aloyl chloride[10] (mp 113–115°) was stirred at 25° for 3 hr. The colorless mixture turned dark red in 30 min then became light yellow in 3 hr. Various amino acids required 3–8 hr for this color change. The solution was treated with decolorizing carbon and filter aid, filtered, and brought to pH 4 with concentrated HCl, cooled at 10° for 12 hr, and filtered to give 6.94 g (85.5%) of white powder, mp 230–231°, $[\alpha]^{26}D$ +99.7° (*c* 1, aqueous 5% $NaHCO_3$). The product was recrystallized from hot water to give 4.80 g (59.4%) of analytically pure material, mp 237–238°, $[\alpha]^{26}D$ +123.7° (*c* 1, aqueous 5% $NaHCO_3$).

(10) H. C. Koppel, I. L. Honigberg, R. H. Springer, and C. C. Chang, *J. Org. Chem.*, **28**, 1119 (1963).

The Acetylation of 1-(β-D-Arabinofuranosyl)cytosine[1]

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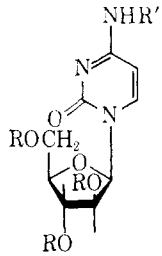
The tri-*O*-acetate (II) and the tetraacetate (III) of 1-(β-D-arabinofuranosyl)cytosine (I) have been prepared as compounds that may be pharmacologically more useful forms of I which has antitumor properties.[2] The tri-*O*-acetate was obtained by selective acetylation of the hydrochloride of I under mild conditions. Standard acetylation conditions readily converted I to III.



I, R = R′ = H
II, R = Ac; R′ = H
III, R = R′ = Ac

Experimental Section[3]

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine (II).—A solution of acetic–trifluoroacetic anhydride was prepared by mixing 1.90 g (91 mmoles) of trifluoroacetic anhydride and 30 ml (0.52 mole) of acetic acid and allowing this solution to stand at room temperature for 30 min. The solution was cooled and slowly added (over about 10 min) to a solution of 3.0 g (10.7 mmoles) of I·HCl in 35 ml of trifluoroacetic acid[4] so that the temperature did not rise above 10°. After 30 min at 10° and about 12 hr at room temperature,[5] the clear solution was cooled and the temperature maintained below 25° during treatment with 5.5 ml of absolute ethanol to decompose excess anhydride. After 0.5 hr at room temperature, the solution was evaporated *in vacuo* (water-bath temperature 40–50°). The residue was dissolved in 60 ml of water and neutralized to pH 6 with solid $NaHCO_3$. The aqueous solution[6] was extracted with two 450-ml portions of ethyl acetate[7] which were combined, dried, and concentrated to about 90 ml to afford 2.36 g (60%) of highly crystalline II, mp 189–190°, homogeneous by thin layer chromatography. Evaporation of the ethyl acetate filtrate afforded 0.82 g (21%) of amorphous product, mostly II with a trace of less acylated material. A third ethyl acetate extract of the aqueous solution afforded 0.47 g more of material that was composed of II and less acylated material in about equal amounts.

Recrystallization of product from a previous run with ethyl acetate afforded the analytical sample of II: mp 189.0–189.5°; λ_{max}^{Nujol} (μ) 2.90, 3.00, 3.20 (N–H), 5.72 (C=O of acetate); $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 13.8 × 10³); $\lambda_{max}^{pH\ 7}$ 233 mμ (ε 8.1 × 10³), 270 (9.1 × 10³);[8] $\lambda_{max}^{pH\ 13}$ 274 mμ (ε 10.0 × 10³); [α] +68°. The methyl protons of the *O*-acetates were located between τ 7.85 and 8.01. It was homogeneous by thin layer chromatography[4] and by paper chromatography in these solvents: A, R_{Ad} 1.44, and B, R_{Ad} 2.43.

Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.8; H, 5.19; N, 11.4. Found: C, 48.5; H, 5.22; N, 11.5.

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-N^4-acetylcytosine (III).—A solution of 4.70 g of I·HCl in 180 ml of dry pyridine was treated with 18.0 ml of acetic anhydride (slight warming). The resultant solution was left overnight (about 20 hr) at room temperature and was then evaporated *in vacuo* (bath temperature 45–50°). The residue was treated with 20 ml of absolute ethanol, diluted with 150 ml of toluene, and again evaporated to dryness. The residue was partitioned between 300 ml of ethyl acetate and 75 ml of water. The ethyl acetate layer was washed with water, dried, concentrated to 50 ml, and then diluted 10-fold with ether. The product which crystallized was collected, washed with ethyl acetate–ether (1:10), and dried to afford 5.86 g (85%) of III, mp 171–172°, homogeneous by thin layer and paper chromatography. Recrystallization from ethyl acetate–ether afforded the analytical example of III: mp 171–171.5°; λ_{max}^{Nujol} (μ) 3.15, 3.23 (N–H), 5.72 (acetate); $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 11.2 × 10³), 302 (9.0 × 10³); $\lambda_{max}^{pH\ 7}$ 247 mμ (ε 16.4 × 10³), 298 (8.6 × 10³);[8] $\lambda_{max}^{pH\ 13}$ 275 mμ (ε 10.5 × 10³); [α] + 87°. The methyl protons of the *O*-acetates appeared at τ 7.84–8.01; the *N*-acetyl, at τ 7.67. It moved as a single spot in thin layer chromatograms (R_f 0.90) and on paper in these solvents: A, R_{Ad} 1.75, and C, R_{Ad} 1.35.

Anal. Calcd for $C_{17}H_{21}N_3O_9$: C, 49.6; H, 5.15; N, 10.22. Found: C, 49.5; H, 5.23; N, 9.86.

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(2) (a) R. W. Talley, and V. K. Vaitkevicius, *Blood*, **21**, 352 (1963); (b) J. S. Evans, E. A. Musser, L. Bostwick, and G. D. Mengel, *Cancer Res.*, **24**, 1285 (1964); (c) J. E. Evans, L. Bostwick, and G. D. Mengel, *Biochem. Pharmacol.*, **13**, 983 (1964).

(3) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Anhydrous $MgSO_4$ was used as the drying agent. Paper chromatograms were run by the descending technique on Whatman No. 1 paper and the spots were located in R_{Ad} units with adenine at 1.00. The solvent systems were: A, 1-butanol–water (saturated); B, water; C, 1-butanol–acetic acid–water (5:2:3). Thin layer chromatograms were run on silica gel HF plates with a solvent system of methanol–$CHCl_3$ (1:4). The spots on plates and paper were detected by ultraviolet light. Optical rotations were determined in 1% solutions in *N,N*-dimethylformamide at 21.6° using the sodium D line. The nmr spectra were determined with a Varian A-60 spectrometer, using $CDCl_3$ solutions containing 4% $Si(CH_3)_4$ as internal standard. The spectra of II and III were compatible with their structures.

(4) The hydrochloride of I was soluble in trifluoroacetic acid but not in acetic acid, acetic anhydride, mixtures of these two, or in the solution of acetic–trifluoroacetic anhydride.

(5) Aliquots were periodically examined by thin layer chromatography for completeness of reaction. Compound II (R_f 0.66) was readily distinguished from less acylated products (R_f <0.5).

(6) In one preparation of II, the product was left in water overnight. The yield of II was low, suggesting that considerable amounts of II had hydrolyzed.

(7) Ethyl acetate cannot be replaced by $CHCl_3$. It was inefficient for extracting the quite water-soluble II from the aqueous phase.

(8) J. Beránek and J. Píťha, *Collection Czech. Chem. Commun.*, **29**, 625 (1964), have reported the ultraviolet spectra in ethanol for 2′,3′,5′-tri-*O*-acetylcytidine (λ_{max} 243 and 268 mμ) and N^4-acetyl-2′,3′-5′-tri-*O*-acetylcytidine (λ_{max} 249 and 299 mμ).