[CONTRIBUTION FROM PARKE, DAVIS AND COMPANY'S MULTIPLE FELLOWSHIP IN MEDICINAL CHEMISTRY, MELLON INSTITUTE]

# Acetylation of D-Ribosylamine[1]

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Pure D-ribosylamine and di-D-ribosylamine have been prepared and characterized. Peracetylation of D-ribosylamine affords *N*-acetyl-tri-*O*-acetyl-D-ribosylamine which is de-*O*-acetylated to *N*-β-D-ribopyranosylacetamide. Unimolar acetylation of D-ribosylamine gives the α anomer and a mixture of the α and β anomers of *N*-D-ribopyranosylacetamide.

D-Ribosylamine is a potentially valuable intermediate in the synthesis of *N*-D-ribosylacylamides (*N*-acyl-D-ribosylamines) and other nitrogen-containing D-ribosyl derivatives. A brief description of its preparation was given by Levene and LaForge[3] in 1915. Their material had an analysis (% N) agreeing with that calculated for a pentosylamine and was a satisfactory intermediate in syntheses; for it, they recorded m.p. 137–138° dec. Later, Levene and Clark[4] mentioned that, if the initial components of the reaction mixture are dry, the yield of D-ribosylamine is 90–95% of the theoretical, but, if moist reagents are used, "the resulting product contains a certain proportion of" di-D-ribosylamine. On repeating the preparation, under conditions as close as possible to those described by Levene and LaForge,[3] it is now found that D-ribosylamine is, indeed, formed in high yield, but its melting point does not agree with that recorded by them; instead, their melting point is that of crude di-D-ribosylamine. Presumably, during the course of their "purification" for determination of melting point, they had unwittingly converted it, in part at least, to di-D-ribosylamine, a transformation readily accomplished. Precise directions for the preparation of both D-ribosylamine and di-D-ribosylamine are now given, together with a description of some of their properties.

Peracetylation of D-ribosylamine affords a crystalline *N*-acetyl-tri-*O*-acetyl-D-ribosylamine which, on de-*O*-acetylation, gives an *N*-acetyl-D-ribosylamine (*A*). On unimolar acetylation of D-ribosylamine in water,[5] the amino group is acetylated (in preference to one or more of the hydroxyl groups). Two fractions (*B* and *C*), each of which had an analysis corresponding to that for an *N*-acetylpentosylamine, were isolated, but neither had the properties of amide *A*. From the optical rotations, melting points, a study of the infrared absorption spectra, and the results of periodate oxidation of *A*, *B*, and *C*, it was decided that *A* is *N*-β-D-ribopyranosylacetamide, *C* is the corresponding α anomer, and *B* is a mixture of *A* and *C* (approx. 31:69).

Recording of infrared absorption spectra (see Fig. 1) proved particularly useful in this work.[6] The spectra are given here for comparison with those of similar derivatives of other sugars.[7]

## EXPERIMENTAL[8]

*D-Ribosylamine.* D-Ribose (from Hoffmann-La Roche, Inc., Nutley, N. J.) was finely powdered and then dried[9]; its infrared absorption spectrum was recorded (see Fig. 1, 1). In a 250-ml. Erlenmeyer flask, closed by a rubber stopper through which passed a long inlet tube and a short outlet tube (closed by a Drierite tube), was placed 100 ml. (78.2 g.) of absolute methanol, and the assemblage was weighed. With cooling to about 5° in an ice water bath, ammonia gas (20 to 22 g.) was passed in, from a cylinder, through an empty, reversed Drechsel bottle. The stopper and tubes were then removed, 100 g. of dry, finely powdered D-ribose was rapidly added, and the flask was quickly stoppered. On gentle swirling, the D-ribose gradually dissolved and the solution became colder; after 15 min. of swirling, the sugar had all dissolved to a straw-yellow solution. After elapse of a further 30 min., the solution was nucleated with a trace of crystalline D-ribosylamine (prepared on a small scale, in a test-tube experiment), the flask was rapidly stoppered, and the solution was swirled occasionally. After 1 hr., one eighth of the volume consisted of colorless crystals (at the bottom). Crystallization now continued, with the formation of crusts of hard rosettes of needles on the walls; these were scraped off from time to time until no more crusts formed (some 6 days, stoppered, at room temperature). The crystals were then removed by suction filtration (rubber dam), collected and washed with two 20-ml. portions of absolute methanol, pressed dry, and dried[9]; yield, 90.4 g. (91.0%); colorless crystals; m.p. 123–126° dec. (softens at 122°). For purification, the dry compound was finely

(1) The work described herein was completed prior to December 26, 1956.

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(3) P. A. Levene and F. B. LaForge, *J. Biol. Chem.*, **20**, 433 (1915).

(4) P. A. Levene and E. P. Clark, *J. Biol. Chem.*, **46**, 19 (1921).

(5) K. Onodera and S. Kitaoka [*J. Org. Chem.*, **25**, 1322 (1960)] have recently described the *N*-monoacylation of certain unsubstituted glycosylamines by reaction with an acid anhydride in *N*,*N*-dimethylformamide or methanol. D-Ribosylamine is only slightly soluble in these solvents in the cold.

(6) The author is indebted to Dr. Foil A. Miller of the Department of Research in Chemical Physics, Mellon Institute, for recording the infrared spectra.

(7) R. S. Tipson and H. S. Isbell, *J. Research Natl. Bur. Standards*, **65A**, 31 (1961).

(8) Analyses by Mr. C. E. Childs, Research Division, Parke, Davis and Co., Detroit 32, Mich.

(9) At room temperature, over potassium hydroxide pellets in a vacuum desiccator (Desiguard) at 0.1 mm.

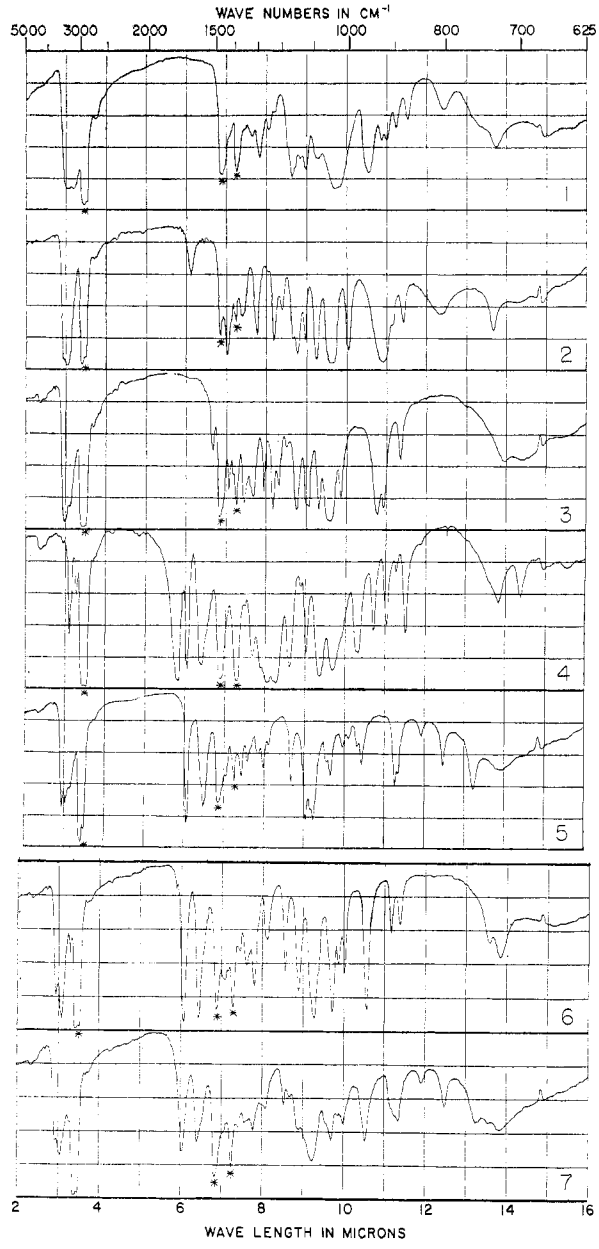


Fig. 1. Infrared absorption spectra of (1) D-ribose, (2) D-ribosylamine, (3) di-D-ribosylamine, (4) *N*-acetyl-tri-*O*-acetyl-D-ribosylamine, (5) *N*-α-D-ribopyranosylacetamide, (6) *N*-β-D-ribopyranosylacetamide, and (7) crystals *B* (of *N*-α- + *N*-β-D-ribopyranosylacetamide). (Asterisks indicate bands of Nujol)

powdered and transferred to a 500-ml. Erlenmeyer flask; absolute methanol (271.2 ml.) was added, the suspension was vigorously swirled mechanically at room temperature for 15 min., filtered with suction (rubber dam), washed with 40 ml. of absolute methanol, and dried as before; wt., 87.0 g. (88%); colorless crystals; m.p. 128–129° dec. (softens at 126°); $[\alpha]_D^{28}$ − 35.3° (2 min.) → −17.4° (43 hr.; *c*, 1.005 in water). Its infrared absorption spectrum was recorded (Fig. 1, 2).

*Anal.* Calcd. for $C_5H_{11}NO_4$: C, 40.26; H, 7.43; N, 9.39. Found: C, 40.56; H, 7.21; N, 9.27.

D-Ribosylamine is soluble in water or 50% aqueous ethanol. It is practically insoluble in acetonitrile, dioxane, or tetrahydrofuran; slightly soluble in 2-aminoethanol, *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, or pyridine; and, on standing overnight at room temperature, it dissolves to a greater extent in either of the last solvents, or in aqueous tetrahydrofuran.

From the mother liquors (from both the preparation and the purification of D-ribosylamine), colorless, crystalline di-D-ribosylamine could be isolated by evaporation to dryness and treatment with methanol (5 vols.).

*Di-D-ribosylamine.* A suspension of D-ribosylamine (5 g.) in 50 mol. of absolute methanol was boiled under reflux (boiling stone; Drierite tube) until all of the compound had dissolved (4 hr.); ammonia was liberated. (In a subsequent preparation, the hot solution was filtered at this stage.) On cooling the pale yellow solution, a material crystallized which, on reboiling of the mixture for 1 hr., did not redissolve. The suspension was cooled, stoppered, kept at room temperature for a week, and then filtered with suction (rubber dam); the colorless crystals were washed with absolute methanol, pressed dry, and dried;[9] yield, 2.6 g. (55%); m.p. 142–143° dec. (softens at 136°); $[\alpha]_D^{26}$ − 58.8° (5 min) → −17.2° (53 hr.; *c*, 1.020 in water[10]). Its infrared absorption spectrum was recorded (Fig. 1, 3).

*Anal.* Calcd. for $C_{10}H_{19}NO_8$: C, 42.70; H, 6.81; N, 4.98. Found: C, 42.59; H, 7.03; N, 5.23.

Impure material, obtained from mother liquors in the preparation of D-ribosylamine, could be purified as follows. The crude di-D-ribosylamine was quickly dissolved, under reflux, in water (2 vols) in a bath at 75°, absolute ethanol (23 vols.) was rapidly added, followed by a small amount of Nuchar, and the hot suspension was immediately swirled and filtered. To the clear, very pale yellow filtrate, absolute ethanol (25 vols.) was added, and the solution was cooled, stoppered, and kept overnight at room temperature; crystallization had then started and was allowed to continue for several days. The purified material was isolated and dried as described above.

N-*Acetyl-tri-O-acetyl-D-ribosylamine.* D-Ribosylamine (7.5 g.) was placed in a 250-ml., three necked flask (equipped with standard-taper joints, stirrer, pentane thermometer, and pressure-equalizing dropping funnel) and was cooled in ice–salt. Dry pyridine (80 ml.) was gradually added with stirring and cooling. As soon as the temperature had reached 2°, slow addition of acetic anhydride (32 ml.) was started from the dropping funnel; addition was made during 30 min., at such a rate that the temperature of the suspension did not rise above 5°. After stirring for a further 50 min., all of the D-ribosylamine had dissolved to a very pale yellow solution which was kept overnight (stoppered) in the refrigerator. The solution was now poured slowly onto crushed ice, with stirring, but no precipitate formed. The clear solution was thoroughly extracted with three successive portions of chloroform. The chloroform extracts were combined, extracted with aqueous sodium bicarbonate solution until free from acid, dried with anhydrous sodium sulfate, filtered, and evaporated to dryness under diminished pressure at 30°, giving 11.2 g. of a pale yellow, flaky glass which crystallized on adding a little dry ether. A total of 112 ml. of dry ether was added, the suspension was stirred, and the colorless crystals were removed by suction filtration, washed with 25 ml. of dry ether, and dried; wt., 9.6 g.; m.p. 128–130°; $[\alpha]_D^{22}$ + 35.3° (*c*, 1.316 in chloroform). Its infrared absorption spectrum was recorded (Fig. 1, 4).

*Anal.* Calcd. for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.03; N, 4.42; *N*-acetyl, 13.57; *O*-acetyl, 40.70. Found: C, 49.34; H, 6.40; *N*, 4.49; *N*-acetyl, 13.45; *O*-acetyl, 39.10.

*De-O-acetylation of* N-*acetyl-tri-O-acetyl-D-ribosylamine to* N-β-D-*ribosylacetamide* (*A*). *N*-Acetyl-tri-*O*-acetyl-D-ribosylamine (6 g.) was dissolved in 100 ml. of anhydrous methanol in a 500-ml., round bottomed flask; 10 ml. of 0.1*N* barium methoxide in absolute methanol was added, and the flask was stoppered and kept at room temperature for 1 hr. The solution was then evaporated to dryness under

(10) This determination was made by Miss Beverly A. Pawson.

diminished pressure at room temperature, affording a colorless crystalline mass which was dissolved in 25 ml. of distilled water. The solution was passed through a column (50 ml.) of Amberlite IR-100($H^+$), washed in with 25 ml. of water, and the material eluted with five successive 50-ml. portions of water [the final aqueous wash had $\alpha$ — 0.04° (l, 2 dm.)]. The effluents were then passed, in the same order, through a column (50 ml.) of Amberlite IRA-400($OH^-$) and six 50-ml. portions of effluent were collected [the final aqueous wash had $\alpha$ — 0.04 to 0.00° (l, 2 dm.)]. The effluents were combined, evaporated to dryness under diminished pressure at 30°, and dried by adding absolute ethanol and reevaporating. The resulting colorless, crystalline mass was dried at 0.1 mm.; wt., 3.6 g. This was dissolved in 117 ml. of boiling absolute ethanol under reflux, and the solution was cooled, affording colorless crystals (*A*); wt., 2.4 g.; m.p. 195–197°; $[\alpha]_D^{21}$ — 23.4° (*c*, 1.006 in water) with no observable mutarotation—when diluted 1:10 with water, this solution gave no peaks in the ultraviolet and no change was observed after 42 hr. at room temperature. Periodate oxidation at *p*H 7.2 indicated that compound *A* had a pyranoid structure.[11] Its infrared absorption spectrum was recorded (Fig. 1, 6).

*Anal.* Calcd. for $C_7H_{13}NO_5$: C, 43.98; H, 6.85: N, 7.33; *N*-acetyl, 22.51. Found: C, 44.55; H, 6,85; N, 7.51; *N*-acetyl, 22.25.

*"Unimolar" acetylation of* D-*ribosylamine.* Glacial acetic acid (19 ml.) and 19 ml. of distilled water were placed in a 500-ml., round bottomed flask and cooled in ice to 4°. D-Ribosylamine (7.5 g., 0.05 mole) was added and the suspension was swirled and cooled; the temperature rose to 13° and then rapidly fell to 9°. Acetic anhydride (7 ml., 0.075 mole) was now added in one portion and the mixture was swirled; no rise in temperature occurred. The cooling bath was removed and, after the mixture had been swirled for 20 min., the D-ribosylamine had all dissolved; evaporation under diminished pressure (bath temp., 30°) was immediately started and, after 35 min., a yellow sirup resulted which was immediately dried at 0.1 mm., giving (after 30 min.) a colorless, crystalline mass which was processed within 3 hr. (if not used immediately, it was refrigerated). This material was dissolved in 100 ml. of distilled water, passed through a column of 300 ml. of mixed anion- and cation-exchange resin (Amberlite MB-3, which had previously been cautiously back-washed with just enough water to remove air bubbles), and eluted with water. The first 100 ml. of effluent was evaporated to dryness and dried at 0.1 mm., giving a colorless crystalline mass (*M*), wt., 2.0 g. The next five 100-ml. effluents were combined, evaporated, and dried at 0.1 mm., giving a clorless, crystalline mass (*N*), wt., 5.4 g. The next eight 100-ml. effluents were combined, evaporated, and dried at 0.1 mm., giving a colorless mixture of sirup and crystals (*P*), wt., 1.7 g. Crystals *M* were suspended in 20 ml. of absolute ethanol and boiled under reflux; the suspension was cooled, refrigerated, and filtered, giving colorless crystals *B*, wt., 1.2 g., m.p. 172–174°, $[\alpha]_D^{23}$ +5.1° (*c*, 1.170 in water). Its infrared spectrum was recorded (Fig. 1, 7).

*Anal.* Calcd. for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33; *N*-acetyl, 22.51. Found: C, 43.83; H, 6.79; N, 7.47; *N*-acetyl, 22.28.

Crystals *N* were treated with 54 ml. of absolute ethanol as for crystals *M*, giving colorless crystals *B*, wt., 3.2 g., m.p. 172–174°, $[\alpha]_D^{23}$ + 5.6° (*c*, 1.072 in water). Its infrared absorption spectrum was identical with that of the first crop of *B*.

*Anal.* Found: C, 43.92; H, 6.96; N, 7.29.

Crystals *P*, treated with 10 volumes of absolute ethanol, as above, gave colorless crystals *C*, wt., 0.3 g., m.p. 198–200° (dec., softening and browning at 195°); $[\alpha]_D^{23}$ +17.8° (*c*, 1.013 in water). Its infrared spectrum was recorded (Fig. 1, 5). Periodate oxidation at *p*H 7.2 indicated that materials *B* and *C* had a pyranoid structure.[11]

*Anal.* Found: C, 43.23; H, 6.73, N, 7.04; *N*-acetyl, 20.34.

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(11) The author thanks Dr. Calvin L. Stevens for this determination.

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[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

# Interaction of Alkoxysilanes and Acetoxysilanes[1]

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In the presence of Lewis acid catalysts, mixtures of ethoxysilanes and acetoxysilanes give good yields of ethyl acetate. Thermal decomposition of the acetoxysilane with the intermediate formation of acetic anhydride does not have a role in the formation of the ethyl acetate. Ferric chloride was a satisfactory catalyst at temperatures as low as 130° while low yields of ethyl acetate were obtained from other catalysts, aluminum isopropylate, *p*-toluenesulfonic acid, and sodium methoxide. Although extensive redistribution of silicon-attached functional groups and cleavage of silicon-phenyl bonds occurred at elevated temperatures in the presence of acid catalysis, a transesterification reaction also took place under these conditions.

Transesterification reactions, which have been very successful in the preparation of metallosiloxanes,[2–7] offer a potentially valuable tool for the preparation of siloxanes, provided side reactions

$$R_3SiOAc + R_3'SiOEt \longrightarrow R_3SiOSiR_3' + EtOAc$$

can be avoided. Although O'Brien[8] failed to obtain such a condensation, Henglein[9] and Andrianov[10]

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