was added to **1i** (410 mg, 2.0 mmol) in $CHCl_3$ (5 mL), and the solution was allowed to reflux for 6 h. Workup in the usual way followed by preparative thin-layer chromatography gave pyruvamide **8** (15%) in the first band followed by the mixture of fluorohydrin diastereomers (10%) and finally acetoacetamide **9** (28%): NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.88 (s, 3 H), 2.97 (s, 3 H), 4.84 (s, 1 H), 7.30 (broad s, 5 H).

3-Methyl-4-phenyl-3-pyrazolin-5-one was prepared in the usual way.[4a,b] Preparative TLC, eluting with ethyl acetate, and finally recrystallization from ethanol–water gave the pure pyrazolone, mp 210–211 °C. The mixture melting point with authentic pyrazolone[4a] was not depressed, and the IR spectrum was identical with that of the authentic material.

Rearrangement of 7a. Boron trifluoride etherate (0.25 mL) was added to **7a** (113 mg) in anhydrous methylene chloride (5 mL), and the solution was allowed to reflux for 3 h before quenching with water (5 mL). This was then refluxed for 15 min and worked up in the usual way. Purification by preparative TLC followed by NMR analysis of the separated products indicated the presence of pyruvamide **8** (10% yield), acetoacetamide **9** (4%), and a 55:45 mixture (35%) of fluorohydrin **7a** together with its diastereomer.

Acknowledgment. This research was supported in part by a Research Corporation Frederick Gardner Cottrell Grant. We thank Professors Carl Johnson and Morton Raban of the Chemistry Department at Wayne State University for the use of their 60-MHz NMR facilities.

Registry No.—**1a,** 64754-77-4; **1b,** 64754-78-5; **1c,** 64754-79-6; **1d,** 64754-80-9; **1e,** 64754-81-0; **1f,** 64754-82-1; **1g,** 64754-83-2; **1h,** 64754-84-3; **1i,** 64754-85-4; **2a,** 64754-86-5; **2b,** 64754-87-6; **2c,** 64754-88-7; **2d,** 64761-01-9; **2e,** 64761-02-0; **2f,** 64761-03-1; **2g,** 64761-04-2; **2h,** 64761-05-3; **2i,** 64761-96-4; **3,** 32870-22-7; **4,** 64761-0705; **5a,** 64761-08-6; **5b,** 64761-09-7; **5c,** 64761-10-0; **5d,** 64761-11-1; **5e,** 64761-12-2; **5f,** 64754-59-2; **6,** 64754-60-5; **7a,** 64754-62-7; **7a** isomer, 64754-61-6; **7b,** 64754-64-8; **7c,** 64771-36-4; **8,** 64754-64-9; **9,** 64771-37-5; *N,N*-diphenyl-2-chloroacetamide, 5428-43-3; benzaldehyde, 100-52-7; acetophenone, 98-86-2; *N*-methyl-*N*-phenyl-2-chloropropionamide, 64754-68-3; *N,N*-dimethyl-2-chloroacetamide, 2675-89-0; *N,N*-dimethyl-2-chloropropionamide, 10397-68-9; (*E*)-*N,N*-diphenylcinnamamide, 64754-65-0; boron trifluoride etherate, 109-63-7; *p*-toluenesulfonyl chloride, 98-59-9; *N,N*-diphenylamine, 122-39-4; phenylpropiolyl chloride, 7299-58-3; (*E*)-3,4-dihydro-1,3-dimethyl-3-hydroxy-4-phenyl-2(1*H*)-quinolinone, 64754-66-1; 3-methyl-4-phenyl-3-pyrazolin-5-one, 64754-67-2; *n*-methylaniline, 100-61-8; 2-chloropropionyl chloride, 7623-09-8; hydrazine, 302-01-2.

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New Synthesis of a 9-Substituted Adenine

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A new sequence of reactions, utilizing as the key intermediate 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, has been employed to allow the preparation of a 9-substituted adenine from 4,5,6-triaminopyrimidine. Specifically, 9-(2-chloro-6-fluorobenzyl)adenine was readily prepared, uncontaminated with other positional isomers in a series of mild transformations. The method holds promise as a route to a wide variety of specifically substituted adenine derivatives.

The biological activity of adenine nucleosides and nucleotides[1,2] has prompted vigorous chemical activity directed toward the synthesis of specifically substituted adenine derivatives.[3,4] Specifically, adenine derivatives substituted at position 9 have received considerable attention.[5–8] We describe in this paper a new approach to the synthesis of 9-substituted adenine derivatives which allows the unambiguous introduction of the 9 substituent through a sequence of mild, efficient reactions.

Taylor et al.[8] have reported that 9-substituted adenines (**2**) may be prepared via reductive cleavage and subsequent cyclization of 7-amidofurazano[3,4-*d*]pyrimidines (**1**). Although a wide variety of adenine derivatives was prepared, the authors were unable to effect the conversion of 5-unsubstituted 7-amidofurazano[3,4-*d*]pyrimidines (**1**, R = H) to 2-unsubstituted adenines (**2**, R = H) due to the hydrolytic instability of the former compounds. We wish to report that the highly active coccidiostat 9-(2-chloro-6-fluorobenzyl)adenine[9] (**9**), a derivative possessing a hydrogen in the 2 position, may be readily prepared without isomer contamination (see Scheme I).

Treatment of 4,5,6-triaminopyrimidine (**3**) with thionyl chloride afforded 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (**4**)[10] in 79% yield. Nucleophilic displacement of the 7-amino group[11] of **4** was effected by reaction at 100 °C with 2-chloro-6-fluorobenzylamine (**5**) to provide **6** in 93% yield. Alternatively, **6** could be prepared from **4** in 25% yield by treatment of **4** with ammonia and 2-chloro-6-fluorobenzyl

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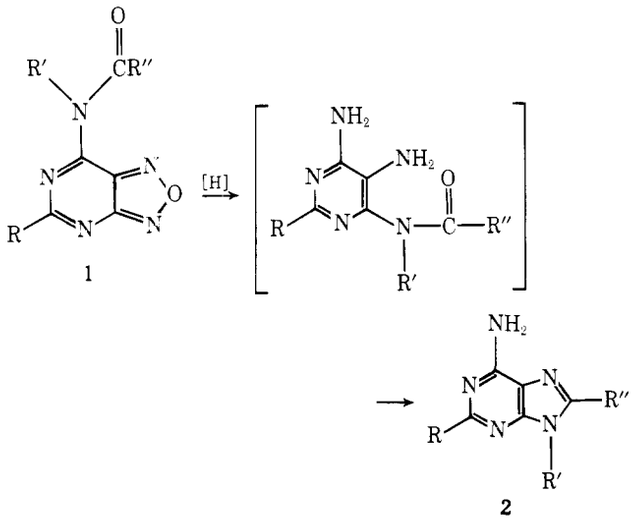
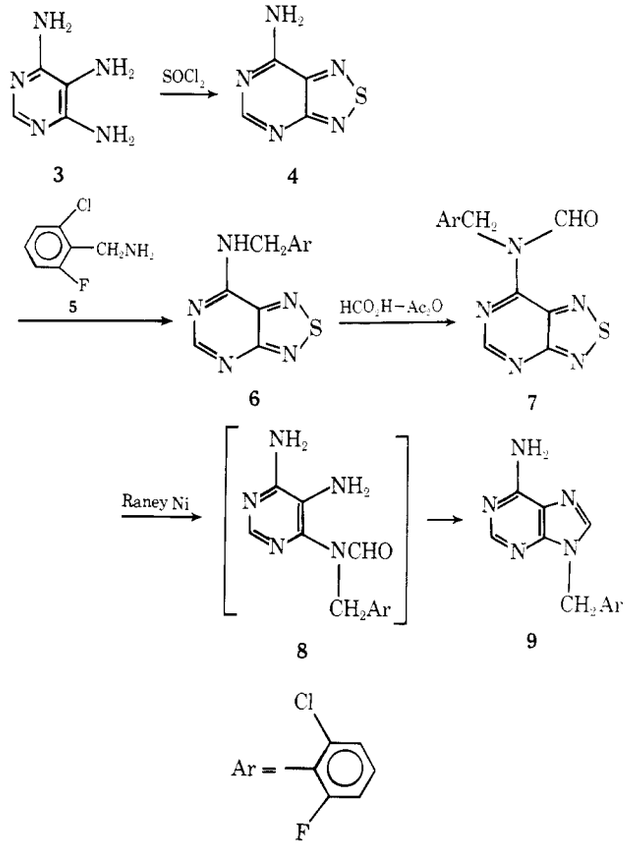


chloride in a sealed vessel at 110 °C. Formylation of **6** was carried out at room temperature with formic acetic anhydride yielding **7** as a stable solid in 91% yield. At this point some difficulty was encountered in the reductive cyclization as some of the better known methods, i.e., zinc–acetic acid, zinc–acetic acid–ethanol, and iron–acetic acid, failed to produce any **9**. However, treatment of **7** in ethanol–water with Raney nickel at room temperature resulted in smooth desulfurization and formation of **9** in 40% yield.[12]

The present method thus constitutes a new, mild route to 9-alkylated adenines which are unsubstituted in the 2 position.

Scheme I



Experimental Section

NMR spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane as internal standard.

7-Amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine[10] (4). A flask was charged with 19.78 g (0.15 mol) of **3** and 163.0 g (137 mol) of thionyl chloride, and the mixture was stirred at reflux for 18 h. The dark orange reaction mixture was then taken to dryness on the rotary evaporator and to the residue were added 500 mL of water and 40 mL of methanol. The pH of the resulting solution was adjusted to 7.5–8.0 with saturated sodium bicarbonate solution and this solution was heated to reflux. The hot mixture was filtered and the filtrate was cooled to 0–5 °C in an ice bath. The solid was collected and washed with 2 × 50 mL of ice water and then 2 × 50 mL of ether. The resulting tan product was dried under vacuum at 70 °C overnight to afford 18.2 g (79%) of **4**: mp 247–249 °C (lit.[10] mp 248 °C); TLC on silica gel (8:1 chloroform–methanol) showed one spot at R_f 0.4.

2-Chloro-6-fluorobenzylamine (5).[13] An autoclave was charged with 89.0 g (0.5 mol) of 2-chloro-6-fluorobenzyl chloride, 170.0 g (10 mol) of ammonia, and 50 mL of benzene. The reaction vessel was sealed and the contents heated at 10 °C for 15 h. The excess ammonia was then carefully evaporated off (nitrogen stream) from the cooled contents of the autoclave. The residue was then washed with water, and the dried ($MgSO_4$) organic phase was fractionated to afford 72.4 g (90%) of **5** as a clear liquid: bp 99–100 °C (20 mm) [lit.[12] bp 94–96 °C (18 mm)]; NMR ($CDCl_3$) δ 1.46 (s, 2 H), 3.88 (d, 2 H), 7.00 (m, 3 H).

7-(2-Chloro-6-fluorobenzyl)amino[1,2,5]thiadiazolo[3,4-*d*]-pyrimidine (6). A flask was charged with 1.54 g (0.01 mol) of **4** and 4.0 g (0.025 mol) of **5**. This suspension was stirred and heated at 105 °C for 18 h. Then, 10 mL of water and 20 mL of hexane were added in one portion, and the resulting solid was collected. The cake was washed with hexane and then dried at 50 °C under vacuum to afford 2.86 g (97%) of the desired product: mp 224–226 °C; TLC on silica gel (8:1 chloroform–methanol) shows a single fluorescent blue spot at R_f 0.8; NMR (Me_2SO-d_6) δ 4.92 (2 H, s), 7.21 (br s, 3 H), 8.44 (s, 1 H), 9.45 (s, 1 H). Anal. Calcd for $C_{11}H_7ClFN_5S$: C, 44.68; H, 2.38; N, 23.68. Found: C, 44.36; H, 2.38; N, 24.24.

Pyrimidine **6** was also prepared from **4** via the following route. An autoclave was charged with 1.54 g (0.01 mol) of **4**, 5.1 g (0.3 mol) of ammonia, and 4.48 g (0.025 mol) of 1-chloro-6-fluorobenzyl chloride. The vessel was then sealed and the contents heated at 110 °C for 15 h. After cooling and evaporation of the excess ammonia, the resulting solid was collected and washed successively with water and hexane to afford a 25% yield of **6**.

7-(*N*-Formyl-*N*-2-chloro-6-fluorobenzyl)amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (7). Formic acetic anhydride was prepared by stirring for 1 h at 0–5 °C a solution of 18.4 g (0.4 mol) of 98% formic acid and 40.8 g (0.4 mol) of acetic anhydride. Then, 40 mL of this solution was added to 2.0 g (0.0067 mol) of **6** and the solution stirred overnight. At this time any insoluble material was filtered off and the filtrate stripped in vacuo at 50 °C. The solid residue was washed with ether and then recrystallized from methanol to afford 2.0 g (91%) of the desired compound: mp 133–135 °C; TLC on silica gel (16:1 chloroform–methanol) showed one spot with R_f 0.8; IR ($CHCl_3$) 1730, 1540, 1120, 940 cm^{-1}; NMR (Me_2SO-d_6) δ 5.55 (s, 2 H), 7.30 (br s, 3 H), 9.11 (s, 1 H), 10.33 (s, 1 H).

9-(2-Chloro-6-fluorobenzyl)adenine (9). A flask was charged with 0.5 g (0.0016 mol) of **7**, 15 mL of ethanol, 15 mL of water, and 7.0 g of Raney nickel. This dark suspension was stirred at room temperature for 2 h, at which time TLC analysis showed that all of **7** had been consumed. The reaction mixture was filtered through Celite and the cake was washed with 200 mL of boiling methanol. The clear filtrate was stripped to afford a white solid which was recrystalized from methanol–water to afford 0.18 g (40%) of the desired adenine derivative: mp 245–246 °C; TLC on silica gel (16:1 chloroform–methanol) gave one spot with R_f 0.4; NMR (acetic acid-d_4) δ 5.70 (2 H, d), 7.35 (3 H, m), 8.15 (1 H, s), 8.43 (1 H, s). Anal. Calcd for $C_{12}H_9ClFN_5$: C, 51.90; H, 3.27; N, 25.22; Cl, 12.77. Found: C, 51.77; H, 3.30; N, 25.43; Cl, 12.49.

Registry No.—**3**, 118-70-7; **4**, 2829-57-4; **5**, 15205-15-9; **6**, 64825-52-1; **7**, 64825-53-2; **9**, 55779-18-5; thionyl chloride, 7719-09-7; 2-chloro-6-fluorobenzyl chloride, 55117-15-2; formic acetic anhydride, 2258-42-6; formic acid, 64-18-6; acetic anhydride, 108-24-7.

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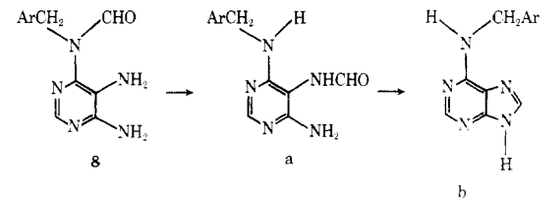

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9-(6-Deoxyhexofuranosyl)adenine Nucleosides. Further Studies on the Acetolysis of Hexofuranosides

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Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside was treated with a 10:1 mixture of acetic acid–acetic anhydride containing 5% sulfuric acid. The crude product was coupled with 6-benzamidochloromercuripurine by the titanium tetrachloride method. Removal of blocking groups and chromatography afforded a mixture of nucleosides which were separated by rechromatographing the mixture on an anion-exchange resin. 9-(6-Deoxy-α-L-talofuranosyl)adenine and 9-(6-deoxy-β-L-galactofuranosyl)adenine were obtained in similar amounts. In a like manner, methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside was subjected to the same reaction sequence. In this case too, a mixture of nucleosides was obtained. Separation of the desired 9-(6-deoxy-α-D-altrofuranosyl)adenine was achieved by selective destruction of the allo nucleoside. This was accomplished by short-term oxidation with periodate, reduction of the aldehyde groups with borohydride, and chromatography on an anion-exchange resin. Unlike previous experiments in which only C-2′, C-3′ trans nucleosides were obtained, the sugar derivatives in the present experiments did not undergo complete epimerization at C-2.

In a previous article,[2] reasons for the preparation of nucleosides derived from 6-deoxyhexofuranoses were mentioned and, over the past few years, papers concerned with this subject matter have appeared from this laboratory.[3-5]

A key reaction in some of the synthetic schemes has been acetolysis of appropriately blocked glycosides. During the reaction, acid-labile groups such as anomeric methoxyls and isopropylidene groups are exchanged for acetyl or acetoxyl groups.[6] However, when the acetolysis reaction is performed with a furanose sugar derivative containing three contiguous hydroxyl groups linked to the ring, epimerization at C-2 often occurs if the hydroxyls at C-2 and C-3 are in a cis relationship.[7-9] The best reaction conditions appeared to be a 10:1 acetic acid–acetic anhydride mixture containing 3–5% sulfuric acid.[5,7-9] The reaction has also been scaled up into a useful synthetic tool for the preparation of novel carbohydrates and nucleosides.[2,5,10-12] In the latter case, a number of hexofuranosyl nucleosides with a trans relationship at the C-2′,C-3′ hydroxyl groups have been prepared from hexofuranosides that originally had these hydroxyls in a cis orientation.[5,11,12] In each case, the only major nucleoside product obtained was the one having the C-2′,C-3′ trans arrangement. It was also necessary that C-5 of the sugar be blocked with a benzoyl group rather than an acetate so that acetate exchange and ring rearrangement to the pyranose form did not occur; otherwise, epimerization was incomplete and a substantial amount of the hexopyranosyl nucleoside of the starting sugar was obtained.[5,10-12] The preparation of some new 9-(6-deoxyhexofuranosyl)adenine nucleosides and some interesting developments with the acetolysis reaction are the subject of this article.

The sugar derivatives needed for the preparation of the nucleosides reported herein were obtained starting from 6-deoxy-L-mannose (L-rhamnose). The synthetic pathway is illustrated in Scheme I for purposes of clarity and was based upon literature methods.[13-15]

Acetolysis of methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-α-L-talofuranoside (**6**) gave a syrup (**7**) which was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method.[16] The blocking groups were removed with sodium methoxide in boiling methanol. Chromatography on an anion-exchange column using Dekker's technique[17] of elution with aqueous methanol gave a product which was shown to be a mixture of at least two nucleosides from the value of the optical rotation and from the rate of consumption of periodate. In the latter case, there was a very rapid initial uptake of periodate corresponding to 50–60% of the total material and then a slow uptake over several days until completion of the oxidation. The mixture was rechromatographed with a more dilute aqueous methanol solution. Two nucleosides separated, both of which were crystallized. The first nucleoside to come off the column was 9-(6-deoxy-α-L-talofuranosyl)adenine (**8**). It had previously been prepared from **6** but had not been obtained in crystalline form.[15] More recently, it was obtained by the reaction of 2′,3′-*O*-isopropylideneadenosine-5′-aldehyde with methylmagnesium iodide and crystallized from ethanol as an hemialcoholate.[18] In the present work, **8** was obtained in an anhydrous, unsolvated form having a melting point considerably higher than that of the hemialcoholate. The optical rotation, rate of periodate consumption, and substrate activity with adenosine deaminase (adenosine aminohydrolase EC 3.5.4.4) verified the identity of **8**.

The second nucleoside eluted from the column was 9-(6-

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