as benzoic acid, and that the acidic strength of the second hydrogen of II is about the same as that of the phenol. These results are given in Table II.

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Potential Anticancer Agents.[1] III.
3'-Amino-3'-deoxyadenosine

ELMER J. REIST AND B. R. BAKER

The synthesis of 3'-amino-3'-deoxyadenosine from chloromercuri-6-benzamidopurine and 2,5-di - O - benzoyl - 3 - deoxy - 3 - phthalimido - β - D-ribofuranosyl chloride was described by Baker, Schaub, and Kissman in 1955.[2] Since additional amounts of this biologically active nucleoside were required for pharmacological evaluation, its synthesis was repeated; the opportunity was taken to use two later modifications in nucleoside synthesis.

The first modification was the use of pure chloromercuri-6-benzamidopurine, prepared by the Fox method;[3] this procedure has previously led to higher yields of nucleosides.[4] The second modification employed was the deacylation of the blocked nucleoside with n-butylamine in boiling methanol.[5] By these two modifications, 3'-amino-3'-deoxyadenosine crystallized from the methanolic butylamine reaction mixture in 66% yield (based on chloro sugar) and was pure as shown by paper chromatography.

The earlier described procedure[2] required ion exchange chromatography for isolation and the over-all yield from the sugar halide was 31%. Thus, the above two new modifications in nucleoside synthesis more than doubled the previous yield.

EXPERIMENTAL[6,7]

3'-Amino-3'-deoxyadenosine. A mixture of 11.8 g. of

chloromercuri-6-benzamidopurine[8] and 11.8 g. of Celite[9] suspended in 1180 ml. of xylene was distilled with stirring until no more water was removed (about 360 ml. of distillate). After a warm solution of 10.2 g. of crystalline 2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl chloride[10] in 210 ml. of xylene had been added, the mixture was heated under reflux for 3 hr. The hot solution was filtered and the filter cake was washed with 200 ml. of hot toluene. The combined filtrate and washings were concentrated to dryness *in vacuo.* The filter cake was extracted with five 100-ml. portions of boiling chloroform. The residue from the toluene-xylene concentration was dissolved in the combined chloroform extracts. The chloroform solution was washed with two 200-ml. portions of 30% aqueous potassium iodide solution, then with 200 ml. of water. The chloroform solution was dried over magnesium sulfate, then evaporated to dryness to yield 17.0 g. of cream colored solid; λ_{max}^{KBr} 2.92μ (NH, OH); 5.63μ (imido C=O); 5.81μ (benzoate and imido C=O); 7.90μ (benzoate O=C—O); 8.96μ (C—O—C).

The crude blocked nucleoside (17.0 g.) was dissolved in 210 ml. of methanol containing 30 ml. of n-butylamine. This solution was heated under reflux for 6 hr. After 3 hr. heating, the solution began to deposit a white, crystalline solid. The mixture was cooled at 0° overnight, then filtered. The white, crystalline precipitate was washed with methanol, then dried to yield 3.57 g. (66% based on chloro sugar) of 3'-amino-3'-deoxyadenosine, m.p. 265–267° (dec.); λ_{max}^{KBr} 3.00, 3.17μ (OH, NH); 6.00, 6.23, 6.37μ (adenine double bond structure); 9.08, 9.28, 9.64μ (C—O—). The paper chromatogram[7] contained a single spot at R_{Ad} 1.25.

Baker, Schaub, and Kissman[2] reported a m.p. 260–261° (dec.).

The methanol mother liquors contained an additional 2% of 3'-amino-3'-deoxyadenosine along with about 2% of adenine, as shown by paper chromatography.[7]

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(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research.

(2) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Am. Chem. Soc.*, **77**, 5911 (1955).

(3) Footnote 21 of reference (4).

(4) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(5) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

(6) The infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. The melting point was taken on a Fisher-Johns apparatus and is uncorrected.

(7) The paper chromatograms were run with 5% aqueous disodium phosphate by the descending procedure on Whatman No. 1 paper. Adenine was used as a standard and arbitrarily assigned R_{Ad} 1.00. The distance moved by the nucleoside spot was assigned an R_{Ad} value with reference to adenine. The spots were located by visual examination with an ultraviolet lamp.

(8) From 6-benzamidopurine as described for the preparation of chloromercuri-2,6-diacetamidopurine by B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(9) An analytical grade product of Johns-Manville Corp.

(10) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

Preparation of Acetals and Ketals from Enol Esters

D. H. HIRSH, R. I. HOAGLIN, AND D. G. KUBLER

The reaction of an alcohol and an enol ester to form acetals or ketals is catalyzed by mercuric oxide in combination with boron trifluoride (or mercuric sulfate alone).[1] This catalyst combination was observed to effect a very vigorous reaction, as has been reported. However, we have found that the reaction of ethanol and isopropenyl acetate had an induction period of 5 to 8 minutes when the ester was added to the ethanol containing the mixed catalyst at 30°.

The induction period was eliminated and the yields of ketals were improved by using mercuric

(1) W. J. Croxall, F. J. Glavis, and H. T. Neher, *J. Am. Chem. Soc.*, **70**, 2805 (1948).

acetate instead of mercuric oxide or by milling the mercuric oxide in ethanol with a mortar and pestle.[2] A comparison of the results using these mercuric catalysts for the preparation of diethyl ketal is shown in Table I.

TABLE I

COMPARISON OF MERCURIC CATALYSTS FOR THE REACTION OF ETHANOL AND ISOPROPENYL ACETATE[a]

Hg^{++} Catalyst, G.	Induction Time, Min.	Total Reaction Time, Min.	Yield, %
Red HgO, 12.5	6	24	61[b]
Red HgO (milled), 12.5	1	17	71[c]
Hg(OAc)₂, 18.4	<1	17	70[d]

[a] For each of these experiments, 12.5 moles of isopropenyl acetate was reacted with 37.5 moles of ethanol at 45 to 50° in the presence of 6.2 g. (contained) of BF₃ in ethyl ether. [b] This yield is the average of 8 experiments for which the yields varied from 53 to 68%. [c] This yield is the average of 3 experiments for which the yields varied from 67 to 74%. [d] This yield is the average of 8 experiments for which the yields varied from 68 to 73%.
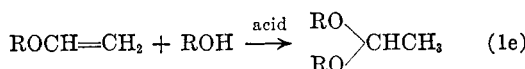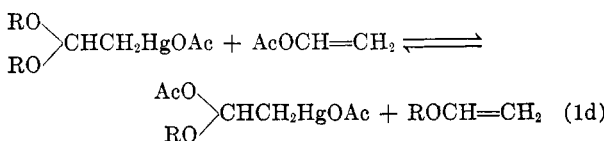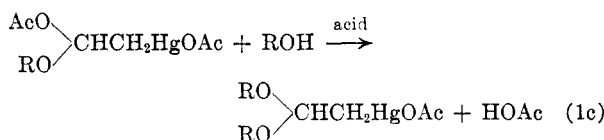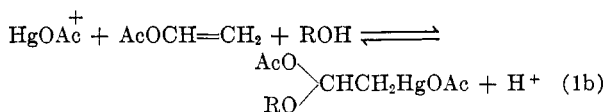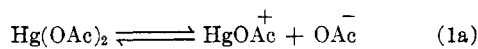
Although these experiments were conducted with a 3 to 1 molar ratio of ethanol to isopropenyl acetate, in general, a 2.2 to 1 mole ratio provides yields which are nearly as good. Excess amounts of water-soluble alcohols in the reaction mixture preferably are extracted by water after neutralizing the co-product acetic acid. If this is not done sufficient water is retained in the mixture to effect partial hydrolysis of the ketal during distillation.

A comparison of our results to those reported in the literature[1] is given in Table II. For the preparation of dibutyl acetal, our results are the same as the reported yields but for the preparation of ketals we obtained better yields.

The results obtained in this study suggest, in agreement with those of Watanabe and Conlon,[3] that the effective form of mercury acting as a catalyst for general exchange reactions of vinyloxy compounds is mercuric acetate (or mercuric salts of organic acids) rather than mercuric oxide,[1] mercuric phosphate,[1] or mercuric sulfate.[4] The addition of mercuric acetate in the presence of alcohols to carbon-carbon double bonds proceeds according to Markownikoff's rule.[5] Addition compounds of this type and their derivatives have been isolated in

many instances.[6-8] This reaction also has been adapted to the quantitative determination of carbon-carbon double bonds.[9]

Intermediates similar to those proposed by Watanabe and Conlon can be written in conjunction with acid-catalyzed steps to explain the conversion of vinyl ester to vinyl ether to acetal. We believe, however, that these steps can be simplified somewhat as follows:[10]

$$Hg(OAc)_2 \rightleftharpoons Hg\overset{+}{O}Ac + \overset{-}{O}Ac \quad (1a)$$

$$Hg\overset{+}{O}Ac + AcOCH{=}CH_2 + ROH \rightleftharpoons$$
$$\underset{RO}{\overset{AcO}{>}}CHCH_2HgOAc + H^+ \quad (1b)$$

$$\underset{RO}{\overset{AcO}{>}}CHCH_2HgOAc + ROH \xrightarrow{acid}$$
$$\underset{RO}{\overset{RO}{>}}CHCH_2HgOAc + HOAc \quad (1c)$$

$$\underset{RO}{\overset{RO}{>}}CHCH_2HgOAc + AcOCH{=}CH_2 \rightleftharpoons$$
$$\underset{RO}{\overset{AcO}{>}}CHCH_2HgOAc + ROCH{=}CH_2 \quad (1d)$$

$$ROCH{=}CH_2 + ROH \xrightarrow{acid} \underset{RO}{\overset{RO}{>}}CHCH_3 \quad (1e)$$

Equations 1a and 1b are essentially the same as those which have been given for the start of vinyl transetherification or transesterification.[3] Step 1c must be acid-catalyzed to permit the over-all reaction to proceed.[11] Equation 1d for the formation

(2) The water solubility of red HgO can be increased by grinding. See F. Ephraim, *Inorganic Chemistry*, 6th Ed., Interscience Publishers, Inc., N. Y., 1954, p. 490.

(3) W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

(4) R. L. Adelman, *J. Am. Chem. Soc.*, **75**, 2678 (1953); D. D. Coffman, G. H. Kalb, and A. B. Ness, *J. Org. Chem.*, **13**, 223 (1948).

(5) F. C. Whitmore, *Organic Compounds of Mercury*, New York Chemical Catalogue Company, N. Y., 1921, p. 31.
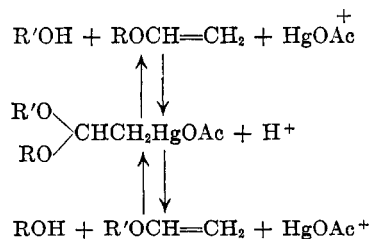
(6) R. Adams, F. L. Roman, and W. N. Sperry, *J. Am. Chem. Soc.*, **44**, 1781 (1922).

(7) G. Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935).

(8) I. F. Lutsenko, R. M. Khomutov, and L. V. Eliseeva, *Bull. acad. sci. U.S.S.R. Div. Chem. Sci. S.S.R.* (English translation), **No. 2**, 173 (1956).

(9) R. W. Martin, *Anal. Chem.*, **21**, 921, 1194 (1949).

(10) For vinyl transetherification (or transesterification) a "symmetrical intermediate" would not seem to be an essential requirement.[3] The following equation would lead to the same result:

$$R'OH + ROCH{=}CH_2 + Hg\overset{+}{O}Ac$$
$$\uparrow\downarrow$$
$$\underset{RO}{\overset{R'O}{>}}CHCH_2HgOAc + H^+$$
$$\uparrow\downarrow$$
$$ROH + R'OCH{=}CH_2 + HgOAc^+$$

The over-all conversion obtained would depend upon the mole ratios of reactants, the relative reactivities of the alcohols and vinyl ethers, and whether or not one of the products is removed, as for example, by distillation.

(11) One of the referees has suggested that BF₃ creates more of the reactive species, HgOAc[+] by:

$$Hg(OAc)_2 + BF_3 \rightleftharpoons Hg\overset{+}{O}Ac + BF_3{\cdot}\overset{-}{O}Ac$$
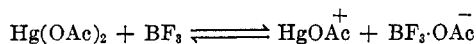
which is the initiating step of the reaction sequence.

TABLE II

PREPARATION OF ACETALS AND KETALS

Enol Acetate, Moles	Alcohol, Moles	Tempera-ture[a]	Product	Observed Yield, %	Literature[1] Yield, %
Vinyl, 2.0	Butyl, 4.2	26–54°	Dibutyl acetal	88	88
Isopropenyl, 14.0	Methyl, 29.4	29–54°	Dimethyl ketal	53[b]	—
Isopropenyl, 12.5	Ethyl, 37.4	30–50°	Diethyl ketal	70[c]	55
Isopropenyl, 10.0	Butyl, 22.0	10–55°	Dibutyl ketal	83[d]	63
Isopropenyl, 6.0	Allyl, 12.6	20–25°	Diallyl ketal	50[e]	32

[a] These values represent the temperature ranges from the start of ester addition until the temperatures were moderated by cooling. The temperatures were then controlled at 50 ± 5° by cooling. For the preparation of diallyl ketal no cooling was required. [b] For this experiment, 3.6 g. BF₃ and 10.0 g. Hg(OAc)₂ were used. The ester addition time was 13 mins. and the total reaction time was 23 mins. The yield is the average of three expts. for which the values varied from 51 to 55%. [c] For this experiment, 7.2 g. BF₃ and 18.4 g. Hg(OAc)₂ were used. The ester addition time was 16 min. and the total reaction time was 18 min. The yield is the average of eight experiments for which the values varied from 68 to 73%. [d] For this experiment, 4.0 g. BF₃ and 12.0 g. Hg(OAc)₂ were used. The ester addition time was 10 min. and the total reaction time was 20 min. The yield is the average of two experiments for which the values were 80 and 86%. [e] For this experiment, 4.0 g. BF₃ and 12.0 g. Hg(OAc)₂ were used. The ester addition time was 45 min. and the total reaction time was 170 min.

of vinyl ether is a necessary consequence of Adelman's[4] demonstration that vinyl ethers are intermediates in the conversion of vinyl esters to acetals or ketals. Finally, equation 1e is for the well-established, acid-catalyzed reaction of a vinyl ether and an alcohol to form acetals.[12]

At temperatures in excess of 25°, the reaction represented by step 1e proceeds fairly rapidly. At 40° this reaction is extremely rapid so that at these temperatures one would not expect to isolate the vinyl ether intermediate. We have found that at −25° the rate of the acid-catalyzed addition of an alcohol to a vinyl ether is very slow (see Experimental section) and hence under Adelman's conditions for vinyl ester exchange with an alcohol,[4] the vinyl ether has a sufficiently long existence to permit its isolation in good yields. The effective catalyst system under Adelman's conditions is probably mercuric acetate and sulfuric acid, not mercuric sulfate. These two reagents were added to the reaction mixtures, presumably to form mercuric sulfate. Even if mercuric sulfate were added, one should expect sufficient exchange with the by-product acetic acid to provide some mercuric acetate.

EXPERIMENTAL

Diethyl ketal. To a mixture of 1725 g. (37.5 moles) of ethanol, 18.4 g. of mercuric acetate, and 28 ml. of 26% boron trifluoride in diethyl ether at 30°, there was added 1250 g. (12.5 moles) of isopropenyl acetate over a period of 15 min. while maintaining the mixture at 45 to 50° by external cooling. Two minutes after all of the isopropenyl acetate was added, the mixture was poured into 2200 g. of 25% sodium hydroxide with stirring and cooling. The water layer was removed and the organic layer washed first with 400 ml. of 0.01N sodium hydroxide followed by 3 washings with 200 ml. of 0.01N sodium hydroxide. Rapid distillation of the

organic layer provided 1145 g. (69% yield) of diethyl ketal which boiled at 110–113°.

Dibutyl ketal. A mixture of 1635 g. (22 moles) of butanol, 12.5 ml. of 32% boron trifluoride in diethyl ether, and 12 g. of mercuric acetate was cooled to 5° and 1010 g. (10.1 moles) of isopropenyl acetate was added over a period of 10 min. The temperature of the reaction mixture was maintained at 45 to 55° during the addition by means of an ice water bath. The mixture was cooled to 18° over a 10-min. period and then 1500 g. of 30% aqueous sodium hydroxide was added over a 3-min. period (max. temp. of 53°). The upper layer (1924 g.) was distilled to provide 1521 g. (80% yield) of dibutyl ketal which boiled at 74°/10 mm. Hg.

Addition of butanol to vinyl butyl ether. A. Reaction at 40°. To 111 g. (1.5 moles) of butanol there was added 0.21 g. of concentrated sulfuric acid and the mixture was warmed to 40°. One mole (100 g.) of vinyl butyl ether was added as rapidly as possible (3 min.) and the temperature maintained between 39 and 41° by cooling. As soon as all of the ether was added, a sample was removed and analyzed immediately for vinyl butyl ether.[13] More than 95% of the vinyl butyl ether had reacted during this time.

B. Reaction at −25°. A mixture of 50 g. (0.5 mole) of vinyl butyl ether and 54 g. (0.73 mole) of butanol was added to a 2- by 4-in. wide-mouth tube which narrowed to a 1- by 6-in. round bottom tube. The tube and contents were immersed in a Dewar flask and the temperature was adjusted to −25° by means of Dry Ice and acetone. The mixture was analyzed for vinyl butyl ether, then acidified with 0.1 g. of sulfuric acid in 1 ml. of butanol. During the entire experiment the temperature was maintained at −25° ± 4°. The conversions of vinyl butyl ether to dibutyl acetal after 1 hr., 4 hr., and 6.5 hr. were 4.9%, 12.5%, and 16.8%, respectively. The mixture was then allowed to warm slowly to room temperature. When the temperature reached 30°, the reaction was proceeding at a sufficiently rapid rate for the temperature to rise to 40° in 3 min. The mixture was cooled to room temperature and analyzed for vinyl butyl ether. More than 98% of the vinyl butyl ether was converted to the acetal.

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(12) H. S. Hill, *J. Am. Chem. Soc.*, **50**, 2725 (1928); W. Reppe and K. Baur, U. S. Patent 2,000,252 (May 7, 1935).

(13) The analysis for vinyl butyl ether involved a method which has not been published and uses a mercuric acetate reagent which is a modification of that reported by Martin.[9]