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Note

An improved preparation of 5′-deoxyadenosine by coupling methods

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A number of procedures for the preparation of 5′-deoxyadenosine directly from adenosine are known[1–4], and most of these have been reviewed by Wang *et al.*[3]. These preparations give yields that range from quite modest[1,2] to quite good[3,4]; however, what did seem rather strange was the lack of reported coupling procedures, especially since the preparation of 5-deoxy-D-ribose is fairly easy by a number of approaches[5–7]. In fact, the only report of the synthesis of 5′-deoxyadenosine by coupling was its very first preparation[6], in which 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose was converted into the sugar chloride and condensed with 6-benzamido-9-(chloromercuri)purine by the standard method of Davoll and Lowy[8] in hot xylene. Only a 2% yield of pure 5′-deoxyadenosine was obtained after the blocking groups had been removed. A much better yield (21%) was obtained when the sugar chloride was condensed with 6-chloro-9-(chloromercuri)purine first, and then converted into 5′-deoxyadenosine with ammonia[6]. It appeared rather odd that the titanium tetrachloride method[9] of coupling with 6-benzamido-9-(chloromercuri)purine was not employed since this method was already in use in Baker's laboratory at the time. Recently, 5′-deoxyadenosine was needed in this laboratory as a starting material for interconversion to other nucleosides, so it was decided that it may be of interest to reinvestigate the synthesis by coupling techniques in addition to the preparation directly from adenosine[1].

The first coupling technique applied was the titanium tetrachloride method[9,10], which has often been used in this laboratory with generally excellent results. Coupling of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose and 6-benzamido-9-(chloromercuri)purine by this method resulted in a nearly 30% overall yield of 5′-deoxyadenosine, a dramatic improvement over the earlier synthesis[6]. When the silylated base–stannic chloride method[11] of coupling as applied to purines[12] was used, the yield approached nearly 50%. This reaction required refluxing conditions, for at room temperature the yield fell to 14%. Another feature of the preparations

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reported herein is that the nucleoside was purified in each case by passage through an anion-exchange resin (OH^-) and eluted with water. All of the dark color and presumably all or most of the impurities remained on the resin. There appear to be some discrepancies in the literature concerning the m.p. of 5′-deoxyadenosine and this may be due to the formation of isomorphic crystalline forms. All of the preparations in this laboratory, whether from adenosine or by coupling procedures, had a double m.p., with the first one not clearly defined between 130–145°, and the final one at 212–214°. These values are in agreement with those of McCarthy *et al.*[1] (preparation from adenosine), and Kissman and Baker[6] (coupling method).

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler micro hot-stage and are corrected values. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter, and i.r. spectra recorded with a Perkin–Elmer Model 21 spectrophotometer. Paper chromatography was performed on descending sheets of Whatman No. 1 paper in 5% aqueous Na_2HPO_4 and 43:7 (v/v) butanol–water. Evaporations were performed under reduced pressure with a rotary evaporator and a bath temperature of 40–45°. Moist organic solutions were dried with anhydrous $MgSO_4$.

*1,2,3-Tri-O-acetyl-5-deoxy-*D*-ribofuranose.* — A mixture of methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside[7] (3 g) and water (150 mL) was treated with Amberlite IR-120 (H^+) resin (25 mL) for 1 h at reflux temperature. The flask was cooled to room temperature, the contents were filtered through a sintered-glass funnel, and the resin was washed three times with water. The water was evaporated to a volume of ~30 mL, and a small amount of Darco G-60 activated charcoal was added to discharge the pale-yellow color. Filtration into a tared flask and evaporation afforded a clear, colorless syrup, which was dried for 4 days at 4 kPa in the presence of P_2O_5. The yield of 5-deoxy-D-ribose was 2.07 g (97%). Acetylation in the usual manner[6,13] afforded 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (3.99 g, 99% yield).

5′-Deoxyadenosine. — *Method A.* N^6-Benzoyladenine (4.1 g, 17.1 mmol) was suspended in dry 1,2-dichloroethane (80 mL), the mixture was stirred, protected from moisture, and 25 mL of the solvent was distilled by means of a take-off adapter in order to ensure that traces of moisture were removed. Hexamethyldisilazane (7.2 mL) and chlorotrimethylsilane (0.43 mL) were added, the mixture was heated under reflux for 1 h (the mixture became homogeneous after 0.5 h), cooled to room temperature (turbidity), and evaporated while protecting the product from moisture. To the residue were added 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (3.99 g, 15.4 mmol) in 1,2-dichloroethane (55 mL) and $SnCl_4$ (2.75 mL, 23.5 mmol), and the mixture was refluxed for 2 h, protected from moisture. The dark mixture was cooled to room temperature and carefully poured into a vigorously stirred solution of saturated $NaHCO_3$ (100 mL). An additional 50 mL of

1,2-dichloroethane (in three portions) was used to rinse out the reaction flask, and this was combined with the rest of the material. The mixture was filtered by suction through a pad of Celite, the pad was washed with warm 1,2-dichloroethane (50 mL), and the organic layer was separated, washed with water (75 mL), and dried. After evaporation, a dark foam (7.82 g) was obtained, which was dissolved in methanol (100 mL), M methanolic sodium methoxide (10 mL) was added, and the mixture was heated under reflux for 1 h. The solution was cooled to room temperature and neutralized with Amberlite CG-120 (H^+) resin, the resin was removed by filtration on a sintered-glass funnel and washed three times with methanol. The washings were combined with the filtrate and evaporated, and then methyl benzoate was coevaporated by three additions of water. The residue was dissolved in hot water and placed on top of a column (33 × 2.4 cm) of Bio-Rad AG 1-X2 (200–400 mesh, OH^-) ion-exchange resin. The column was eluted with water and 20-mL fractions were collected. Tubes 8–88, which had u.v. absorption, were pooled and evaporated. The white residue was crystallized from water (~40 mL) to afford 1.328 g, which was dried under high vacuum at 100° in the presence of P_2O_5. Two additional crops of crystals were obtained from the mother liquors to give a total yield of 1.770 g (46%) of 5′-deoxyadenosine, m.p. 213–214.5°, with prior melting beginning after 130° and slow hardening after 145°. The mixed m.p. with a sample of 5′-deoxyadenosine prepared from adenosine, as described by McCarthy *et al.*[1], showed the same behavior with no lowering of the final m.p. (212–214°). The i.r. spectra of the two preparations were identical, as were the mobilities on paper chromatograms; $[\alpha]_D^{26}$ −53.5° (*c* 1.01, ethanol); lit. $[\alpha]_D^{27}$ −53.2° (c 1.0, ethanol) (ref. 1), $[\alpha]_D^{25}$ −52.7° (*c* 1.0, ethanol) (ref. 6).

Method B. 6-Benzamido-9-(chloromercuri)purine (13.7 g, 28.9 mmol), Celite 545 (13.7 g), 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (6.25 g, 24 mmol), and dry 1,2-dichloroethane (700 mL) were stirred in a reaction flask and 100 mL of the solvent was distilled (take-off adapter) to ensure removal of any traces of water. Titanium tetrachloride (3.6 mL, 32.7 mmol), dissolved in 100 mL of fresh 1,2-dichloroethane, was added and the mixture was heated under reflux for 18 h, protected from moisture. A portion of the solvent (300 mL) was removed by distillation, the reaction mixture was cooled to room temperature, saturated $NaHCO_3$ solution (400 mL) was cautiously added, and vigorous stirring was continued for 2 h. The solids were removed by filtration through a Celite pad, and the filter cake was washed with hot 1,2-dichloroethane (300 mL). The organic layer was separated and evaporated to dryness, the residue was dissolved in chloroform (150 mL), washed with 30% KI solution (2 × 150 mL) and water (200 mL), and dried. Evaporation of the solvent afforded an orange-brown foam (4.60 g). This was dissolved in methanol, treated with sodium methoxide, and purified as described in Method A to yield 1.756 g (29%). Recrystallization from ethanol gave 1.057 g of 5′-deoxyadenosine in three crops. The melting point behavior was exactly identical as described in Method A. The mixed m.p. gave no depression and the i.r. spectrum was also identical.

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