24. Found: C, 39.84; H, 5.19; N, 22.90. UV mμ: $\lambda_{max}^{pH\ 1}$ 255, $\lambda_{max}^{pH\ 6}$ 252. $[\alpha]_D^{23}$ +20.5° (c=1.0, 0.1N NaOH). NMR (D_2O) δ: 6.22 (doublet, J=4.5 cps, $H_{1'}$).

6-Benzylthiopurine (13.4 mmoles) (9) and the boron trichloride complex

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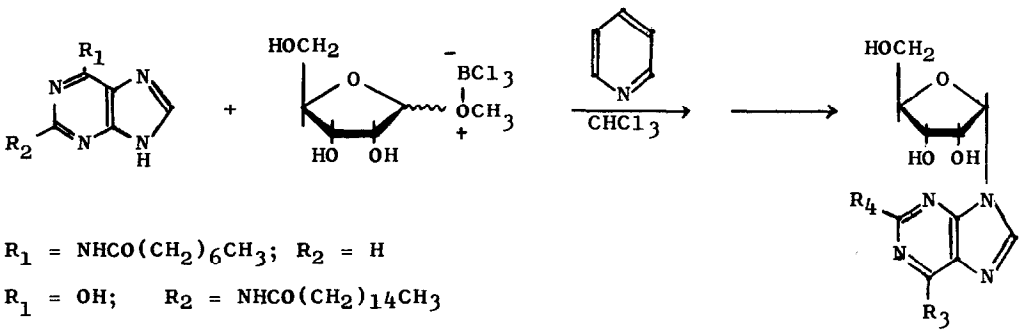
* The selective phosphorylation at 5'-hydroxyl group of II and III with pyrophosphoryl chloride gave α-adenosine- and α-guanosine-5'-phosphate, respectively (K. Imai, S. Fujii, K. Takanohashi, Y. Furukawa, T. Masuda and M. Honjo, Biochemistry, in contribution).

** M_{GR} = mobility ratio, sample/guanosine, M_{6MPR} = mobility ratio, sample/6-thiopurine riboside.

*** The structure of this substance was not clarified.

of I (17 mmoles) were refluxed in chloroform (120 ml) in the presence of pyridine (30 mmoles) for 2 hr. The reaction mixture was poured into an aqueous sodium bicarbonate solution. The aqueous layer was desalted by charcoal treatment. Concentration of the solvent and crystallization from 20% ethanol afforded 9-α-D-ribofuranosyl-6-benzylthiopurine (IV) as colorless needles, mp 168° (52% yield). Anal. Calcd. for $C_{17}H_{18}N_4O_4S \cdot H_2O$: C, 52.10; H, 5.13; N, 14.26; S, 8.16. Found: C, 52.11; H, 5.11; N, 13.89; S, 8.09. UV mμ (ε): $\lambda_{max}^{pH\ 1}$ 295 (16.9 x 10^3), $\lambda_{max}^{pH\ 5}$ 292 (22.4 x 10^3). $[\alpha]_D^{22}$ +54.0 (c=1.0, EtOH). NMR (d_6-DMSO) δ : 6.44 (doublet, J=4.6 cps, $H_{1'}$). Investigation of the mother liquor by NMR spectrum measurement indicated the absence of other possible isomers. Compound IV was treated with sodium in liquid ammonia and applied on a column of cellulose powder. The column was eluted with n-butanol-water (86:14 v/v) to give two ultraviolet absorbing fractions. Evaporation of the second fraction followed by precipitation from methanol-acetone gave 9-α-D-ribofuranosyl-6-thiopurine (V) as an amorphous powder (53% yield). PE: M_{6MPR}^{**} = 1.0, paper chromatography (n-butanol-water, 86:14): Rf 0.18. Anal. Calcd. for $C_{10}H_{12}N_4O_4S \cdot \frac{1}{2}\ CH_3OH$: C, 42.00; H, 4.70; N, 18.65; S, 10.69. Found: C, 42.34; H, 4.84; N, 18.35; S, 10.95. UV mμ: $\lambda_{max}^{pH\ 5}$ 322, $\lambda_{max}^{pH\ 13}$ 310. $[\alpha]_D^{22}$ +50.7° (c=1.0, 0.1N NaOH).



R_1 = $NHCO(CH_2)_6CH_3$; R_2 = H

R_1 = OH; R_2 = $NHCO(CH_2)_{14}CH_3$

R_1 = $SCH_2C_6H_5$; R_2 = H

II, R_3 = NH_2; R_4=H

III, R_3 = OH; R_4=NH_2

V, R_3 = SH; R_4=H

Chart 1.

As is evident in the above described experiments, the present synthetic method of purine α-ribonucleosides has some advantages over the known methods (7,8,10) in that i) methyl D-ribofuranoside (I) can be obtained in a single

step from D-ribose, ii) there is no need of protecting the hydroxyl groups, and iii) purine α-ribonucleosides can selectively be synthesized in fairely good yields.

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References

1. A M. Michelson, The Chemistry of Nucleosides and Nucleotides, p.51. Academic Press, London and New York (1963).
2. G. Shramm, H. Grötsch and W. Pollmann, Angew. Chem. 74, 53 (1962).
3. G. Shramm, G. Lünzmann and F. Bechmann, Biochim. Biophys. Acta 145, 221 (1967).
4. J. A. Carbon, Chemistry and Industry 529 (1963).
5. T. G. Bonner, E. J. Bourne and S. McNally, J. Chem. Soc. 761 (1962).
6. Y. Furukawa and M. Honjo, Chem. Pharm. Bull. (Tokyo), 16, 1076 (1968).
7. R. S. Wright, G. M. Tener and H. G. Khorana, J. Am. Chem. Soc. 80, 2004 (1958).
8. K. Onodera, S. Hirano and B. Masuda, Abstracts of Papers, Annual Meeting of the Agricultural Chemical Society of Japan, p.237 (1966).
9. T. P. Johnston, L. B. Holum and J. A. Montgomery, J. Am. Chem. Soc. 80, 6265 (1958).
10. B. Shimizu, M. Asai and T. Nishimura, Chem. Pharm. Bull. (Tokyo) 15, 1847 (1967).