Tetrahedron Letters No.49, pp. 5013-5016, 1967. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS AND CHEMISTRY OF 5-AMINO-5-DEOXYRIBOSE DERIVATIVES. PREPARATION OF MODIFIED NUCLEOSIDES (1 a).

Jean Hildesheim, Janine Cléophax and Stephan D. Géro
Institut de Chimie des Substances Naturelles, C.N.R.S., 91-Gif-sur-Yvette, France.
and R. D. Guthrie
Chemical Laboratory, University of Sussex, Brighton, Great Britain.

(Received in UK 28 June 1967)

Kinetin (6-furfurylaminopurine) and its biological activity were discovered in 1955 by Miller et al. (2a). A large number of structurally related substances have been synthesized and tested for cytokinin activity. Until recently it seemed that the biological activity of these substituted purines was restricted to 6-substituted adenins such as zeatin (2b) 6-(4-hydroxy-3-methylbut-trans-2-enylamino)purine, 6-(γ,γ-dimethylallyl-amino)purine (2c) and (-)-dihydrozeatin (2d). The recent isolation of the corresponding ribosides of zeatin (3) and 6-(γ,γ-dimethylallylamino) purine (4,5) suggest that other 6- and 9- substituted derivatives also could have considerable biochemical interest.

Particularly interesting is the fact that nucleoside 6-(γ,γ-dimethylallyl-amino)-9-β-D-ribofuranosylpurine) (4,5) is found in soluble RNA.

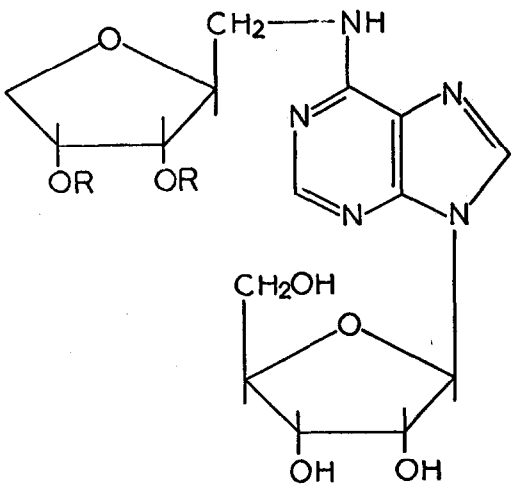
In order to in vestigate further the structural prerequisite for this biological activity, we synthesized two types of modified nucleosides (II,IV).

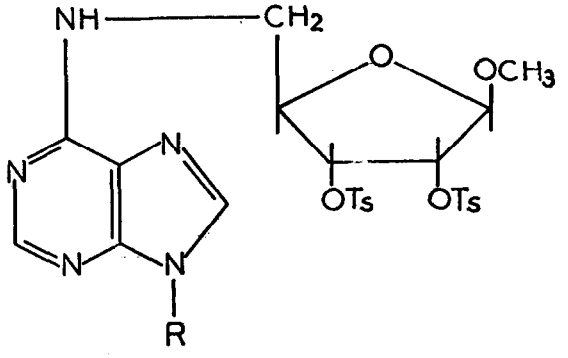
Treatment of 6-chloro-9-β-D-ribofuranosylpurine with 1-amino-2,5-anhydro-1-deoxy-3,4-O-isopropylidene-D-ribitol (6) in butanol in the presence of triethylamine afforded 6-(1'-amino-2', 5'-anhydro-1-deoxy-3', 4'-O-isopropylidene-D-ribitol)-9-β-D-ribofuranosylpurine (I). The latter was not isolated, but was hydrolysed with aqueous acetic acid at 70° over an hour. The nucleoside II was obtained in 55% yield, m.p. 209-210°, $[\alpha]_D$ - 94° (c,0.5; H_2O) ; (found : C, 46.13 ; H, 5.83 ; N, 17.87, $C_{15}H_{21}N_5O_7 \frac{1}{2} H_2O$, requires : C, 45.92 ; H, 5.61 ; N, 17.85). It had R_f 0.39 in butanol-acetic acid-water (4:1:5) ; λ_{max} 214 mμ (ε 9500) and 269 mμ (ε 13100) in water.

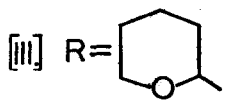
6-(1'-amino-2', 5'-anhydro-1-deoxy-D-ribitol)-9-β-ribofuranosylpurine (II) shows cytokinin activity in the tobacco bioassay. The minimum detectable growth-promoting activity was found at a concentration of 10^{-5}M.

It is interesting to note that 6-(1'-amino-2',5'-anhydro-1'-deoxy-D-ribitol)-purine recently synthesized by us (6), has no detectable growth promoting activity.

The synthesis of the second type of modified nucleoside (IV), required the synthesis of methyl 5-amino-5-deoxy-2,3-di-O-tosyl-3-D-ribofuranoside (VII).







[I] R= $(CH_3)_2C<$

[II] R=H

[IV] R=H

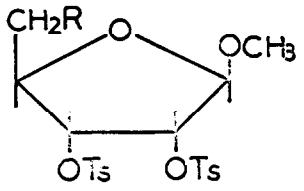
When methyl 2,3,5-tri-O-tosyl-3-D-ribofuranoside (V) (1b) was heated with sodium azide in N,N-dimethylformamide at 120° for 0.5 hour, crystalline methyl 5-azido-5-deoxy-2,3-di-O-tosyl-β-D-ribofuranoside (V) was isolated (90%), m.p. 122-123°, $[\alpha]_D^{28}$ + 80.5° (c, 0.63 ; $CHCl_3$) ; (found : C,48.29 ; H,4.66 ; N, 8.23 ; S, 13.09, $C_{20}H_{23}N_3O_8S_2$; requires: C, 48.29 ; H, 4.62 ; N, 8.45 ; S, 12.87.

Hydrogenation of the azide (V) using Adams catalyst gave the corresponding methyl 5-amino 5-deoxy-2,3-di-O-tosyl-β-D-ribofuranoside (VII). The amine could not be crystallised, but was characterised as its N-2,4-dinitrophenyl derivative (VIII), m.p. 70-72°, $[\alpha]_D^{28}$ + 61.5° (c, 0.65 ; $CHCl_3$) ; (found : C, 49.08 ; H, 4.27 ; N, 6.33 ; S, 9.94, $C_{26}H_{27}N_3O_{12}S_2$; requires C, 48.97 ; H,4.23 ; N, 6.59 ; S, 10.04).

The amine (VII) by treatment with acetic anhydride in methanol was readily converted into its N-acetyl derivative (IX), m.p. 60-62°, $[\alpha]_D^{26}$ + 27° (c, 0.97 ; $CHCl_3$) ; (found : C, 49.60 ; H, 4.75 ; N, 11.37 ; S, 10.84, $C_{22}H_{27}NO_9S_2 . H_2O$; requires: C, 49.41 ; H, 4.81 ; N, 11.53 ; S, 10.54). The infrared spectrum showed strong absorption at 3300 cm^{-1} attributed to NH, strong absorption at 1650 (amide I), 1560 (amide II) owing to N-Ac, and a very

characteristic absorption at 1600 cm^{-1}, due to the O-tosyl groups.

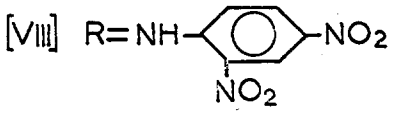
Methyl 5-acetamido-5-deoxy-2,3-di-O-tosyl-β-D-ribofuranoside (IX) provides an excellent opportunity to study the anchimerically assisted 1,3 displacement reactions effected by different nucleophiles.



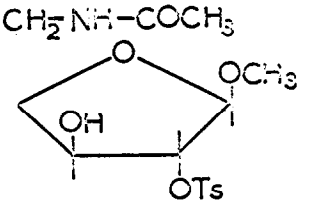
[V] R=OTs

[VI] R=N_3

[VII] R=NH_2



[IX] R=NH-$COCH_3$



[X]

It was anticipated that the acetamido function of (IX), which is trans to the sulphonyloxy group at C-3, in systems such as sodium azide, sodium benzoate, or sodium fluoride in N-N-dimethylformamide might effect the inversion of the configuration at C-3. This 1,3 type of neighbouring acetamido-O-tosyl participation across the furanose ring would then result in the formation of xyloside (X). Such a system with the trans-arrangement of groups at C-2 and C-3, is considered, as one of the most versatile intermediates in synthetic carbohydrate and nucleoside chemistry (7).

When methyl 5-acetamido-5-deoxy-2,3-di-O-tosyl-β-D-ribofuranoside (IX) was heated with sodium azide in N,N-dimethylformamide at 130° for 2 hours, t.l.c. showed the presence of a major product with a low R_f value. There was also some unchanged starting acetamide, and in addition a small amount of an unknown compound, whose R_f value resembled that of the starting acetamide (IX). The infrared spectrum of the crude reactions product, showed strong absorption at 3500 cm^{-1} attributable to OH, and the azido at 2120 cm^{-1}, O-tosyl 1600 cm^{-1}, N-Ac at 1650 cm^{-1} and 1560 cm^{-1} absorptions.

The major component of the reaction product, methyl-5-acetamido-5-deoxy-2-O-tosyl-β-D-xylofuranoside (X) was obtained as fine crystalls (45%), m.p. 106-108°, $[\alpha]_D^{27}$ - 30.7° (c, 0.52 ; $CHCl_3$) (found : C, 50.39 ; H, 6.02 ; N, 3.68 ; S, 8.84, $C_{15}H_{21}NO_7S$; requires : C, 50.13 ; H, 5.89 ; N, 3.90 ; S, 8.91). Similar results have recently been reported for this type of participation (9) and also in O-benzoyl-O-tosyl function (8).

Methyl 5-acetamido-5-deoxy-2-O-tosyl-β-D-xylofuranoside (X) was also obtained as a major product, by treating methyl 5-acetamido-5-deoxy-2,3-di-O-tosyl-β-D-ribofuranoside (IX) with either sodium benzoate or sodium fluoride in N-N, dimethylformamide. The best

yields from the solvolysis of (IX) were obtained using sodium fluoride -N-N-dimethylformamide system.

Treatment of 6-chloro-9-(-tetrahydropyranyl)purine (10) with methyl 5-amino-5-deoxy-2,3-di-O-tosyl-β-D-ribofuranoside (VII) in butanol in the presence of triethylamine gave methyl 5-deoxy-2,3-di-O-tosyl-5-[9-(2-tetrahydropyranyl)purine-6-yl] amino-β-D-ribofuranoside (III). The structure of the condensation product (III) follows from its NMR and mass spectral data. The use of the pyranyl blocking group in such condensation reactions is advantageous, because it confers greater solubility and reactivity on the compound. Considerable difficulties were experienced previously, using 6-chloropurine in similar cases.

The pyranyl group of (III) was removed by mild acid treatment and the modified nucelside (IV) was obtained in 42% yield, m.p. 142-145°, $[\alpha]_D^{29}$ + 17.1 (c, 1.11 ; H_2O) (found : C, 49.60 ; H, 4.75 ; N, 11.37 ; S, 10.87, $C_{25}H_{27}N_5O_8S_2 . H_2O$; requires : C, 49.41; H,4.81; N, 11.53 ; S, 10.54). λ_{max} 230 mμ (ε 16200) and 267 mμ (ε 18200) in water.

REFERENCES

(1) (a) Part VI. Part V,"Displacement on furanoid systems" see J. Cléophax, J. Hildesheim and S. D. Géro, Bull. Soc. Chim. Fr., in press.

(1) (b) J. Hildesheim, J. Cléophax and S. D. Géro, Tetrahedron Letters, 1685 (1967).

(2) (a) C. O. Miller, F. S. Koog, F. S. Okumura, M. H. Von Saltza and F. M. Strong, J. Amer. Chem. Soc., 77, 2662 (1955).

(b) D. S. Letham, J. S. Shannon and I. R. McDonald, Proc. Chem. Soc., 230 (1964).

(c) J. P. Helgeson and N. J. Leonard, Proc. Natl. Acad. Sci. USA, 56, 60 (1966).

(d) K. Koshimizu, T. Kusaki, T. Mitsui and S. Matsubara, Tetrahedron Letters, 1317 (1967).

(3) D. S. Letham, Life Sci., 5, 1999 (1966).

(4) R. H. Hall, M. J. Robins, L. Stasiuk and R. Thedford, J. Amer. Chem. Soc., 88, 2614 (1966).

(5) H. G. Zachau, D. Dütting and H. Feldmann, Angew. Chem., 78, 392 (1966).

(6) J. Cléophax, J. Defaye and S. D. Géro, Bull. Soc. Chim. Fr., 104 (1967).

(7) B. R. Baker and T. L. Hullar, J. Org. Chem., 30, 4053 (1965) and references therein.

(8) G. Schneider and L. K. Lang, Chem. Comm., 13 (1967).

(9) S. Hanessian, J. Org. Chem., 32, 163 (1967).

(10) R. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis and A. Jackson, J. Amer. Chem. Soc., 83, 2574 (1961).

Acknowledgments:

The authors wish to express their sincere gratitude to Professor E. Lederer for the constant encouragement with which he supported this work.

Thanks are due to Dr. H. Felkin for stimulating discussions. Grateful acknowledgment is made to Dr. J. P. Nitsch, Laboratoire du Phytotron, C. N. R. S., Gif/Yvette, for the biological experiments. This work was supported by a research grant from the Délégation Générale à la Recherche Scientifique et Technique, n°61 FR 172.