Synthesis of 7-(5′-Benzyloxymethyltetrahydro-2′-furyl)adenine

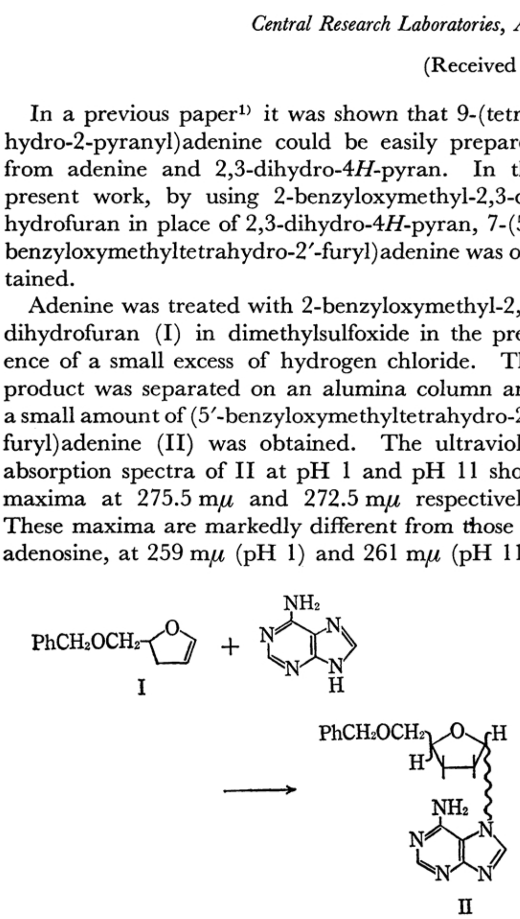
Noriko Nagasawa, Izumi Kumashiro and Tadao Takenishi

Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, Kanagawa

(Received January 23, 1967)

In a previous paper[1] it was shown that 9-(tetrahydro-2-pyranyl)adenine could be easily prepared from adenine and 2,3-dihydro-4*H*-pyran. In the present work, by using 2-benzyloxymethyl-2,3-dihydrofuran in place of 2,3-dihydro-4*H*-pyran, 7-(5′-benzyloxymethyltetrahydro-2′-furyl)adenine was obtained.

Adenine was treated with 2-benzyloxymethyl-2,3-dihydrofuran (I) in dimethylsulfoxide in the presence of a small excess of hydrogen chloride. The product was separated on an alumina column and a small amount of (5′-benzyloxymethyltetrahydro-2′-furyl)adenine (II) was obtained. The ultraviolet absorption spectra of II at pH 1 and pH 11 show maxima at 275.5 mμ and 272.5 mμ respectively. These maxima are markedly different from those of adenosine, at 259 mμ (pH 1) and 261 mμ (pH 11), and of 9-methyladenine, at 260 mμ (pH 1) and 260 mμ (pH 11), but they are similar to those of 3-methyladenine, at 274 mμ (pH 1) and 273 mμ (pH 11), and of 7-methyladenine, at 272 mμ (pH 1) and 270 mμ (pH 11).[2] Leonard and Deyrup provided a general method for distinguishing between 3- and 7-substituted adenines by a comparison of their dissociation constant data.[2] They reported that the p$K_a{}'$ values (in 50% DMF) of 3-substituted adenines were about 5, while those of 7-substituted adenines were about 3. Since the p$K_a{}'$ value of II (in 50% DMF) was 2.9, II is probably 7-(5′-benzyloxymethyltetrahydro-2′-furyl)adenine.



2-Benzyloxymethyl-2,3-dihydrofuran (I) was prepared by the general method shown in Scheme 1. When diethylacetal of 5-benzyloxy-4-hydroxypentanal (IV) was heated with acid, not I, but rather 2-benzyloxymethyl-5-ethoxytetrahydrofuran (VIII′), resulted. The hydrolysis of IV under mild conditions also gave VIII′. VIII′ could not be converted to I by heating it with acid. In order to prevent the formation of VIII′, the acetylated product (V) of the acetal (IV) was hydrolyzed to aldehyde (VI), and then deacetylated with a 10% sodium hydrogen carbonate solution. Since the aldehyde (VII) thus produced readily polymerized under the conditions necessary to complete deacetylation, the yield of the distilled product was low. The distillate was found to be a mixture by the observation of its IR spectrum,

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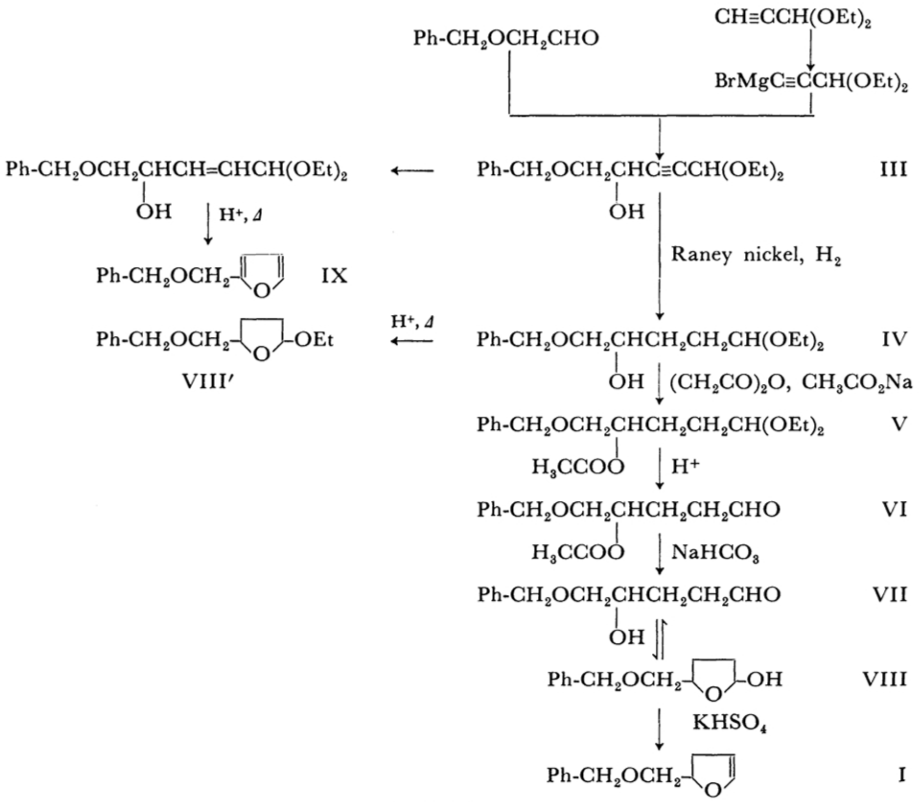
[1] N. Nagasawa, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **31**, 2685 (1966).

[2] N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).



Scheme 1

which showed bands due to $\rangle C{=}C\langle$, –OH, and –CHO groups. The mixture was redistilled over potassium hydrogen sulfate, and, after several redistillations, a small amount of I was obtained.

The NMR spectrum of I was assigned by comparison with that of 2-benzyloxymethylfuran (IX), which was prepared from the diethyl acetal of 5-benzyloxy-2-pentynal (III). Two signals, due to olefinic protons of I, appear at about 5.2 and 3.8 τ. The complicated signals at about 7.5 τ are assigned to the methylene protons of C_3, the signals of which are expected to be of an ABXYZ type. The multiplet of an ABX type at about 6.6 τ is assigned to the methylene group attached to C_2. The signal due to the C_2 proton appears at about 5.5 τ.

Experimental

Benzyloxyacetaldehyde. The diethyl acetal of benzyloxyacetaldehyde was prepared from the diethyl acetal of chloroacetaldehyde[3] and sodium benzyloxide in the usual manner, and was hydrolyzed with 1 N HCl to yield benzyloxyacetaldehyde.

Diethyl Acetal of 5-Benzyloxy-4-hydroxy-2-pentynal (III). An ether solution of ethyl magnesium bromide was prepared from 9 g (0.37 g-atom) of magnesium and 45 g (0.41 mol) of ethyl bromide in 190 m*l* of ether and diluted with 135 m*l* of dry tetrahydrofuran. To the solution 48 g (0.37 mol) of the diethyl acetal of propargyl aldehyde[4–6] in 90 m*l* of ether was added drop by drop, while a gentle refluxing was maintained. Stirring was continued at room temperature for 30 min, after which 48 g (0.32 mol) of benzyloxyacetaldehyde in 90 m*l* of ether was added over 1 hr. The mixture was then stirred at room temperature for one more hr and allowed to stand overnight. A cold, saturated aqueous solution of ammonium chloride was then added to the mixture with stirring. The ether layer was separated, and the water layer was extracted with 200 m*l* of ether. The combined ether extracts were then dried and evaporated. The distillation of the residue under reduced pressure gave 60 g of crude III (68%), bp 151—152°C/10^{-2} mmHg. The IR spectrum shows a band at 2200 cm^{-1} (–C≡C–).

Diethyl Acetal of 5-Benzyloxy-4-hydroxypentanal (IV). Forty-five grams (0.16 mol) of III in 400 m*l* of ethanol were hydrogenated with Raney nickel at room temperature. After the removal of the catalyst, the solution was distilled under reduced pressure to give 43 g of IV (90%), bp 131—132°C/10^{-2} mmHg. The IR spectrum shows no band at about 2200 cm^{-1}.

Found: C, 68.38; H, 9.28%. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28%.

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3) P. Fritsch, *Ann.*, **279**, 300 (1894).

4) J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc.*, **71**, 1437 (1949).

5) J. A. Van Allan, "Organic Syntheses," Vol. 32, p. 5 (1952).

6) E. Fischer and J. Tafel, *Ber.*, **20**, 3389 (1887).

Diethyl Acetal of 5-Benzyloxy-4-acetoxypentanal (V). A solution of 30 g (0.11 mol) of IV and 18 g of sodium acetate in 180 m*l* of acetic anhydride was heated at 90°C a for 4 hr with stirring. The mixture was then poured into ice-cold water and extracted with ether. The extract was washed with a dilute sodium hydrogen carbonate solution and then with water, and dried. Distillation under reduced pressure gave 26 g of V (75%), bp 136—138°C/10^{-1} mmHg. IR spectrum shows no band in the -OH region.

Found: C, 66.47; H, 8.67%. Calcd for $C_{18}H_{28}O_5$: C, 66.68; H, 8.70%.

5-Benzyloxy-4-acetoxypentanal (VI). A mixture of 20 g (0.06 mol) of V and 200 m*l* of 0.1 N hydrochloric acid was refluxed for 1 hr, cooled, and extracted with ether. The ether layer was washed with water, dried, and distilled. 12 g of VI (77%), bp 140°C/5 mmHg, was thus obtained.

Found: C, 66.89; H, 7.36%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

2-Benzyloxymethyl-2,3-dihydrofuran (I). A mixture of 10 g (0.04 mol) of VI and 100 m*l* of a 10% sodium hydrogen carbonate solution was refluxed for 15 hr and then extracted with ether. The ether layer was washed with water, dried, and distilled under reduced pressure. More than a half of the material was undistillable. The distillate was then further redistilled in the presence of a small amount of potassium hydrogen sulfate. Almost all of the distillate boiled at over 140°C/3 mmHg, and its IR spectrum showed no bands due to —OH or $\rangle C{=}C\langle$ groups. Only 1 g of the fraction with a bp of 70—130°C/3 mmHg was obtained. In larger-scale runs of this reaction, the yield of this fraction was even poorer, so the reaction was repeated many times in order to obtain more of this fraction. The combined material was redistilled several times to give I, bp 101°C/5 mmHg. The IR spectrum shows a band at 1620 cm^{-1} due to $\rangle C{=}C\langle$ and no band in the -OH region.

Found: C, 76.05; H, 7.61%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

7-(5′-Benzyloxymethyltetrahydro-2′-furyl)adenine (II). Three grams (0.022 mol) of adenine were dissolved in 30 m*l* of dimethylsulfoxide, along with 5 m*l* of a solution of hydrogen chloride in dioxane (5 N). To the mixture, 4.5 g (0.022 mol) of I was then added, and the solution was kept at 50°C for 16 hr with stirring. The mixture was made alkaline with 2 m*l* of concentrated ammonium hydroxide and concentrated under reduced pressure. The treatment of the residue with acetone deposited the residual adenine. After 2.5 g (0.018 mol) of adenine was separated, the filtrate was applied to an alumina column. The products were eluted with acetone-ethanol (ethanol; 0, 1, 5, 10, 50%). From the fraction of acetone, a yellow oil was obtained, while from the fraction of 1% ethanol/acetone, small amounts of II and adenine were obtained. Recrystallization from ethyl acetate gave 15 mg (0.05 mmol) of II, mp 118—120°C.

$\lambda_{max}^{pH\,1}$ 275.5 mμ, (ε=15900), $\lambda_{max}^{pH\,11}$ 272.5 mμ, (ε=14500), λ_{max}^{EtOH} 267.5 mμ, (ε=17000), 227.5 mμ (shoulder). pK_a' in 50% DMF : 2.9.

Found: C, 62.57; H, 6.37; N, 21.32%. Calcd for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.89; N, 21.53%.

2-Benzyloxymethylfuran (IX). Five grams (0.018 mol) of III were hydrogenated with W_2 Raney nickel in 50 m*l* of ethanol. When one mole of hydrogen had been absorbed, the hydrogenation was stopped. After the separation of the catalyst, the solution was evaporated and then distilled under reduced pressure. The distillate was further redistilled over 2 drops of concentrated phosphoric acid. Redistillation gave 2 g of IX, bp 99°C/3 mmHg. The IR spectrum shows bands characteristic of the furan ring at 1503 cm^{-1} and 885 cm^{-1}. NMR: 2.7_5, 2.8_5, 3.8, 5.6, 5.6_5 τ.

Found: C, 76.22; H, 6.76%. Calcd for $C_{12}H_{12}O_2$: C, 76, 57; H, 6.43%.