Purine Nucleosides of β-D-Lyxofuranose[1,2]

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Treatment of a mixture (2) of 6-benzamido-9-(3,5-di-O-benzoyl-2-O-methylsulfonyl-β-D-xylofuranosyl)-9H-purine and its 1- (or 6-) N-benzoate with sodium fluoride in N,N-dimethylformamide (DMF) resulted in intramolecular displacement of the sulfonate ester by a neighboring *trans*-O-benzoate to give, after deacylation, 9-(β-D-lyxofuranosyl)adenine (6) with 9-(β-D-xylofuranosyl)adenine (4) and 9-(β-D-arabinofuranosyl)adenine (5) as contaminants. The use of other reagents, such as sodium benzoate in DMF or sodium acetate in DMF gave a higher proportion of *trans* products (4 and 5). The 6-mercaptopurine derivative (16) was prepared from 6 in the usual fashion. Acetal formation from lyxofuranosyladenine (6) and acetone in ethanesulfonic acid or benzaldehyde and zinc chloride gave, in each case, a mixture of 3′,5′-O-acetals (7 and 8) and 2′,3′-O-acetals (9 and 10), with the latter predominating. The two different kinds of acetals could be differentiated by nmr spectroscopy and by their behavior on an ion-exchange resin.

Two analogs of adenosine that contain fraudulent pentofuranose sugars, 9-(β-D-xylofuranosyl)adenine (4)[3] and 9-(β-D-arabinofuranosyl)adenine (5),[4] show interesting antitumor effects.[5] These biological activities illustrate the importance of subtle changes in the sugar moiety; accordingly it was of interest to prepare nucleosides of 9-β-D-lyxofuranose, the last of the series of β-D-pentofuranosyl purines, for biological evaluation.

The direct coupling of a tri-O-acyl-D-lyxofuranosyl derivative with an adenine derivative would be expected to give predominantly the α-nucleoside by consideration of the C_1–C_2 *trans* rule.[6] Accordingly an indirect method was sought which would result in a β-lyxofuranoside.

The use of neighboring-group participation of an O-benzoate has been used to convert L-xylofuranose and L-arabinofuranose into L-ribofuranose derivatives.[7] Such a method was successful for preparation of 9-(β-D-lyxofuranosyl)adenine (6) and is described in this manuscript.

Benzoylation of 9-(2-O-methylsulfonyl-β-D-xylofuranosyl)adenine (1)[3] afforded an amorphous powder whose analysis indicated it to be a mixture of tribenzoate and tetrabenzoate, designated as 2. Treatment of 2 with sodium benzoate in N,N-dimethylformamide (DMF) followed by debenzoylation gave a product which proved to be a mixture of nearly equal quantities of xyloside (4), arabinoside (5), and lyxoside (6) as shown by paper chromatography.[8] Substitution of sodium acetate or sodium bicarbonate in anhydrous or aqueous DMF failed to increase the amount of 6 relative to the *trans* products (4 and 5). (See Scheme I.)

A recent report by Baker and Haines[9] described the use of sodium fluoride in DMF to give effective participation by a neighboring benzoate. Treatment of 2 with sodium fluoride in DMF was, indeed, effective and a 2.5-fold increase of lyxoside (6) was obtained relative to the *trans* products (4 and 5). Table I describes the relative amounts of the nucleosides 4, 5, and 6 obtained under the various reaction conditions.

TABLE I[a]

Reagent[b]	Relative amounts 4	5	6
NaOBz, anhydrous DMF	0.7	0.8	1.0
NaOBz, DMF with 10% H_2O	0.9	1.6	1.0
NaOAc, anhydrous DMF	1.0	1.0	1.0
NaOAc, DMF with 10% H_2O	1.0	1.7	1.0
$NaHCO_3$, anhydrous DMF	3.0	1.0	1.0
$NaHCO_3$, DMF with 10% H_2O	4.2	7.0	1.0
NaF, anhydrous DMF	0.3	0.4	1.0

[a] Reference 8. [b] Typical reaction conditions are described in the Experimental Section for the reaction using NaF in anhydrous DMF.

Ion-exchange chromatography[10] of the nucleoside mixture permitted the isolation of a 55% yield of analytically pure 9-(β-D-lyxofuranosyl)adenine (6) as an amorphous solid.

It is interesting to note that the use of aqueous DMF as a solvent resulted in an increase in the proportion of arabinoside (5) relative to xyloside (4). A logical explanation which could account for this change in the ratio of *trans* products involves the initial hydrolysis of the 3-O-benzoate followed by solvolysis of the *trans*-O-sulfonate with the formation of a 2,3-anhydrolyxoside. This peroxide is known to open almost exclusively at C-3 to give the arabinoside (5).[4] Jeanloz and Jeanloz[11] reported epoxides and materials derived from epoxides as products from solvolytic reactions of pyranoside sugars that contain a *trans*-3-benzoyloxy-2-sulfonate ester system. In a furanose sugar system that is similar to the situation in the sugar portion of 2, Kuzuhara and

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(2) Certain portions of this work have been described previously; see E. J. Reist, D. F. Calkins, and L. Goodman, *Chem. Ind.* (London), 1561 (1965).

(3) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(4) (a) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2648 (1960); (b) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

(5) G. A. LePage and I. G. Junga, *Cancer Res.*, **23**, 739 (1963); J. J. Brink and G. A. LePage, *Can. J. Biochem.*, **43**, 1 (1965); D. B. Ellis and G. A. LePage, *ibid.*, **43**, 617 (1965).

(6) B. R. Baker, CIBA Foundation Symposium, "The Chemistry and Biology of Purines," Little, Brown and Co., Boston, Mass., 1957, pp 120–130.

(7) E. M. Acton, K. J. Ryan, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 5352 (1964).

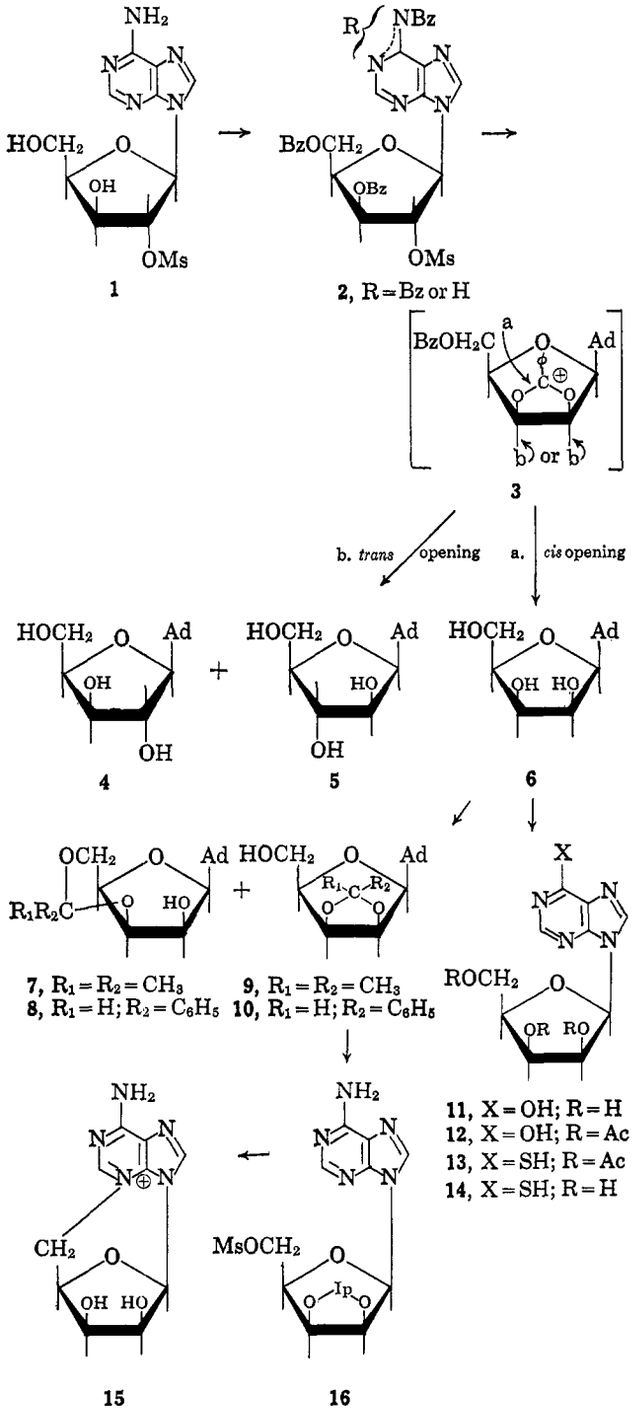
(8) Paper chromatographic analysis of the nucleoside mixture was carried out on Whatman No. 1 paper using 65% aqueous 2-propanol–ethyl acetate (35:65) as the developing agent (night system). The spots were located by visual examination with an ultraviolet lamp. Adenine was the standard for comparison and was arbitrarily assigned a value R_{Ad} 1.00, xylofuranosyladenine (4) had R_{Ad} 0.89, arabinofuranosyladenine (5) had R_{Ad} 0.75, and lyxofuranosyladenine (6) had R_{Ad} 0.40. The intensities of these nucleoside spots were determined by measuring the ultraviolet extinctions on the chromatograms. The extinctions are reported relative to lyxofuranosyl adenine.

(9) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963).

(10) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).

(11) R. W. Jeanloz and D. A. Jeanloz, *ibid.*, **80**, 5692 (1958).

SCHEME I

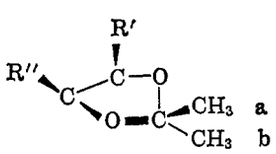


Emoto[12] could correlate the products observed with concurrent reactions *via* an ortho ester ion intermediate and 2,3-anhydro sugar. The solvolysis under anhydrous conditions, where initial hydrolysis should not occur, generally gives equal amounts of xyloside (**4**) and arabinoside (**5**), although one case (sodium bicarbonate in anhydrous DMF) gave more xyloside (**4**). It is possible that small amounts of water were present to account for the amounts of arabinoside (**5**) formed under anhydrous conditions although the results can be reconciled with the intervention of the ortho ester ion (**3**). Attack at a would give, after treatment with water, the lyxoside (**6**) while attack at $C_{2'}$ or $C_{3'}$ by path b would give the xyloside (**4**) and arabinoside (**5**), respectively. This intramolecular displacement of a C-2 sulfonate in DMF differs from that of a C-3′ sulfonate ester where the only product of the participation reaction even under aqueous conditions was the *cis*-diol resulting from the path a type reaction.[7]

The preparation of 9-(β-D-lyxofuranosyl)-9H-purine-6-thiol (**14**) from the adenine lyxoside (**6**) was accomplished in the standard fashion by a nitrous acid deamination of **6** to give **11**, followed by acetylation to **12**, thiation with phosphorus pentasulfide to **13**, then deacetylation to the crystalline thiol **14**.

At this point it was of interest to investigate the chemistry of the sugar portion of the lyxoside (**6**). It can be seen that **6** is theoretically capable of forming two different isopropylidene derivatives—the 3,5-O-isopropylidene derivative (**7**) or the 2,3-O-isopropylidene derivative (**9**). When **6** was treated with acetone and ethane sulfonic acid—conditions used to prepare 9-(3,5-O-isopropylidene-β-D-xylofuranosyl)adenine[13]—a mixture of isopropylidene nucleosides was obtained which could be separated by ion-exchange chromatography.[10] One of the isopropylidene derivatives was eluted with water (in 52% yield) while the other (in 20% yield) required aqueous methanol as the elution solvent. On the basis of this differential exchange on the resin, the derivative eluted by water was assumed to have no free C-2′ hydroxyl; hence it was assigned the 2,3-O-isopropylidene structure (**9**) while the other was given the 3,5-O-isopropylidene assignment (**7**). The nmr spectra of **7** and **9** were in agreement with these assignments.

A recent communication by Brimacombe, *et al.*,[14] describes a correlation of the nmr signals for the methyl protons in isopropylidene groups as a function of their steric environment. Thus, if one considers the upper methyl group of the isopropylidene group in **17** (a-



17

methyl), if R′ = R″ = H, the methyl is classified as α, if R′ = H, R″ = alkyl, the methyl is classified as β; if R′ = R″ = alkyl, the methyl is classified as γ. The α-methyl groups were found to give an nmr peak at higher fields than the β methyls which in turn occurred at higher fields than γ methyls. Such an interpretation could be useful to distinguish between the two isomeric isopropylidene structures **7** and **9**. It can be seen that the 3,5-O-isopropylidene of **7** contains α and β methyls, whereas in the 2,3-O-isopropylidene derivative **9** the methyls are α and γ. Table II contains a summary of the nmr bands of the methyl groups of a number of isopropylidene derivatives of adenine nucleosides along with the distance between them (in τ units). It can be seen that α,γ-*gem*-dimethyl groups appear to be more widely separated than α,β-*gem*-dimethyl groups. On the basis of this difference in separation, the structural assignments for the 2-isopropylidene nucleosides

(12) H. Kuzuhara and S. Emoto, *Agr. Biol. Chem.*, **28**, 900 (1964).

(13) A. Benitez, O. P. Crews, Jr., L. Goodman, and B. R. Baker, *J. Org. Chem.*, **25**, 1946 (1960).

(14) J. S. Brimacombe, M. E. Evans, E. J. Forbes, A. B. Foster, and J. M. Webber, Abstracts of the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 26D.

TABLE II

POSITION OF ISOPROPYLIDENE METHYL IN NMR[a]

Adenine nucleoside of	α	β	γ	Difference
3,5-O-Isopropylidene-β-D-xylofuranose[b]	8.79	8.63		0.16
3,5-O-Isopropylidene-α-D-xylofuranose[c]	8.72	8.63		0.09
3,5-O-Isopropylidene-4-thio-β-D-xylofuranose[d]	8.77	8.64		0.13
2,3-O-Isopropylidene-β-D-ribofuranose	8.68		8.46	0.22
2,3-O-Isopropylidene-4-thio-β-D-ribofuranose[e]	8.67		8.44	0.23
2,3-O-Isopropylidene-β-D-lyxofuranose (9)	8.74		8.53	0.21
3,5-O-Isopropylidene-β-D-lyxofuranose (7)	8.65	8.59		0.06

[a] Expressed in τ units. [b] Reference 13. [c] See W. W. Lee, A. P. Martinez, G. T. Long, and L. Goodman, *Chem. Ind.* (London), 2007 (1963). [d] E. J. Reist, L. V. Fisher, and L. Goodman, unpublished data. [e] E. J. Reist, D. E. Gueffroy, and L. Goodman, unpublished data.

(**7** and **9**) were the same as the assignments made by the ion-exchange chromatographic behavior.

Treatment of the 2,3-O-isopropylidene derivative with methanesulfonyl chloride gave crystalline 9-(2,3-O-isopropylidene-5-O-methylsulfonyl-β-D-lyxofuranosyl)adenine (**16**) in good yield. When efforts were made to deactonate **16** to give 9-(5-O-methylsulfonyl-β-D-lyxofuranosyl)adenine, deacetonation was accompanied by simultaneous cyclization to give what appeared to be the cyclonucleoside (**15**) together with a slight trace of uncyclized material. A periodate titration of this cyclonucleoside showed a rapid uptake of 1 mole of periodate, thus demonstrating the presence of the *cis* glycol of **15**. These latter experiments proved conclusively the position of the isopropylidene group to be at C-2–C-3. In the 3,5-O-isopropylidene derivative (**7**), the resulting methylsulfonate is not in a position for elimination to give a cyclonucleoside. Furthermore, the resulting deacetonated 2-O-methylsulfonate has no *cis* glycol; hence, there would be no periodate uptake.

It is interesting to record that the primary 5′-O-methylsulfonate of **16** has been extraordinarily resistant toward nucleophilic displacement. Neither sodium iodide in acetone 100° nor sodium ethylmercaptide in ethanol was able to effect a displacement of the methylsulfonate. This is not surprising when a molecular model of **16** is examined. In the most likely conformation of the various groups on **16**, the primary carbon at C_5 is sterically very hindered from all directions; hence approach by a nucleophile to displace the methylsulfonate is all but impossible.

When lyxofuranosyl adenine (**6**) was treated with benzaldehyde and zinc chloride, a mixture of 2,3-acetal and 3,5-acetal again resulted. Separation was accomplished using a Dowex 1 (OH) column as in the case of the isopropylidene derivatives, **7** and **9**. Elution with water and 30% aqueous methanol gave 9-(2,3-O-benzylidene-β-D-lyxofuranosyl)adenine (**10**). Further elution with 60% aqueous methanol gave 9-(3,5-O-benzylidene)-β-D-lyxofuranosyl)adenine (**8**). The nmr spectra of **8** and **10** had qualitative similarities to the analogous isopropylidene derivatives, **7** and **9**, that gave additional confirmation of the location of the benzylidene group.

Experimental Section[15]

9-(β-D-Lyxofuranosyl)adenine (6).—A solution of 1.96 g (5.7 mmoles) of 9-(2-O-methylsulfonyl-β-D-xylofuranosyl)adenine (**1**)[3] in 22.3 ml of dry pyridine was cooled to 0° in an ice bath; then 4.05 ml (34.9 mmoles) of benzoyl chloride was added dropwise with stirring and continued cooling. After the addition was complete, the reaction was kept at 0° for 18 hr, then was poured with stirring into 50 ml of ice–water, and was extracted with three 50-ml portions of chloroform. The chloroform layers were washed with saturated aqueous sodium bicarbonate and water, then were dried, and evaporated to dryness *in vacuo*. The last traces of pyridine were removed by the addition and removal *in vacuo* of two 25-ml portions of toluene. The brown oil obtained was put on a column of silica gel (2.2 × 26 cm) and eluted with chloroform. After elution of some benzoic anhydride, the blocked nucleoside (**2**) was eluted. Crystallization from absolute ethanol gave 3.0 g of **2**, mp 97–107°, which probably contained *ca.* 40% tribenzoate according to analytical data and nmr and which was of satisfactory purity for subsequent use.

The nmr spectrum showed the presence of two sets of protons for H_2 and H_8 in the ratio *ca* 3:2. The H'_1 proton occurred as two doublets (J_{12} = 2.5 cps), again in the ratio 3:2.

Anal. Calcd for $C_{36.2}H_{29}N_5O_{9.6}S$ (40% tribenzoate and 60% tetrabenzoate): C, 60.2; H, 4.04; N, 9.72; S, 4.42. Found: C, 59.6; H, 4.16; N, 9.36; S, 3.84.

A mixture of 3.0 g of crude **2** and 3.0 g of sodium fluoride was dried at room temperature at 0.2 mm for 1 hr then was dissolved in 70 ml of freshly dried (over alumina) N,N-dimethylformamide and was heated under a nitrogen atmosphere at 140° for 24 hr (on a larger scale, reaction times up to 120 hr were required to effect complete reaction). The reaction was cooled, then 5 ml of water was added, and the mixture was stirred at 55–60° for 1 hr. The dark suspension was poured into 200 ml of water, then extracted with 200 ml of chloroform. The chloroform layer was washed with water, then dried, and evaporated to dryness to a dark oil. This oil was dissolved in 50 ml of methanol, which had been saturated previously with ammonia at 0°, and kept at room temperature for 18 hr. At the end of this time, the solution was evaporated to dryness *in vacuo* and the residue was partitioned between 50 ml each of chloroform and water. The aqueous phase was evaporated to dryness *in vacuo* to give 1.26 g of a mixture of **4**, **5**, and **6** as a brown oil.

A solution of this mixture in 25 ml of water was applied to a column of Dowex 1 × 2 (OH)[10] (2.2 × 22.5 cm) and the column was eluted with 750 ml of CO_2-free water, 100 ml of methanol–water (10:90), then 500 ml of methanol–water (60:40). Evaporation of the 60% methanol gave 578 mg (55%) of lyxofuranosyl adenine (**6**) as an amorphous solid: $[\alpha]^{21.5}D$ −21° (*c* 0.3, water); $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 14,200); $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 14,900); $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 14,300).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot 0.6H_2O$: C, 43.2; H, 5.10; N, 25.2. Found: C, 42.9; H, 5.27; N, 25.3.

The material was homogeneous on paper chromatography in solvent A and had R_{Ad} 0.70. It consumed 0.975 mole of periodate within 15 min, indicating the presence of a *cis* glycol.[16]

Further elution of the ion-exchange column with methanol–water (60:40) gave an incompletely resolved mixture of 9-(β-D-xylofuranosyl)adenine (**4**) and spongoadenosine (**5**).

9-(2,3,5-Tri-O-acetyl-β-D-lyxofuranosyl)hypoxanthine (12).—To a solution of 840 mg (11 mmoles) of sodium nitrite in 12 ml of water which contained 2.6 ml of glacial acetic acid was added 500

(15) Melting points were determined with the Thomas–Hoover apparatus and are corrected. Optical rotations were determined with the Rudolph photoelectric polarimeter. Thin layer chromatograms were run on silica gel HF (E. Merck A.-G. Darmstadt). Spots were detected by spraying with sulfuric acid, then developing at *ca.* 100° for a few minutes. Paper chromatograms were run by the descending method on Whatman No. 1 paper. The spots were located by visual examination with an ultraviolet lamp. The solvent systems used were A, 1-butanol–acetic acid–water (4:1:5); and B, 1-butanol–water (50:8). Organic solutions were dried over magnesium sulfate. Nmr spectra were run as solutions in dimethyl sulfoxide-d_6 using 5% tetramethylsilane in tetrachloroethane as an external standard. The nmr spectrometer used was the Varian A-60 or HA-100.

(16) J. J. Fox, N. Yung, and A. Bendich, *J. Am. Chem. Soc.*, **79**, 2775 (1957).

mg (1.9 mmoles) of lyxofuranosyladenine (**6**). The solution was stored at room temperature for 24 hr, then evaporated to dryness *in vacuo*. The gummy hypoxanthine lyxoside (**11**) was purified *via* its lead salt in the standard manner[17] to give 500 mg (100%) of **11** as a white foam which was homogeneous on paper chromatography with R_{Ad} 0.55 in solvent A and which was satisfactory for the next step. It showed ultraviolet maxima at 249 (pH 1) and 253 (pH 13).

A solution of 500 mg (1.9 mmoles) of 9-β-D-lyxofuranosylhypoxanthine (**11**) in 45 ml of pyridine and 3.14 ml (33.2 mmoles) of acetic anhydride was kept at room temperature for 3 days, then worked up in the usual fashion to give 745 mg of a yellow gum. Trituration with 20 ml of hot benzene gave 524 mg (70%) of white crystals: mp 210.5–212.0°; $[\alpha]^{22}D$ −53° (*c* 0.51, chloroform); $\lambda_{max}^{pH\ 1}$ 248 mμ (ε 13,700); $\lambda_{max}^{pH\ 7}$ 248 mμ (ε 13,200); $\lambda_{max}^{pH\ 13}$ 253 mμ (ε 14,800).

Anal. Calcd for $C_{16}H_{18}N_4O_8$: C, 48.7; H, 4.60; N, 14.2. Found: C, 48.8; H, 4.65; N, 14.1.

9-(2,3,5-Tri-O-acetyl-β-D-lyxofuranosyl)-9H-purine-6-thiol (13).—A mixture of 1.31 g (3.32 mmoles) of 9-(2,3,5-tri-O-acetyl-β-D-lyxofuranosyl)hypoxanthine (**12**) and 3.5 g (15.7 mmoles) of phosphorus pentasulfide in 135 ml of dry pyridine was stirred at 135° under a nitrogen atmosphere for 22 hr. The brown solution was poured into 1 l. of boiling water. After it had cooled, the aqueous mixture was extracted with three 100-ml portions of chloroform. The chloroform extracts were washed with 25 ml of water, then dried and evaporated to dryness *in vacuo*. The syrupy residue was triturated with 150 ml of toluene to give 729 mg (54%) of white solid (**13**). Two recrystallizations of 300 mg of crude **13** from ethanol gave 184 mg of white solid: mp 206–207.5°; $[\alpha]D$ −63° (*c* 0.53, chloroform); $\lambda_{max}^{pH\ 1}$ 322 mμ (ε 25,600); $\lambda_{max}^{pH\ 7}$ 318 mμ (ε 23,600); $\lambda_{max}^{pH\ 13}$ 310 mμ (ε 24,400).

Anal. Calcd for $C_{16}H_{18}N_4O_7S \cdot 0.25H_2O$: C, 46.0; H, 4.47; N, 13.4; S, 7.68. Found: C, 46.1; H, 4.46; N, 13.7; S, 7.80.

9-(β-D-Lyxofuranosyl)-9H-purine-6-thiol (14).—A solution of 525 mg (1.28 mmoles) of 9-(2,3,5-tri-O-acetyl-β-D-lyxofuranosyl)-9H-purine-6-thiol (**13**) and 87 mg (1.6 mmoles) of sodium methoxide in 45 ml of methanol was stirred under a nitrogen atmosphere for 18 hr. The pale yellow solution was cooled to 0° and acidified with acetic acid. The resulting precipitate was filtered to yield 327 mg (90%) of product as a white powder, mp 220–221° dec. Purification was effected by dissolving in *ca.* 0.05 *M* aqueous ammonia and reprecipitating with acetic acid. The analytical sample had mp 218–221° dec; $[\alpha]^{21.5}D$ −43° (*c* 0.99, 0.1 *N* sodium hydroxide); $\lambda_{max}^{pH\ 1}$ 324 mμ (ε 22,000); $\lambda_{max}^{pH\ 13}$ 310 mμ (ε 23,300).

Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C, 42.2; H, 4.22; N, 19.7; S, 11.3. Found: C, 42.2; H, 4.45; N, 19.6; S, 11.4.

9-(2,3-O-Isopropylidene-β-D-lyxofuranosyl)adenine (9) and 9-(3,5-O-Isopropylidene-β-D-lyxofuranosyl)adenine (7).—A solution of 589 mg (2.2 mmoles) of 9-(β-D-lyxofuranosyl)adenine (**6**) and 0.91 ml (11.0 mmoles) of ethanesulfonic acid in 50 ml of dry acetone was stirred at room temperature for 22 hr, and then it was poured into an ice-cold solution of 1.58 g of sodium bicarbonate in 30 ml of water. The solution was stirred at room temperature for 1 hr and then it was evaporated to dryness *in vacuo*. The white residue was continuously extracted for 18 hr with chloroform. The chloroform extract was evaporated to dryness *in vacuo* to give 0.79 g of crude mixture of **7** and **9**. This material was dissolved in 5 ml of methanol–water (30:70) and applied to a column of Dowex 1 × 2 (OH)[10] (1.4 × 35 cm); it was eluted with water and then with methanol–water (98:2). Evaporation of the water fraction gave 365 mg (52%) of 2,3-acetonide (**9**). Evaporation of the methanol gave 143 mg (20%) of 3,5-acetonide (**7**).

Both fractions were homogeneous on paper chromatography with R_{Ad} values of 1.22 and 1.45, respectively, for **7** and **9** in solvent A and R_{Ad} 1.1 and 1.6, respectively, for **7** and **9** in solvent B.

Recrystallization of **7** from 30 ml of water gave 124 mg of product as white needles: mp 233.5–234.0°; $[\alpha]^{23.5}D$ −55° (*c* 0.5, pyridine); $\lambda_{max}^{pH\ 1}$ 257.5 mμ (ε 14,200); $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 14,000); $\lambda_{max}^{pH\ 13}$ 259 mμ (ε 15,000).

Anal. Calcd for $C_{13}H_{17}N_5O_4 \cdot 0.75H_2O$: C, 48.8; H, 5.81; N, 21.8. Found: C, 48.9; H, 6.00; N, 21.6.

The nmr spectrum of **7** was compatible with the assigned structure and showed, in addition to the two methyl bands of the isopropylidene group mentioned in Table II, other well-resolved bands occurring at τ 1.55 and 1.93 (H_2 and H_8) and 3.83 (doublet, J = 7 cps, H'_1).

Recrystallization of the water eluate from methanol gave 240 mg of 2,3-acetonide (**9**): mp 267.5–268.5°; $[\alpha]^{21}D$ +17.8° (*c* 0.52, pyridine); $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 14,800); $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 14,800); $\lambda_{max}^{pH\ 13}$ 258 mμ (ε 14,900).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.9; H, 5.69; N, 22.8. Found: C, 50.9; H, 5.71; N, 23.0.

The nmr spectrum showed the aromatic protons of H_2 and H_8 at τ 1.80 and 1.88, while H'_1 appeared as a doublet at 3.95 ($J_{1,2}$ = 2.4 cps).

9-(3,5-O-Benzylidene-β-D-lyxofuranosyl)adenine (8) and 9-(2,3-O-Benzylidene-β-D-lyxofuranosyl)adenine (10).—A mixture of 500 mg of 9-(β-D-lyxofuranosyl)adenine (**6**) and 1.4 g of freshly fused zinc chloride in 70 ml of benzaldehyde was stirred at room temperature for 63 hr. The resulting clear yellow solution was poured into 100 ml of diethyl ether, and the resulting precipitate was separated by filtration. It was dissolved in 35 ml of 2-methoxyethanol and stirred with 4.8 ml of 10% aqueous sodium hydroxide for 10 min. The suspension was neutralized to a phenolphthalein end point with carbon dioxide, and the precipitated inorganic salts were removed by filtration. The filtrate was concentrated to 5 ml, then diluted to 25 ml with water. The resulting gummy precipitate, a mixture of **8** and **10** weighing 325 mg, was dissolved in methanol and applied to a Dowex 1 × 2 (OH) column[10] containing 35 g of resin. A total of 121 mg (18%) of 9-(2,3-O-benzylidene-β-D-lyxofuranosyl)adenine (**10**) was eluted with water and methanol–water (30:70). Elution with methanol–water (60:40) yielded 88 mg (13%) of 9-(3,5-O-benzylidene-β-D-lyxofuranosyl)adenine (**8**).

Recrystallization of the water fraction from absolute ethanol gave 75 mg of **10** as white crystals: mp 219–222°; $[\alpha]^{24.5}D$ +118° (*c* 0.5, pyridine); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,700); $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 14,700); $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 15,200).

Anal. Calcd for $C_{17}H_{17}N_5O_4 \cdot 0.75H_2O$: C, 55.4; N, 5.05; N, 19.0. Found: C, 55.4; H, 5.12; N, 19.1.

The nmr spectrum was similar to that of the 2,3-O-isopropylidine derivative (**9**). The aromatic protons at H_2 and H_8 occurred at τ 1.89 and 2.11, while H'_1 appeared as a doublet at τ 3.91 ($J_{1,2}$ = 3 cps). The remaining sugar protons exhibited a pattern similar to that of **9**.

Recrystallization of the fraction eluted with the 60% methanol from absolute ethanol gave 47 mg of **8** as fine white needles: mp 251.5–253.0°; $[\alpha]^{24.5}D$ −86° (*c* 0.51, pyridine); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,750); $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 14,750); $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 15,200).

Anal. Calcd for $C_{17}H_{17}N_5O_4 \cdot 0.75H_2O$: C, 55.4; H, 5.05; N, 19.0. Found: C, 55.5; H, 5.05; N, 19.2.

The nmr spectrum was similar to that of the 3,5-O-isopropylidene derivative (**7**). The aromatic protons at H_2 and H_8 appeared at τ 1.64 and 1.94, while H'_1 appeared as a doublet at τ 3.74 ($J_{1,2}$ = 7.5 cps).

9-(2,3-O-Isopropylidene-5-O-methylsulfonyl-β-D-lyxofuranosyl)adenine (16).—A solution of 152 mg (0.5 mmole) of **9** in 25 ml of dry pyridine was treated with 0.18 ml (2.3 mmoles) of methanesulfonyl chloride at 0° for 41 hr. The reaction was worked up by pouring into water, then extracting with chloroform in the usual fashion. The product obtained (184 mg) was a pale yellow solid. Purification was effected by recrystallization from chloroform–methanol (1:1) to give a total of 137 mg (72%) of white precipitate, mp *ca.* 180°, which was homogeneous on thin layer chromatography with R_f 0.55 in ethyl acetate–methanol (1:1).

The analytical sample had mp 185.5–187.5°; $[\alpha]^{24}D$ +24° (*c* 0.5, pyridine); $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 14,100); $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 14,750); $\lambda_{max}^{pH\ 13}$ 258 mμ (ε 15,100).

Anal. Calcd for $C_{14}H_{19}N_5O_6S$: C, 43.7; H, 4.97; N, 18.2; S, 8.33. Found: C, 43.4; H, 5.24; N, 18.0; S, 8.29.

A solution of 51 mg of the mesylate (**16**) in 10 ml of 90% aqueous acetic acid was heated at 100° for 18 hr and then evaporated to dryness *in vacuo* to a syrup which had $\lambda_{max}^{pH\ 1}$ 270 mμ (ϵ_1^1 355); so it is assumed to be cyclonucleoside **15**. A periodate titration of this sirup consumed 0.91 mole of periodate within 15 min, demonstrating the presence of *cis* glycol.[16] Clark, Todd, and Zussman[18] reported that 2′,3′-O-isopropylidene-3,5′-cycloadenosine *p*-toluenesulfonate had $\lambda_{m\mu}^{0.05\ N\ HCl}$ 272 mμ (ε 16,310).

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

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The Preparation of 2(5H)-Furanones and Dyes Derived from Them

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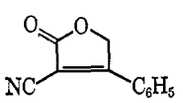
Alkali metal salts of acetic acids substituted with one electron-withdrawing group react with α-halocarbonyl compounds to give α-oxoalkyl esters which cyclize to 2(5H)-furanones. The acidic C_5-methylene groups in these furanones may be used to form hydrazones, azomethines, and a variety of polymethine dyes.

A recent review article has summarized the known methods of making 2(5H)-furanones.[1] We report here a new method involving the reaction of α-halo ketones with alkali metal salts of acetic acids substituted with one electron-withdrawing group. For example, sodium cyanoacetate and 2-bromoacetophenone were condensed to give 3-cyano-4-phenyl-2(5H)-furanone (**1**). Data



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for **1** and other 2(5H)-furanones made by this procedure are given in Table I.

TABLE I

2(5H)-FURANONES

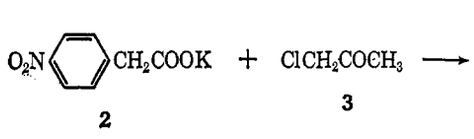
Compound	% yield	Recrystn solvent	Mp, °C	Analyses
3-Cyano-4-phenyl-2(5H)-furanone (**1**)	39.4	Acetonitrile	164–167	Calcd for $C_{11}H_7NO_2$: C, 71.3; H, 3.79; N, 7.5. Found: C, 70.9; H, 3.4; N, 7.4.
4-*p*-Bromophenyl-3-cyano-2(5H)-furanone	32.1	Acetonitrile	215–218	Calcd for $C_{11}H_6BrNO_2$: C, 50.0; H, 2.27; Br, 30.3. Found: C, 49.9; H, 2.2; Br, 30.1.
4-*p*-Bromophenyl-3-*p*-nitrophenyl-2(5H)-furanone	19.2	DMF	214.5–216	Calcd for $C_{16}H_{10}BrNO_4$: C, 53.4; H, 2.78; Br, 22.2; N, 3.89. Found: C, 53.1; H, 2.6; Br, 22.4; N, 4.0.
3,4-Di-*p*-nitrophenyl-2(5H)-furanone	46.6	Acetonitrile	207–208.5	Calcd for $C_{16}H_{10}N_2O_6$: C, 58.9; H, 3.07; N, 8.59. Found: C, 59.0; H, 3.0; N, 8.9.
4-Methyl-3-*p*-nitrophenyl-2(5H)-furanone (**4**)	34.0	Acetic acid	142–144	Calcd for $C_{11}H_9NO_4$: C, 60.3; H, 4.11; N, 6.38. Found: C, 59.9; H, 4.1; N, 6.1.

The structure of **1** was established by instrumental evidence and by a two-step conversion in low yield to the known[2] 3-carbamoyl-4-phenylmaleic anhydride.

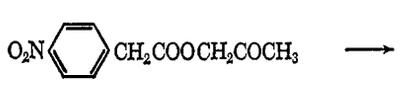
The reaction path for this 2(5H)-furanone synthesis involves initial formation of the α-oxoalkyl ester and then cyclodehydration. Treatment of potassium *p*-nitrophenylacetate (**2**) with chloroacetone (**3**) for 20 hr in boiling methanol gave 4-methyl-3-*p*-nitrophenyl-2(5H)-furanone (**4**) and a small amount of acetonyl *p*-nitrophenylacetate (**5**). When **2** and **3** were stirred for 24 hr in methanol at room temperature, only **5** was isolated. Boiling **2** and **3** for 72 hr in methanol gave **4**, methyl *p*-nitrophenylacetate, and no **5**. The cyclization of **5** to **4** was accomplished by boiling **5** for 1 hr in methanol containing a trace of **2**.

A limitation on the scope of this method is that the electron-withdrawing group on the acetic acid must be strong in order for cyclization of the α-oxoalkyl ester to occur. For example, the treatment of 2,4′-dibromoacetophenone with **2** gave 4-*p*-bromophenyl-3-*p*-nitrophenyl-2(5H)-furanone, but sodium phenylacetate gave *p*-bromophenacyl phenylacetate. Efforts to cyclize this ester by using concentrated sulfuric acid, potassium *t*-butoxide, polyphosphoric acid, and ammonium acetate–acetic acid were unsuccessful.

The reactivity of the methylene group in 2(5H)-furanones obtainable by this procedure makes them useful dye intermediates. For instance, **1** coupled with benzenediazonium chloride to give 4-cyano-3-phenyl-2,5-dihydrofuran-2,5-dione-2-phenylhydrazone (**5**) (Chart I), with N,N-dimethyl-*p*-nitrosoaniline to give



2 **3**



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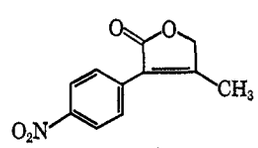

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the azomethine, 3-cyano-5-*p*-dimethylaminophenylimino-4-phenyl-2(5H)-furanone (**7**), with Fischer's aldehyde (2-methylene-1,3,3-trimethylindoline-ω-carboxaldehyde) to give the merocyanine, 3-cyano-4-phenyl-5-[2-(1,3,3-trimethylindolin-2-ylidene)ethylidene]-2(5H)-

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