Tetrahedron Letters No.35, pp. 3095-3102, 1965. Pergamon Press Ltd.
Printed in Great Britain.

A NEW CATALYST FOR THE SYNTHESIS OF NUCLEOSIDES
(ORGANOPHOSPHORUS COMPOUNDS, PART VI)

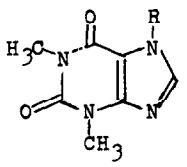
Takeshi Hashizume and Hajime Iwamura
Department of Agricultural Chemistry,
Kyoto University, Kyoto, Japan

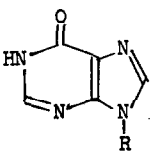
(Received 3 July 1965)

We wish to report that bis-(p-nitrophenyl) hydrogen Phosphate and the methyl derivative act as effective catalysts for the fusion method developed recently for the synthesis of purine nucleosides.[1-5] The method has involved heating fully O-acetylated D-pentoses and hexoses with various purines in the presence of catalysts like p-toluenesulfonic acid,[1] zinc chloride,[2,3] concentrated sulfuric acid,[4] sulfamic acid,[5] and chloroacetic acid.[6]

Recently, we investigated the fusion of penta-O-acetyl-β-D-glucopyranose(I) and two purines(II and III) employing bis-(p-nitrophenyl)hydrogen phosphate(VIII)[7] and the related compounds as catalysts.

Bis-(p-nitrophenyl) hydrogen phosphate was used after drying for thirty minutes at 100° under a pressure 1 mm. Hg.





II. R: H

III. R: H

IV. R: 2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl residue

V. R: 2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl residue

VI. R: β-D-glucopyranosyl residue

VII. R: β-D-glucopyranosyl residue

When theophylline(II) was fused with I in the presence of VIII at 140°-160° for one hour, N^7-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)theophylline(IV) was obtained in 47% yield. m.p. 145°-146°.

Anal. Calcd. for $C_{21}H_{26}O_{11}N_4$: C, 49.41; H, 5.13; N, 10.97.
Found: C, 49.38; H, 5.16; N, 10.95.

Removal of the acetyl groups from IV in methanolic ammonia afforded N^7-(β-D-glucopyranosyl) theophylline(VI) in 75% yield. Recrystallization from aqueous methanol gave colorless needles. m.p. 266°-268°.

Anal. Calcd. for $C_{18}H_{18}O_7N_4$: C, 45.61; H, 5.30; N, 16.37.
Found: C, 45.58; H, 5.29; N, 16.23.

$\lambda_{max.}^{H_2O}$ 275 mμ.(ε 8800), $[\alpha]_D^{19}$ -3.56°(c, 1.49, water).

(Reported: m.p. 267-269°,[8] 272°,[9] $[\alpha]_D$ -2.33°(water),[9] $[\alpha]_D^{19}$ +39.09°(c,0.92,water).[10])

The formation of the glycoside link at position 7 of theophylline was supported by the ultraviolet absorption spectra of the compound VI, N^7-methyltheophylline (caffeine, $\lambda_{max.}^{pH\ 5}$ 273 mμ.), and N^9-methyltheophylline (isocaffeine, $\lambda_{max.}^{pH\ 5}$ 239 and 267 mμ.).[11] The anomeric configuration was assigned as β- from the coupling constant for the C_1, proton of glucose (FIG. I., $J_{1',2'}$=8.7-8.8 c.p.s.).[12,13] The infrared spectra of the compound VI and N^7-(β-D-glucopyranosyl)theophylline synthesized according to the Fischer-Helferich procedure[9] were superimposable. Further, the optical rotatory dispersion curve was negative plain as shown in FIG.II.[14]

Similarly, the fusion of II with I employing bis-(p-nitrophenyl) methylphosphate(IX) instead of VIII afforded IV in 31% yield, whereas the desired product(IV) could not be obtained when tris-(p-nitrophenyl) phosphate was used and unreacted theophylline was recovered almost quantitatively.

For the comparison of the catalytic effects of these organophosphorus compounds with that of previously known catalysts, p-toluenesulfonic acid and ethyl polyphosphate were used in similar manner described above.[15,16,17] But the yield of IV were 20% employing p-toluenesulfonic acid and 31% when ethyl polyphosphate was used. Moreover, earlier paper reported a few percent yield in the synthesis of IV using zinc chloride.[3] Thus, it is apparent that the catalytic effect of bis-(p-nitrophenyl) hydrogen phosphate is superior than known catalysts for fusion procedure. Considerable activity of bis-(p-nitrophenyl) methylphosphate may be explained by the demethylation during the fusion.

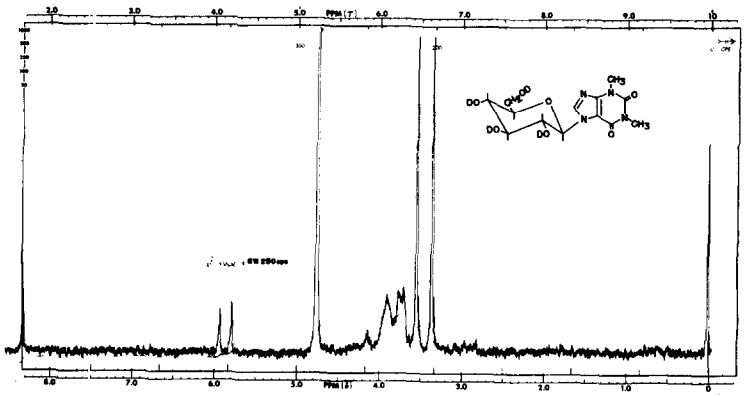


FIG.I. N.m.r. spectrum of VI measured in D_2O.

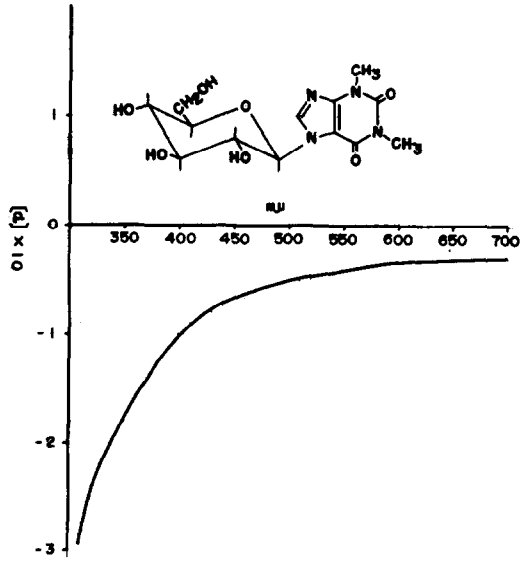


FIG.II. Optical rotatory dispersion curve of VI.

In addition, the fusion of N^1-acetyl hypoxanthine* and I in the presence of **VIII** at 150°-160° for thirty minutes gave N^9-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)hypoxanthine (V) in 13% yield after recrystallization from ethyl acetate. m.p. 276°-277°.

Anal. Calcd. for $C_{19}H_{22}O_{10}N_4$: C, 48.93; H, 4.75; N, 12.01.
Found: C, 48.92; H, 4.85; N, 12.01.

$\lambda_{max.}^{abs.EtOH}$ 244 mμ.(13,300), $[\alpha]_D^{19}$ -26.4°(c, 0.73, chloroform).
(18)
(Reported: m.p. 265-267.5°, $[\alpha]_D^{28}$ -19.2°(c, 3.06, chloroform).

Removal of the acetyl groups from V in methanolic ammonia gave N^9-(β-D-glucopyranosyl) hypoxanthine(VII) in 78% yield. m.p. 272°-273°(from 50% aqueous ethanol).

Anal. Calcd. for $C_{11}H_{14}O_6N_4.H_2O$: C, 41.77; H, 5.10; N, 17.72.
Found: C, 41.70; H, 5.15; N, 17.64.

$\lambda_{max.}^{H_2O}$ 248.5 mμ.(ε 12,600), $\lambda_{max.}^{0.05N-HCl}$ 248.5 mμ.(ε 12,100), $\lambda_{max.}^{0.05N-NaOH}$ 253.5 mμ.(ε 13,700), $[\alpha]_D^{20}$ -38.4°(c, 2.11, N-NaOH).

The allocation of C_1, of glucose to position 9 of hypoxanthine was based on the ultraviolet spectra of the compound obtained, authentic N^9-(VII)**N^7-(β-D-glucopyranosyl) hypoxanthine ($\lambda_{max.}^{0.05N-HCl}$ 254 mμ., $\lambda_{max.}^{0.05N-NaOH}$ 263 mμ.)**N^9-, and N^7-methyl-
(19)
hypoxanthine. The assignment of the β-configuration at C_1, of

---

* This derivative was prepared in refluxing hypoxanthine with acetic anhydride and N,N-dimethylformamide. m.p.238°-240°. The position of the acetyl group linked was inferred from the infrared spectra.

** Kindly given to us by Mr. H. Yamazaki who prepared both N^9-, and N^7-(β-D-glucopyranosyl) hypoxanthine by Davoll-Lowy method.

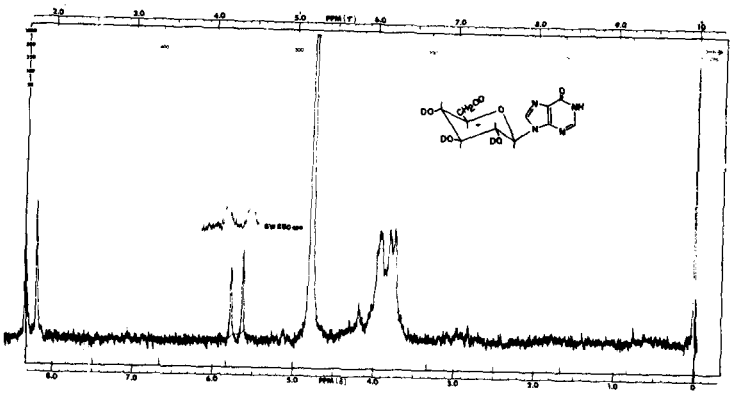


FIG.III. N.m.r.spectrum of VII measured in D_2O.

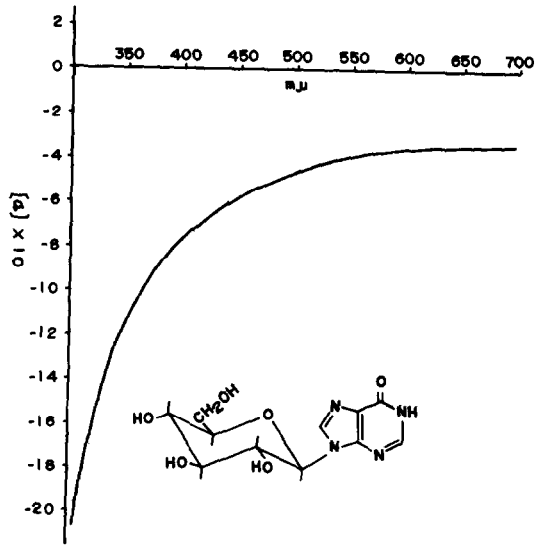


FIG.IV. Optical rotatory dispersion curve of VII.

the compound was based on the coupling constant, $J_{1',2'}$ of the proton at $C_{1'}$ and the equation of Karplus.[20] (FIG.III., $J_{1',2'}$= 8.7-8.8 c.p.s.). Moreover, upon admixture with an authentic specimen, the compound showed no depression of melting point. Further, the optical rotatory dispersion curve is shown in FIG.IV. The o.r.d. curves were measured on a JASCO automatic recording spectropolarimeter and the n.m.r. spectra were recorded on a Varian A-60 spectrometer.

Work with other bases and sugars in this fusion procedure using VIII is in progress and an improved synthesis of nebularine, a nucleoside antibiotics, will be reported independently.

We are grateful to Dr. T. Mitsui for performing the microanalyses and Dr. T. Okuda for measuring the o.r.d. curves.

REFERENCES

(1) T. Simadate, Y. Ishido, and T. Sato, Nippon Kagaku Zasshi, 82, 938(1961).

(2) T. Simadate, ibid., 82, 1268, 1270 (1961).

(3) T. Simadate, ibid., 83, 212 (1962).

(4) Y. Ishido, and T.Sato, Bull. Chem. Soc. Japan, 34, 1347(1961).

(5) Y. Ishido, A. Hosono, S. Isome, A. Maruyama, and T. Sato, ibid., 37, 1389 (1964).

(6) M. J. Robins, W. A. Bowles, and R. K. Robins, J. Amer. Chem. Soc. 86, 1251 (1964).

(7) T. Hashizume and H. Hiro, Japanese Pat. 437,638 (Jan. 18, 1965).

(8) J. M. Gulland, and T. F. Macrae, J. Chem. Soc., 1933, 662.

(9) E. Fischer, and B. Helferich, Ber., 47, 210 (1914).

(10) K. Onodera, and H. Fukumi, Agr. Biol. Chem. 27, 864 (1963).

(11) J. M. Gulland, E. R. Holiday, and T. F. Macrae,
J. Chem. Soc., 1934, 1639.

(12) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and
W. G. Schneider, J. Amer. Chem. Soc., 80,6098(1958).

(13) R. U. Lemieux and J. W. Lown , Can. J. Chem.,41, 889 (1963).

(14) I. Listowsky, G. Avigad,and S. Englard,
J. Amer. Chem. Soc., 87, 1765 (1965).

(15) G. Schramm, Angew. Chem., 74, 53 (1962)

(16) W. Pollmann and G. Schramm, Biochim. Biophys. Acta,
80, 1 (1964).

(17) G. Burkhardt, M. P. Klein, and M. Calvin,
J. Amer. Chem. Soc., 87, 591 (1965).

(18) T. Nishimura and B. Shimizu, Agr. Biol. Chem., 28,224(1964).

(19) J. M. Gulland and E. R. Holiday, J. Chem. Soc., 1936, 765.

(20) M. Karplus, J. Chem. Phys., 30, 11 (1959).