The Synthesis of 9-(5-Azido- and 5-Amino-5-deoxy-β-D-arabinofuranosyl)adenine

Mason G. Stout and Roland K. Robins

ICN Nucleic Acid Research Institute, 2727 Campus Drive, Irvine, California 92664

Received January 27, 1971

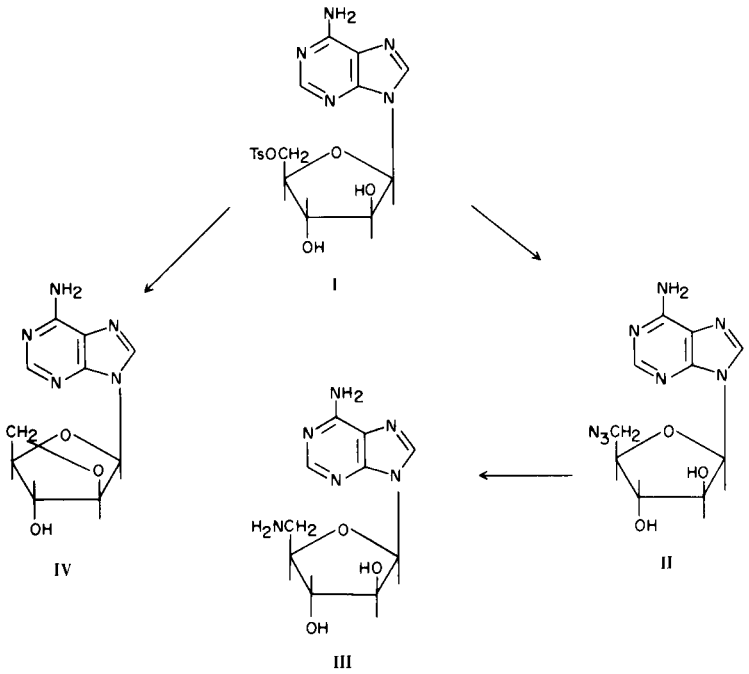
9-β-D-Arabinofuranosyladenine has been shown to exhibit marked antiviral activity (1). The spectrum of activity of 9-β-D-arabinofuranosyladenine includes *in vivo* activity against vaccinia virus (2) and cytomegalovirus (3). 5′-Azido- and 5′-amino-5′-deoxyadenosine have also been shown to exhibit antiviral activity in tissue culture (4). It thus appeared that a combination of the 5′-amino and the arabinosyl features might produce superior antiviral activity. The synthesis of 9-(5-azido-5-deoxy-β-D-arabinofuranosyl)adenine (II) and 9-(5-amino-5-deoxy-β-D-arabinofuranosyl)adenine (III) is the subject of this paper.

The selective tosylation of 9-β-D-arabinofuranosyladenine at the 5′ position was reported during the course of our work by Hubert-Habart and Goodman (5). 9-(5-*O*-Tosyl-β-D-arabinofuranosyl)adenine (I) did not crystallize from the diluted reaction mixture as reported (5) but was obtained by extraction of the aqueous solution with chloroform.

An attempt to synthesize III directly from I using liquid ammonia as had been successful in the preparation of 5′-amino-5′-deoxyadenosine by Schmidt *et al.* (6), produced only 9-(2,5-anhydro-β-D-arabinofuranosyl)adenine (IV). The ease of anhydro formation has previously been noted by Goodman (5). The two competing side reactions of anhydro formation and 5′,N^3-cyclonucleoside formation which is well known for the adenosine series (7) made the choice of reaction conditions for nucleophilic displacement rather narrow. By preheating the reaction medium and then adding the tosyl derivative (I) slowly, a yield of 46% of the desired azide II was achieved. The preparation of III was accomplished by hydrogenation of II in ethanol-water with 5% palladium on charcoal as catalyst.

Neither II nor III showed significant antiviral activity against type 13 Rhino, type 1 Herpes, or type 3 Parainfluenza viruses grown in KB cell culture. Shen (8) has recently noted the synthesis of III by the condensation of

TABLE I



5-phthalamido-2,3-*O*-dibenzylarabinofuranosyl halide with the adenine mercuric chloride complex, although no experimental directions are given. The present work offers a more direct synthesis of III by a relatively simple route.

EXPERIMENTAL

Infrared spectra were determined on a Perkin-Elmer 257 spectrophotometer (potassium bromide), ultraviolet spectra on a Cary 15 spectrophotometer and NMR on a Perkin-Elmer MR-20 using TMS as an internal standard. C, H and N were determined by M. H. W. Laboratories, Garden City, Michigan. The tlc system was 1-propanol-ethylacetate-water (1:4:2) upper phase and alumina plates [Brinkman F 254 (type T)].

9-(5-Azido-5-deoxy-β-D-arabinofuranosyl)adenine (II).

The tosylation of 9-β-D-arabinofuranosyladenine was accomplished essentially as was described by Goodman (5). The reaction mixture was poured onto ice and the cold solution was extracted three times with chloroform, the chloroform extracts were combined, washed with ice-water, dried over sodium sulfate and evaporated to dryness. The resulting solid was coevaporated with ethanol, triturated with a small volume of ethanol, then filtered to give I in 61% yield; the product was homogenous by tlc.

The solution of 0.3 g. (6.1 mmole) of lithium azide in 25 ml. of dry dimethylformamide was heated to 70°. To this stirred solution was added 1 g. (2.4 mmoles) of I in *ca.* 10 portions over 1 hour. The heating and stirring was continued for 15 hours. Tlc indicated the reaction was nearly complete 0.5 hour after the addition of I was finished. The reaction was evaporated to dryness, coevaporated once with an ethanol-toluene mixture and the azide (II) extracted from the residue by five successive treatments with 50 ml. of boiling 2-propanol-ethylacetate (1:4). The cooled extracts contained a slight precipitate which was removed by decantation. The 2-propanol-ethylacetate solution was evaporated and the resulting solid was crystallized from methanol to give 0.32 g. (46%) of II, m.p. 222-223° dec. Recrystallization from methanol provided material which melted at 226-228° dec. Tlc R_f was 0.55. The ir showed a strong band at 2095 cm^{-1}; uv at *p*H 1, λ max 257 mμ (A_m 15.3 x 10^3); *p*H 11, λ max 258 mμ (A_m 15.5 x 10^3). The nmr in DMSO-d_6 was consistent with the structure.

Anal. Calcd. for $C_{10}H_{12}N_8O_4$: C, 41.09; H, 4.14; N, 38.34. Found: C, 40.89; H, 4.19; N, 38.07.

9-(5-Amino-5-deoxy-β-D-arabinofuranosyl)adenine (III).

To a solution of 1.1 g. of II in 60 ml. of ethanol and 20 ml. of water was added 0.7 g. of 5% palladium on carbon and the mixture was then shaken in a hydrogen atmosphere at 34 psi (gauge pressure) and ambient temperature for 18 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness. The resulting solid was crystallized from 7 ml. of hot water to give 0.63 g. (63%) of colorless needles which melted at 232-235° dec. Further crystallization from water gave material which melted at 237-239° dec.; uv at *p*H 1, λ max 257 mμ (A_m 14.8 x 10^3); *p*H 11, λ max 258 mμ (A_m 15.3 x 10^3). The nmr in DMSO-d_6 was consistent with the structure.

Anal. Calcd. for $C_{10}H_{14}N_6O_3$: C, 45.11; H, 5.30; N, 31.57. Found: C, 45.01; H, 5.09; N, 31.86.

Acknowledgment.

The authors would like to thank Dr. Richard L. Tolman for many helpful discussions during the course of the work and for his interpretation of the physical data in the elucidation of the structure of 9-(2,5-anhydro-β-D-arabinofuranosyl)adenine.

REFERENCES

(1) F. M. Schabel, Jr., *Chemother.*, **13**, 321 (1968).

(2) R. W. Sidwell, G. J. Dixon, S. M. Sellers and F. M. Schabel, Jr., *Appl. Microbiol.*, **16**, 370 (1968).

(3) R. W. Sidwell, G. Arnett, G. J. Dixon and F. M. Schabel, Jr., *Proc. Soc. Expl. Biol. Med.*, **131**, 1223 (1969).

(4) A. R. Diwan, R. K. Robins, and W. H. Prusoff, *Experientia*, **25**, 98 (1969).

(5) M. Hubert-Habart and L. Goodman, *Can. J. Chem.*, **48** 1335 (1970).

(6) R. R. Schmidt, V. Schloz and D. Schwille, *Chem. Ber.*, **101**, 590 (1968).

(7) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(8) T. Y. Shen, *Angew. Chem. Intern. Ed. Engl.*, **9**, 678 (1970).