that of the ethyl-1-C^{14} chloride, hence all the C^{14} was in the α-position and no isomerization of the ethyl-1-C^{14} benzene occurred before or during alkylation.

Alkylation of benzene at room temperature by ethyl-1-C^{14} chloride. A mixture of 1.5 g. of aluminum chloride and 21 g. of dry benzene was stirred at room temperature (about 30°) while a solution of 11 g. of ethyl-1-C^{14} chloride (0.578 μc./m. mole) in 27 g. of cold dry benzene was added dropwise. The addition required 5 min.; stirring at room temperature was continued for an additional 1.25 hr. The reaction mixture was decomposed with ice water and worked up in the usual way. Fractional distillation through a 50-cm. glass helix-packed column gave 5.6 g. of ethylbenzene, b.p. 133–136° and 1.2 g. of diethylbenzene, b.p. 172–178°.

A 1-ml. sample of the ethylbenzene fraction was oxidized with 5 g. of potassium permanganate as described above. The benzoic acid produced was recrystallized from 50% ethyl alcohol; m.p. 120–121°. Radioassay of a 5.2 mg. sample gave 0.555 μc./m. mole. The remaining benzoic acid was sublimed; radioassay of an 11.0-mg. sample gave 0.556 μc./m. mole, and of a 13.7-mg. sample, 0.553 μc./m. mole. The difference in the radioactivity of the ethyl-1-C^{14} chloride and the benzoic acid corresponded to 4.0% isomerization accompanying alkylation.

A 1-ml. sample of the diethylbenzene fraction was oxidized by the same procedure, using 11 g. of potassium permanganate. The phthalic acid produced was recrystallized from 50% ethyl alcohol; 327 mg. was obtained. A 6.2-mg. sample radioassayed gave 1.11 μc./m. mole. The phthalic acid was recrystallized; a 5.8-mg. sample radioassayed gave 1.11 μc./m. mole. The difference in the radioactivity of the ethyl-1-C^{14} chloride and the phthalic acid corresponded to 4.0% isomerization *per ethyl group* accompanying alkylation.

A second alkylation was carried out which was identical with the above except that the activity of the ethyl-1-C^{14} chloride was 0.603 μc./m. mole, and the amount of aluminum chloride used was 15.0 g. rather than 1.5 g. The amounts of ethylbenzene and diethylbenzene obtained from this reaction were 2.18 g. and 2.32 g., respectively.

Oxidation of a sample of the ethylbenzene gave benzoic acid, which was recrystallized twice from 50% ethyl alcohol and then sublimed. Radioassay of 13.2-mg. and 11.1-mg. samples gave 0.555 and 0.555 μc./m. mole, respectively, corresponding to 8.0% isomerization.

Oxidation of a sample of the diethylbenzene gave phthalic acid, which was recrystallized twice from 60% ethyl alcohol. Radioassay of 15.0-mg. and 8.3-mg. samples gave 1.11 and 1.13 μc./m. mole, respectively, the average corresponding to 7.8% isomerization *per ethyl group* accompanying alkylation.

Acknowledgment. Professor H. C. Brown suggested repeating the alkylation reaction at a lower temperature. We are indebted to him for this suggestion and for other helpful discussion.

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Acidic Properties of Tetrazole Derivatives in a Nonaqueous Medium[1]

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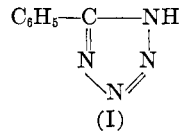
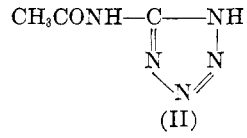
Herbst and co-workers have recently described certain tetrazole derivatives and called attention to their acidic properties.[2,3] They made the prediction[2] that 5-acetylaminotetrazole might react as a dibasic acid in nonaqueous media.

We have titrated 5-phenyltetrazole (I) and 5-



(I)



(II)

acetylaminotetrazole (II)[4] in ethylenediamine solution, using sodium aminoethoxide as the base and determining the endpoints potentiometrically with antimony electrodes.[5]

The results are given in Table I.

TABLE I

NEUTRALIZATION EQUIVALENTS

Substance	Calcd.	Found
5-Phenyltetrazole	146.2	149.9
5-Acetylaminotetrazole		
First hydrogen	127.1	130.4
Both hydrogens	63.6	64.7

Two inflections very near the calculated values in the titration curve for compound II showed that it does behave as a dibasic acid under these conditions.

As the stronger of two acids will titrate before the weaker in a mixture,[5] compound I was titrated in admixture with benzoic acid, and I and II each with 3,5-dimethylphenol in order to get a qualitative comparison of their acidic strengths. It was found that I has approximately the same strength

TABLE II

TITRATION OF MIXTURES

Mixture	Sample (G.)	Titrant: Normality	Titrant: Ml. calcd.	Titrant: Ml. found
5-Phenyltetrazole	0.0532	0.185	1.97	
Benzoic acid	0.0997		4.41	
Total			6.38	6.51
5-Phenyltetrazole	0.0671	0.185	2.48	2.70[a]
3,5-Dimethylphenol	0.1027		4.54	
Total			7.02	7.40
5-Acetylamino-tetrazole	0.1031	0.236	3.44	3.41[a]
			3.44	
3,5-Dimethylphenol	0.0516		1.79	
Total			8.67	8.61

[a] First inflection.

(1) Publication authorized by the Chief, Illinois State Geological Survey.

(2) R. M. Herbst and W. L. Garbrecht, *J. Org. Chem.*, **18**, 1283 (1953).

(3) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

(4) Samples kindly provided by Dr. R. M. Herbst, Michigan State University, East Lansing, Mich.

(5) M. L. Moss, J. H. Elliott, and R. T. Hall, *Anal. Chem.*, **20**, 784 (1948).

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

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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

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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).