phorus pentoxide. In order to induce precipitation, it was sometimes necessary to keep the turbid solution at −20° overnight. Addition of ether to the turbid solution often proved helpful. The alcohol and ether washings, when added to the original mother liquor, usually yielded additional amounts of the aminophosphoric acid.

N-Diisopropylphosphoryl-*dl*-serine methyl ester (4.0 g.) yielded 0.540 g. (21%) of ***dl*-serinephosphoric acid**,[8] melting at 166–167°. When the reflux time was reduced to 4 hours, *dl*-serinephosphoric acid was isolated in 26% yield.

Anal. Calcd. for $C_3H_8O_6NP$: C, 19.47; H, 4.36; N, 7.57; P, 16.74. Found: C, 19.4; H, 4.43; N, 7.45 (Van Slyke), 7.80 (Dumas); P, 16.6.

N-Diisopropyl-*dl*-threonine methyl ester (3.0 g.) yielded 1.04 g. (52%) of **threoninephosphoric acid**,[9] melting at 184°.

Anal. Calcd. for $C_4H_{10}O_6NP$: C, 24.13; H, 5.06; N, 7.04; P, 15.56. Found: C, 24.2; H, 5.30; N, 7.1 (Van Slyke), 7.0 (Dumas); P, 15.8.

N-Diisopropylphosphorylethanolamine (3.0 g.) yielded 350 mg. of **ethanolaminephosphoric acid** (18.6%), melting at 242°.[10]

Anal. Calcd. for $C_2H_8O_4NP$: C, 17.03; H, 5.72; N, 9.93; P, 21.96. Found: C, 16.8; H, 5.6; N, 9.55 (Van Slyke), 9.65 (Kjeldahl); P, 22.10.

Attempts were made to isolate the O-diisopropylphosphorylated esters of serine and threonine by treatment of the corresponding N-phosphorylated isomer, in either methanol or dioxane, with gaseous hydrogen chloride gas. When these attempts proved unsuccessful, the organic solvent was removed under vacuum and the residue hydrolyzed with boiling aqueous hydrochloric acid. The yields of phosphoroamino acids were identical with those obtained by direct treatment of the phosphoramide with boiling aqueous acid. N-Diisopropylphosphoryl-*l*-(+)-cysteine methyl ester yielded only cysteine hydrochloride when subjected to treatment with gaseous and then boiling aqueous hydrochloric acid.

Acknowledgment.—The authors wish to express their sincere appreciation to Pfc. Patrick Tetta, of this Branch, and to the Analytical Branch, Chemical and Radiological Laboratories, Army Chemical Center, Md., for the microanalyses of the compounds encountered in this investigation.

[8] R. H. A. Plimmer (see footnote 4), reports a m.p. of 165–166° for this substance.

[9] R. H. A. Plimmer (see footnote 4), reports a m.p. of 169° for *dl*-threoninephosphoric acid. However, his material is a monohydrate. C. H. de Verdier, *Nature*, **170**, 804 (1952), reports a m.p. of 194° for *l*-threoninephosphoric acid isolated from bovine casein.

[10] E. L. Outhouse, *Biochem. J.*, **31**, 1454 (1937), reports a m.p. of 244° for this compound.

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Some Pyrimidine Derivatives[1]

BY JOSEPH L. RABINOWITZ AND SAMUEL GURIN

RECEIVED JULY 10, 1953

During the course of an antimetabolite project to be reported elsewhere, several new pyrimidine derivatives were prepared. This note concerns their synthesis in addition to modifications or improvements in the preparation of a number of previously known substances.

Experimental[2]

(a) **Thymine-1-acetic Acid.**—To 12.6 g. (0.1 mole) of thymine and 9.6 g. (0.2 mole) of KOH in 75 ml. of H_2O was added slowly 7.85 g. (0.1 mole) of chloroacetic acid in 30 ml. of H_2O.[3] (The corresponding ester can be used with equal success.) The *p*H of the solution was adjusted to and kept at 10 by the dropwise addition of a KOH solution. After refluxing for two hours, the solution was cooled, and acidified to *p*H 2 by the addition of concd. HCl. The resulting precipitate was filtered, washed with a little cold water, dissolved in a saturated $KHCO_3$ solution and reprecipitated with HCl; crude yield 16 g. (*ca.* 85%); recrystallized *ca.* 50% yield, m.p. 260–261°.

Anal. Calcd. for $C_7H_8O_4N_2$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.64; H, 4.41; N, 15.21.

(b) **1,3-Diethylthymine.**—To 13 g. (*ca.* 0.1 mole) of thymine in a solution of 10 g. of NaOH in 60 ml. of water, was added dropwise 30 ml. of ethyl sulfate.[4] The solution was stirred at room temperature for one hour, then kept stirring for another hour just below its boiling temperature. After cooling, the solution was extracted several times with $CHCl_3$; after drying the $CHCl_3$ with $MgSO_4$, it was filtered and evaporated to dryness. The resulting 1,3-diethylthymine can be recrystallized from petroleum–ethyl ether, m.p. 56–57°, b.p. 140–143° (7 mm.), yield 6.5 to 7.8 g. (*ca.* 40%).

Anal. Calcd. for $C_9H_{14}O_2N_2$: C, 59.31; H, 7.74; N, 15.37. Found: C, 58.99; H, 7.61; N, 15.27.

(c) **2,4-Diethoxy-5-nitro-6-methylpyrimidine.**—To a cold mixture consisting of 15 ml. of red fuming nitric acid (d. 1.5) and 15 ml. of concd. H_2SO_4 was added slowly 2.5 g. (0.02 mole) of 2,4-diethoxy-6-methylpyrimidine.[12] The solution was kept at 80° for one hour, then poured onto cracked ice. The mixture was first neutralized with KOH, then acidified to *p*H 2 with HCl. The solution was chilled, filtered and the precipitate washed with cold water, the residue was extracted with 50 ml. of ether, decolorized with charcoal and treated with 50 ml. of MeOH. The ether was removed by warming on a water-bath and the remaining solution treated with cold water to faint turbidity. The suspension was chilled, and fine yellow needles collected. The compound sublimes, m.p. 38°, yield 2.7 g. (*ca.* 60%).

Anal. Calcd. for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.76; N, 18.49. Found: C, 47.93; H, 5.71; N, 18.53.

(d) **2,4-Diethoxy-5-nitropyrimidine.**—Twenty-five grams (0.15 *M*) of 2,4-diethoxypyrimidine[5] was added dropwise to a mixture of 150 ml. of red fuming nitric and 150 ml. of concd. sulfuric acids (prepared by slow addition of chilled sulfuric to chilled nitric). After standing for one hour at room temperature, the solution was placed in warm water (60°) and stirred. The temperature was maintained at 60° for one hour. The solution was then cooled to room temperature and decomposed cautiously with 500 g. of cracked ice. After removal of the first crop by filtration, additional material was recovered from the filtrate by neutralization with concd. KOH to *p*H 7.5 followed by the addition of NaCl and chilling.

All of the precipitated material was combined, dissolved in hot absolute EtOH and decolorized with charcoal. Fine, pale yellow needles were obtained after chilling, m.p. 45°, yield 9.5–11 g. (*ca.* 30%).

Anal. Calcd. for $C_8H_{11}O_4N_3$: C, 45.06; H, 5.20; N, 19.71. Found: C, 44.96; H, 5.21; N, 19.64.

(e) **4-Methoxy-1,6-dimethyl-2-pyrimidone.**—To a mixture of 3 g. of 2,4-dimethoxy-6-methylpyrimidine[6] and 2.1 ml. of methyl iodide a few drops of pyridine were added; after 24 hr. at room temperature a solid deposited. The solid was recrystallized from hot alcohol by the addition of absolute ether, yield 95%, m.p. 112.5°.

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.52; H, 6.54; N, 18.18. Found: C, 54.70; H, 6.55; N, 17.96. Upon hydrolysis with HCl 1,6-dimethyluracil was obtained.

(f) **1,3-Diethyl-6-methyluracil.**[7]—A more convenient method of preparation involved the addition of 45 ml. of

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[1] Supported by a grant of the Cancer Institute of the National Institutes of Health.

[2] All melting points are uncorrected. We wish to thank the Organic Research Laboratory of Sharp and Dohme, Inc., for most of the analyses reported in this paper.

[3] H. L. Wheeler and L. M. Liddle, THIS JOURNAL, **30**, 1152 (1908).

[4] P. A. Levene, L. W. Bass and H. S. Simms, *J. Biol. Chem.*, **70**, 229 (1926).

[5] G. E. Hilbert and T. B. Johnson, THIS JOURNAL, **52**, 2004 (1930).

[6] S. Gabriel and J. Colman, *Ber.*, **32**, 2921 (1899).

[7] J. Hoffmann, *Ann.*, **253**, 68 (1889); M. Hagen, *ibid.*, **244**, 8 (1888); O. Heobel and R. Behrend, *ibid.*, **353**, 246 (1907); O. Buchendorff, *ibid.*, **385**, 314 (1911).

ethyl sulfate to a mixture of 20 g. of 6-methyluracil and 17 g. of sodium hydroxide in 100 ml. of H_2O.[4] After 3 hr. of vigorous stirring, the solution was extracted with chloroform, dried over $MgSO_4$, filtered and the chloroform then distilled off, yield 75%, m.p. 52°. The m.p. of a mixture of material prepared by this method and Behrend's method was unchanged.

(g) **1,5-Dimethyl-4-ethoxy-2-pyrimidone.**[8]—The addition of a few drops of pyridine to a solution containing an excess of methyl iodide with 2,4-diethoxypyrimidine,[6] improves the yield materially.

(h) **1-Ethyl-4-ethoxy-2-pyrimidone.**[9]—Slightly better yields were obtained by the addition of a few drops of pyridine to a solution containing an excess of ethyl iodide with 2,4-diethoxypyrimidine. The reaction is complete after 24 hours instead of 7 days.

(i) **1-Tetraacetyl-β-D-glucosido-2-oxy-4-ethoxy-1,2-dihydropyrimidine.**[10]—An improvement in the reported yield of this compound was obtained when a molecular equivalent of pyridine was added to an equimolecular mixture of 1-bromo-tetraacetyl-D-glucose with 2,4-diethoxypyrimidine[5] in chloroform. The yield is increased from 20 to 50% (calculated from the pyrimidine). The bromoacetylglucose need not be recrystallized when this method is used. The intermediate pyrimidium salt of bromoacetylglucose[11] can be isolated when this reaction is carried out in the presence of chloroform and pyridine.

(j) **1-Tetraacetylglucosido-4-ethoxy-6-methyl-2-pyrimidone or 2-Tetraacetylglucosido-4-ethoxy-6-methylpyrimidine.**—A thick oil was obtained when 9 g. (0.02 mole) of 2,4-diethoxy-6-methyluracil[12] and 9 g. (0.02 mole) of 1-bromotetraacetylglucose were kept in a sealed tube at 65° for four days. The resulting oil was filtered, treated with 30 ml. of ether and chilled for one day. A heavy white crystalline precipitate was filtered and twice recrystallized from EtOH–H_2O using Norite; m.p. 166°, yield 2.9 to 3.2 g. (*ca.* 32%), $[\alpha]^{25}\text{D}$ +119.7 (*c*, 0.5 in C.P. chloroform). Similar results have been reported recently by Newmark and Goodman.[13]

Anal. Calcd. for $C_{12}H_{28}O_{11}N_2$: C, 52.06; H, 5.82; N, 5.78. Found: C, 51.96; H, 5.75; N, 5.78–5.71.

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[8] W. Schmidt-Nickels and T. B. Johnson, THIS JOURNAL, **52**, 4511 (1930).

[9] G. E. Hilbert, *ibid.*, **59**, 330 (1937).

[10] G. E. Hilbert and E. F. Jansen, *ibid.*, **58**, 60 (1936).

[11] E. Fisher and K. Raske, *Ber.*, **43**, 1751 (1910).

[12] B.p. 235°, $n^{23}\text{D}$ 1.4853. *Anal.* Calcd. for $C_9H_{14}O_2N_2$: C, 59.31; H, 7.74; N, 15.37. Found: C, 59.08; H, 7.62; N, 15.30. The compound was prepared before R. Andrisano's work in *Boll. sci. Faculta chim. ind., univ. Bologna*, **5**, 52 (1944); **5**, 56 (1947), became available.

[13] P. Newmark and I. Goodman, A. C. S. 122nd Meeting, 1952, abstract of Papers, 44C.

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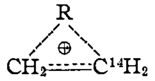
Rearrangement in the Reaction of C^{14}-Labeled *n*-Propylamine (1-Aminopropane-1-C^{14}) with Nitrous Acid[1]

BY JOHN D. ROBERTS[2] AND MARTIN HALMANN[3]

RECEIVED JUNE 24, 1953

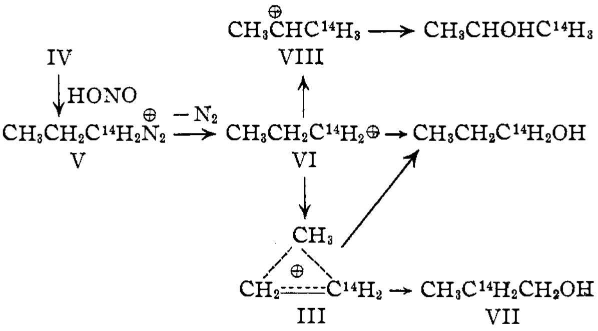
Ethylamine-1-C^{14} on treatment with aqueous nitrous acid has been shown[4] to yield, besides ethylene, a mixture of 98.5% of ethanol-1-C^{14} and 1.5% of ethanol-2-C^{14}. It was concluded that if the ethyl cation is an important intermediate in the reaction of ethylamine with nitrous acid it reacts with water considerably more rapidly than it is converted to the ethyleneprotonium ion (I). Much more rearrangement is found with 2-phenylethylamine-1-C^{14} with nitrous acid and about 56% of the 2-phenylethanol formed appears to result from a symmetrical intermediate such as II.[5]



I, R = H
II, R = C_6H_5
III, R = CH_3

Alkyl-bridged cations analogous to III ("ethylene-alkonium" ions) have been proposed[6] to account for a wide variety of rearrangement reactions of alkyl derivatives but there are very few data which indicate the degree of stability of such ions relative to the isomeric classical carbonium ions like R–$CH_2CH_2^{\oplus}$.

In the present research, the tendency of the *n*-propyl cation to be converted to III was tested in the reaction of 1-propylamine-1-C^{14} (IV) with nitrous acid. The reaction is complicated by elimination and rearrangement to 2-propyl derivatives,[7] but if III is formed from the *n*-propyldiazonium ion (V) or cation VI the 1-propanol obtained from IV should contain at least some 1-propanol-2-C^{14} (VII). A possible reaction sequence for propanol formation is given below in which, for simplicity, it has been assumed that all of the cation isomerization processes are irreversible[8] and further that all of the propanol is formed by carbonium ion processes. The validity of the latter assumption has been discussed before.[4,5]



The following reactions were carried out in the present investigation. The substances represented by formulas in bold-face type were analyzed for radioactive carbon. The degradation procedure was checked for rearrangement as indicated by a blank experiment on authentic 1-propanol-1-C^{14}. The results are presented in Table I. The 1-propanol from the amine–nitrous acid reaction was found to contain 8.5% of isotope-position rearrangement product such as would be expected from hav-

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[1] Supported in part by the program of research of the U. S. Atomic Energy Commission.

[2] Gates and Crellin Laboratories, California Institute of Technology, Pasadena 4, Calif.

[3] Foreign Students Summer Project, Massachusetts Institute of Technology, 1952. The Weizmann Institute of Science, Rehovoth, Israel.

[4] J. D. Roberts and J. A. Yancey, THIS JOURNAL, **74**, 5943 (1952).

[5] J. D. Roberts and C. M. Regan, *ibid.*, **75**, 2069 (1953).

[6] (a) A number of references have been given previously[4,5]; (b) D. P. Stevenson, C. D. Wagner, O. Beeck and J. W. Otvos, *ibid.*, **74**, 3269 (1952).

[7] A. Siersch, *Ann.*, **144**, 137 (1867); F. C. Whitmore and R. S. Thorpe, THIS JOURNAL, **63**, 1118 (1941).

[8] The assumption only becomes important to the qualitative interpretation of the tracer results if VI and VIII are in rapid equilibrium, which event is unlikely since 2-propylamine with nitrous acid gives no 1-propanol and, in other processes, primary and secondary cations do not appear to be at all readily interconvertible; *cf.* J. D. Roberts, R. E. McMahon and J. S. Hine, *ibid.*, **72**, 4237 (1950).