tive involving a single, solvent- and cation-dependent, partially delocalized structure for Ia–c.[11] It is hoped that studies now in progress will eventually supply a definitive answer.

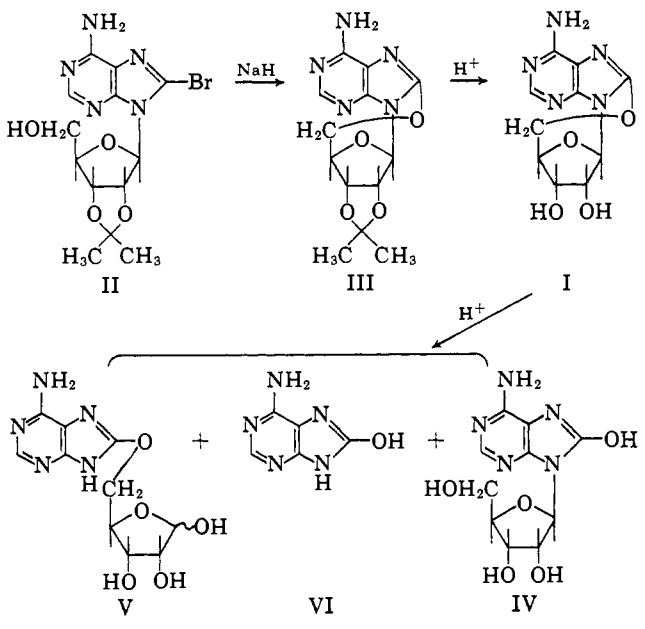
(11) Two previously described (and possibly equivalent) hypotheses can be mentioned: (a) that we are dealing with "contact ion pairs" as postulated for the alkali metal salts of fluorene (T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **88**, 307 (1966)) or (b) a Lewis acid type of anion–cation interaction as suggested for 1,1-diphenyl-*n*-hexyllithium (R. Waack, M. A. Doran, and P. E. Stevenson, *ibid.*, **88**, 2109 (1966)).

V. R. Sandel, S. V. McKinley, H. H. Freedman
Eastern Research Laboratory, The Dow Chemical Company
Wayland, Massachusetts 01778
Received October 7, 1967

A Novel Method for the Synthesis of Cyclonucleosides. Synthesis of 8,5′-O-Anhydro-8-oxyadenosine

Sir:

In recent years knowledge about purine nucleosides has extensively accumulated.[1–6] These cyclonucleosides have O- or S-anhydro linkages between C_8 of the purine and $C_{2'}$ or $C_{3'}$ of the sugar moiety, except for a guanosine cyclonucleoside[2] having a 8,5′-S-anhydro linkage. All of these cyclonucleosides were synthesized *via* intermediates having aryl- or alkylsulfonyl groups on the sugar hydroxyl by back-side attack of oxy or thiol group on the base moieties. However, adenine cyclonucleosides having the 8,5′-O-anhydro linkage could not be synthesized because of the rapid cyclization of 5′-sulfonylated adensosine to the N_3 position to give N_3,5′-cyclonucleoside salts.[7]



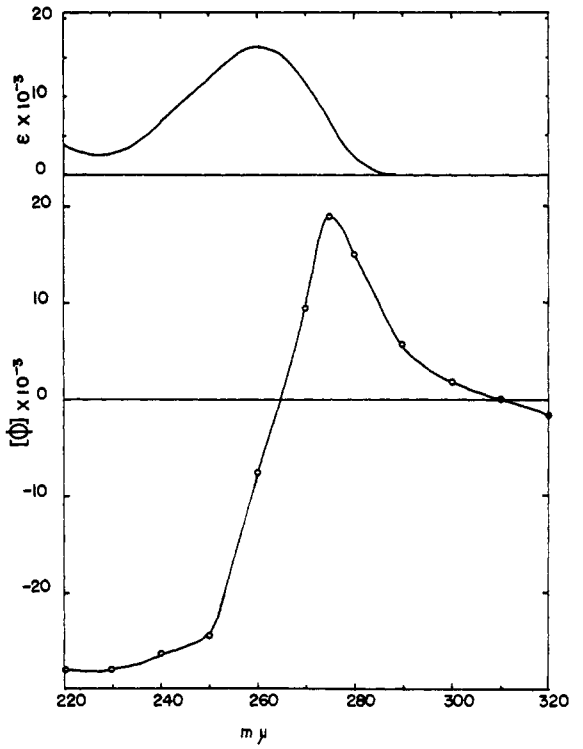


Figure 1. Optical rotatory dispersion curve of 8,5′-anhydro-8-oxyadenosine, 0.870 optical density unit/ml at 20°, 1-cm light path, using a Jasco Model ORD/UV-5 spectrophotometer.

We wish to report a new method for the cyclization of halogenated purine nucleoside and the synthesis of 8,5′-anhydro-8-oxyadenosine (I) by this method.

To a solution of 2′,3′-O-isopropylidene-8-bromoadenosine (II) dissolved in anhydrous dioxane was added portionwise 2 equiv of sodium hydride. The reaction mixture was kept at room temperature for 12 hr. The usual work-up and recrystallization from ethanol gave 8,5′-anhydro-2′,3′-O-isopropylideneadenosine (III), mp 226–226.5°,[8] in a yield of 80%. The structure of III was supported by ultraviolet absorption ($\lambda_{max}^{0.05N HCl}$ 260 mμ (ε 15,400), λ_{max}^{EtOH} 259 mμ (ε 15,100), $\lambda_{max}^{0.05N NaOH}$ 259 mμ (ε 14,900)), infrared absorption (ν_{max}^{KBr} 3360 (6-NH_2), 1040–1090 (sugar C–O–C), 1110–1155 cm^{-1} (isopropylidene)), and elemental analyses. Paper chromatography gave R_f(A)[9] 0.45, R_f(C) 0.83, R_f(D) 0.85 for compound III.

When compound III was heated in 1 *N* sulfuric acid at 60° for 3 hr to remove the isopropylidene group, 8,5′-anhydro-8-oxyadenosine (I) was obtained together with 8-oxyadenosine (IV)[10] and the starting material. Compound I, mp 209–210°, showed ultraviolet absorption properties ($\lambda_{max}^{0.1N HCl}$ 260 mμ (ε 15,000), $\lambda_{max}^{H_2O}$ 260.5 mμ (ε 16,200), $\lambda_{max}^{0.1N NaOH}$ 261 mμ (ε 16,400)) which were similar to those reported for 8-methoxyadenosine[12] and values in

(1) M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963); **87**, 606 (1965).
(2) M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.* (Tokyo), **13**, 639 (1965).
(3) M. Ikehara, H. Tada, K. Muneyama, and M. Kaneko, *J. Am. Chem. Soc.*, **88**, 3165 (1966).
(4) M. Ikehara and H. Tada, *Chem. Pharm. Bull.* (Tokyo), **15**, 94 (1967).
(5) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 3039 (1967).
(6) M. Ikehara and M. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **15**, 126 (1967).
(7) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2959 (1951).
(8) All crystalline compounds reported in this communication gave elemental analyses in satisfactory agreement with the theoretical values.
(9) R_f(A) stands for the R_f value obtained in solvent A. Solvents used were: A, water, adjusted to pH 10; B, 1-butanol–water, 86:14; C, 2-propanol–concentrated ammonia–water, 7:1:2; D, 1-butanol–acetic acid–water, 5:2:3.
(10) Identical with an authentic sample synthesized from 8-bromoadenosine by the acetic acid–sodium acetate procedure[11] (unpublished experiment by M. Kaneko).
(11) M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.* (Tokyo), **13**, 1140 (1965).
(12) R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 1772 (1965).

paper chromatography of R_f(B) 0.32, R_f(C) 0.39, R_f(D) 0.43. The optical rotatory dispersion curve of compound I (Figure 1) has a large peak at 275 mμ and a trough at 220 mμ, giving a Cotton curve around 260 mμ (positive). This suggests that I has the cyclonucleoside structure in conformity with previous observations[13] of other cyclonucleosides of purine. Moreover, an abnormally large amplitude (47,200°) suggests that the base is in the *anti* position. These data together with the following cleavage reaction showed the structure of the compound I to be correct.

When the acidic hydrolysis of III was carried out in 0.1 *N* sulfuric acid for 10 hr, a new compound (V) was obtained together with compound IV and 8-oxyadenine (VI). Compound V, mp 170° dec, obtained by recrystallization from 50% ethanol, showed ultraviolet absorption ($\lambda_{max}^{0.1NHCl}$ 260 (shoulder), 273 mμ, $\lambda_{max}^{H_2O}$ 250 (shoulder), 266.5 mμ, $\lambda_{max}^{0.1NNaOH}$ 273 mμ) which closely resembled that of 8-methoxyadenine[14] and infrared absorption (λ_{max}^{KBr} 1740 cm^{-1} (aldehyde)). R_f values were R_f(B) 0.08, R_f(C) 0.28, and R_f(D) 0.13. These properties together with elemental analyses indicate that compound V has the structure 5-(adenyl-8-)-D-ribose. These hydrolysis experiments prove the anhydro linkage in compound I and III to be in 8,5′ position.

The new method for the cyclization of purine nucleosides could be applied to nucleosides having a sugar moiety in which the secondary hydroxyl group is in the "up" configuration. The method also will be applicable to pyrimidine nucleosides having halogeno substituents in the appropriate positions. Experiments along these lines are in progress.

(13) M. Ikehara, M. Kaneko, K. Muneyama, and H. Tanaka, *Tetrahedron Letters*, 3977 (1967).
(14) R. K. Robins, *J. Am. Chem. Soc.*, **80**, 6671 (1958).

Morio Ikehara, Masakatsu Kaneko
Faculty of Pharmaceutical Sciences
Hokkaido University, Sapporo, Japan
Received September 30, 1967

Exchange Reactions of Carboxylic Acid Salts. A Facile Preparation of α-Deuteriocarboxylic Acids[1]

Sir:

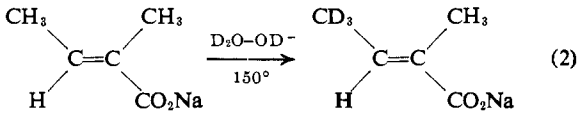
The early literature of deuterium chemistry contains a number of papers on the exchange behavior of carboxylic acids.[2,3] These were largely kinetic studies which were followed by combustion analysis, and did not permit the unambiguous location of exchange in the compounds. Recently, there has been renewed interest in the lability of the α protons of carboxylic acids,[4-6] and we wish to report the results of a detailed reinvestigation of the early exchange reactions with D_2O.[7]

(1) Synthetic Aspects of Stable Isotope Chemistry. IV. For previous papers in this series, see: (a) J. G. Atkinson, D. M. MacDonald, R. S. Stuart, and P. H. Tremaine, *Can. J. Chem.*, **45**, 2583 (1967); (b) J. G. Atkinson, M. O. Luke, and R. S. Stuart, *Chem. Commun.*, 474 (1967); *Can. J. Chem.*, **45**, 1511 (1967); (c) J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, and E. Synnes, *ibid.*, **43**, 1614 (1965).
(2) D. J. G. Ives and R. H. Kerlogue, *J. Chem. Soc.*, 1362 (1940), and earlier papers cited therein.
(3) L. D. C. Bok and K. H. Geib, *Z. Physik. Chem.*, **A183**, 353 (1939).
(4) Y. Kawazoe and M. Ohnishi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1413 (1966).
(5) P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967).
(6) A. T. Bottini and A. J. Davidson, *J. Org. Chem.*, **30**, 3302 (1965).

We have found that simply refluxing a concentrated solution of sodium or potassium acetate in basic deuterium oxide causes ready exchange of the protons of the methyl group with a half-life of 3–5 hr (eq 1). The reaction is quite general and one immediate consequence of this discovery is that it provides a simple, one-step preparation of a wide variety of α-deuteriocarboxylic acids. However, aliphatic substitution on the α carbon of acetic acid slows the exchange rate severalfold so that, although it is possible to exchange higher acids at reflux, the rather long reaction times are best avoided by running the exchange in a stainless-steel bomb at 150°. The general procedure involved dissolving 0.5 mole of the sodium or potassium salt in 200 ml of D_2O containing 0.05 mole of OD^-, heating at 150° for 24 hr, removing the spent D_2O, and adding fresh heavy water. Five such exchanges usually sufficed to bring the isotopic content to >98 atom % D. The free acids were recovered by acidification of the aqueous solutions and could be purified by distillation or recrystallization without loss of deuterium.

The extent and location of deuteration were determined by nmr. In no case of those reported here was there evidence for exchange at any but the α (or vinylogously α) carbon atom. A careful check was made on propionic-α,α-d_2 acid which was converted to the ethyl ester and analyzed by mass spectrometry. A maximum of 0.5% d_3 species was present, indicating that a homoenolic mechanism is not operating.[8,9] Table I contains a list of the deuterated acids prepared in this work.

$$CH_3CO_2Na \xrightarrow[120°]{D_2O\text{-}OD^-} CD_3CO_2Na \qquad (1)$$



(2)

Runs 1–11 in Table I represent the aliphatic monocarboxylic acids exchanged as their potassium salts. The deuteration in all cases was excellent with the exception of cyclopropanecarboxylic acid.[6] A series of aliphatic dicarboxylic acids from C_4 to C_8 was exchanged, with the results shown in Table I, runs 12–16. It can be seen that $\alpha,\alpha,\alpha',\alpha'$-tetradeuteriodicarboxylic acids can be thus readily prepared with high isotopic purity and good chemical yield. Runs 17–20 in Table I show the results of exchange of several arylacetic acids. As might be expected, exchange proceeds quite readily, the half-life of exchange of sodium phenylacetate being 8 min at 85°.[10]

Several α,β-unsaturated carboxylic acids and toluic acids were then investigated to determine whether the activating influence of the carboxylate group would be extended by conjugation. This was found to be the case as shown for tiglic (eq 2) and senecioic acids (runs

(7) Presented in part at the Second International Conference on Methods of Preparing and Storing Labelled Molecules, Brussels, Belgium, Nov 28–Dec 3, 1966.
(8) A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, *J. Am. Chem. Soc.*, **88**, 3354 (1966).
(9) A further check on this possibility is being carried out on trimethylacetic acid.
(10) Detailed studies of the kinetics of exchange of a series of ring-substituted phenylacetic acid salts are being carried out by Dr. P. Bélanger in these laboratories and will be reported shortly.