[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, YALE UNIVERSITY, AND THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF LEEDS, YORKSHIRE]

Pyrimidine Nuclear Organometallic Compounds. The Synthesis of 6-Acyluracils and Orotic Acid-$C^{14}O_2H$

BY B. W. LANGLEY[1,2]

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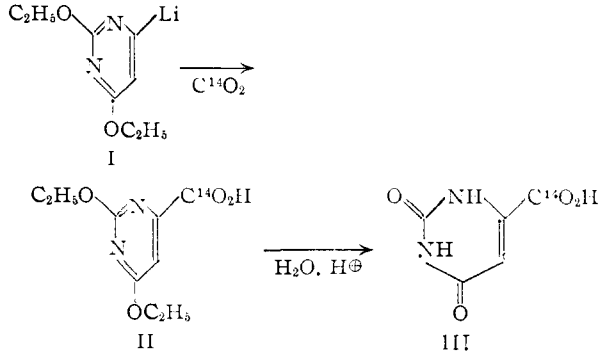
The preparation of 2,4-diethoxy-6-pyrimidylmagnesium bromide and 2,4-diethoxy-6-pyrimidyllithium is described. 2,4-Diethoxy-6-pyrimidylcarbinols obtained from the latter have been converted by successive oxidation and hydrolysis into 6-acyluracils. Carbonation of the lithium compound with $C^{14}O_2$ and hydrolysis of the product gave orotic acid-$C^{14}O_2H$. 2,4-Dimethoxy-5-pyrimidyllithium also has been prepared.

In recent years nuclear organometallic derivatives of heterocyclic nitrogen compounds have found considerable synthetic use.[3,4] Such derivatives of pyrimidines, however, appear to be unknown. This paper describes the preparation of magnesium and lithium derivatives of 2,4-dialkoxypyrimidines and their use in the synthesis of some otherwise difficultly accessible uracil derivatives, several of which were required for biological studies current in the Yale Laboratory.

Chloro compounds were found unsuitable for conversion into organometallic compounds. 2,4-Diethoxy-6-bromopyrimidine, obtained from treatment of 2,4,6-tribromopyrimidine with sodium ethoxide, failed to react satisfactorily with magnesium in ether, even in the presence of ethyl bromide; this failure was due to formation of an insoluble coating of the Grignard reagent on the metal. However, by using tetrahydrofuran as the solvent and a reaction temperature of $-30°$, the desired magnesium bromide was formed smoothly, and was carbonated to 2,4-diethoxy-6-pyrimidinecarboxylic acid in 35% yield.

For preparative purposes the above reaction was less satisfactory, and attention was directed to the corresponding lithium derivatives, which in the pyridine series are known to give better results.[4] With *n*-butyllithium at $-80°$, 2,4-diethoxy-6-bromopyrimidine gave the lithium derivative I. This compound, like those of the pyridine series, could be used successfully for preparative work provided that extremely low temperatures and short reaction times were employed in order to minimize the self-condensation of the lithium derivative I, which itself contains particularly sensitive azomethine links.

Carbonation of the lithium derivative I gave 2,4-diethoxy-6-pyrimidinecarboxylic acid in 40–50% yield. A method of carbonating millimolar quantities of I is described in the Experimental section. This method, which may prove valuable for other isotopic carbonations, was applied to the carbonation of I with $C^{14}O_2$; acid hydrolysis of the intermediate diethoxy-acid II then gave orotic acid-$C^{14}O_2H$ (III) in 39% yield from $BaC^{14}O_3$; previously the preparation[5] of this labeled acid has been tedious and unsatisfactory.



The lithium derivative I was also used to prepare certain 6-acyluracils, a class of which only two representatives, *viz.*, 6-formyl- and 5-methyl-6-formyluracil, were previously known.[6] Since the direct reaction of I with acid halides was expected, by analogy with the reaction of similar compounds, to give poor yields, it was condensed instead with the appropriate aldehyde to give the secondary alcohols IV; in this way IV, R = CH_3, C_2H_5 and C_6H_5 were obtained in yields of 49, 29 and 77%, respectively. Direct acid hydrolysis of these compounds to the corresponding 6-uracil secondary alcohols V was attempted, but was successful only with IV, R = C_6H_5, which gave the alcohol V, R = C_6H_5. Acid treatment of the secondary alcohols V (*e.g.*, where R = CH_3) is known[7] to cause their conversion into the imidazolones VI, and the failure of IV, R = CH_3 and C_2H_5, to furnish on hydrolysis the alcohols V (R = CH_3 and C_2H_5) was due to the intervention of similar reactions, since the corresponding imidazolones VI (R = CH_3 and C_2H_5) were isolated from the hydrolysis products. The successful hydrolysis of IV (R = C_6H_5) to the corresponding aromatic uracil alcohol (V, R = C_6H_5) prompted a closer study of the behavior of the latter toward acids; it was found to be surprisingly stable and underwent conversion into 4-methyl-5-phenylimidazolone-2 (VI, R = C_6H_5) only in the presence of fuming hydrochloric acid at 140°.

(1) University of Leeds, Leeds 2, Yorkshire, England.

(2) Squibb Post-doctoral Fellow, Yale University, 1953–1954; Imperial Chemical Industries Fellow, University of Leeds, 1954–1955.

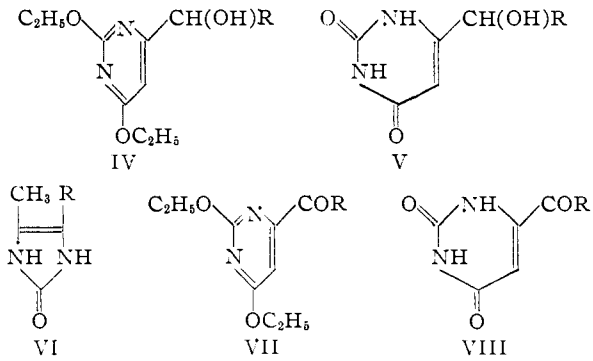
(3) Many examples are given by R. G. Jones and H. Gilman in R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

(4) References to early work are given by H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).

(5) B. W. Langley, *Yale J. Biol. Med.*, **27**, 135 (1954).

(6) (a) T. B. Johnson and L. H. Cretcher, Jr., THIS JOURNAL, **37**, 2144 (1915); (b) T. B. Johnson and E. F. Schroeder, *ibid.*, **53**, 1989 (1931); (c) T. B. Johnson and L. H. Cretcher, Jr., *J. Biol. Chem.*, **26**, 99 (1916).

(7) T. B. Johnson and S. E. Hadley, THIS JOURNAL, **38**, 1844 (1916); **39**, 1715, 1919 (1917); T. B. Johnson, *ibid.*, **39**, 2396 (1917).



Oxidation of the secondary alcohols IV (R = CH_3 and C_6H_5) gave the ketones VII (R = CH_3 and C_6H_5); the phenylcarbinol was oxidized with the pyridine–chromium trioxide complex,[8] the methylcarbinol, which resisted this reagent, with manganese dioxide.[9a,b] Acid hydrolysis of the resulting ketones gave the desired 6-acyluracils (VIII, R = CH_3 and C_6H_5) which, unlike 5-acetyluracil which suffers ring-opening on treatment with cold dilute alkali,[10] were unaffected by boiling 3 *N* sodium hydroxide and 12 *N* hydrochloric acid. The phenyl ketone VIII (R = C_6H_5) was also obtained by chromic acid oxidation of the alcohol V (R = C_6H_5).

The diethoxy ketone VII (R = CH_3) has also been obtained in 60% yield by the action of methyllithium on 2,4-diethoxy-6-pyrimidinecarboxylic acid. This reaction provides an alternative synthesis of 6-acetyluracil (VIII, R = CH_3) and probably is capable of further extension.

The above routes to 6-acyluracils are certainly the most convenient at present available, although no doubt the method[6a] (starting from thiourea and ethyl 3-keto-5,5-diethoxyvalerate) whereby Johnson obtained 6-formyluracil could be extended to the preparation of higher acyluracils.

Halogen–metal interconversion at the pyrimidine-C_5 position has also been briefly investigated. Interaction of 2,4-dimethoxy-5-bromopyrimidine[11] and *n*-butyllithium at −80° gives the corresponding lithium derivative, which is somewhat more stable than 2,4-diethoxy-6-pyrimidyllithium (I) and can be carbonated to give 2,4-dimethoxy-5-pyrimidinecarboxylic acid in 55–75% yield. Acid hydrolysis of the latter gives the known 5-uracilcarboxylic acid.[12] 5-Substituted uracils are reasonably accessible in other ways, but this interconversion reaction may well find application in the synthesis of thymine-$C^{14}H_3$ or biological analogs of thymine.

Some of the compounds described above have been tested for activity in biological systems; the results will be reported elsewhere.

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(8) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(9) (a) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952); (b) D. L. Turner, THIS JOURNAL, **76**, 5175 (1954).

(10) T. B. Johnson and W. Bergmann, *Ber.*, **66B**, 1492 (1933).

(11) G. E. Hilbert and E. F. Jansen, THIS JOURNAL, **56**, 134 (1934).

(12) (a) H. L. Wheeler, T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **37**, 400 (1907); (b) E. Ballard and T. B. Johnson, THIS JOURNAL, **64**, 795 (1942).

Experimental

Materials and Methods.—Melting points are uncorrected. All experiments with organometallic compounds were carried out in an atmosphere of oxygen-free nitrogen; magnetic stirring was used in small-scale experiments which were conducted in flasks fitted with serum caps through which reagents were introduced with hypodermic syringes. Preparative experiments were conducted in the conventional flask fitted with a sealed stirrer and two dropping funnels, one of which was contained in a cooling bath. Ether and tetrahydrofuran were distilled from lithium aluminum hydride shortly before use. Magnesium was freshly filed from a block of cell magnesium. *n*-Butyllithium was prepared by the methods of Gilman starting from *n*-butyl bromide[13] or *n*-butyl chloride[14] and estimated by differential titration.[15] Methyllithium was prepared by the method of Gilman, Zoellner and Selby.[16]

2,4-Diethoxy-6-bromopyrimidine.—The 2,4,6-tribromopyrimidine required for this preparation was obtained by heating a mixture of phosphorus oxybromide[17] (696 g., 2.43 moles), toluene (1 l.), dimethylaniline[18] (126 ml., 1 mole) and barbituric acid (74 g., 0.58 mole) until reaction took place. When this was complete, ice was added to the cooled mixture and 2,4,6-tribromopyrimidine obtained by evaporation of the washed and dried solution (yield 74%). This preparation is more suited for large scale work than that formerly described.[19]

Greenbaum[20] has shown that best results in the preparation of 2,4-dimethoxy-6-chloropyrimidine[21] are obtained by adding methanolic sodium methoxide dropwise to ice-cold methanolic 2,4,6-trichloropyrimidine. This is the basis of this analogous preparation of 2,4-diethoxy-6-bromopyrimidine. Greenbaum and Holmes[22] also use a 30% excess of sodium methoxide in their later preparation of the dimethoxy compound; the greater reactivity of 2,4-diethoxy-6-bromopyrimidine to alkoxides demands the use here of stoichiometric proportions of sodium ethoxide.

A mixture of 2,4,6-tribromopyrimidine (51.4 g., 0.163 mole) and anhydrous benzene (150 ml.) was stirred until solution was complete (1 hour). Absolute ethanol (150 ml.) was then added and the flask cooled in running water. A sodium ethoxide solution, prepared from sodium (7.48 g., 0.326 g. atom) and absolute ethanol (150 ml.) was then added dropwise to the stirred mixture so that the temperature did not rise above 20°. The mixture was stirred overnight at room temperature and then treated with anhydrous ether (150 ml.). The sodium bromide which precipitated from the resulting mixture was removed by filtration and washed with ether (3 portions of 50 ml. each). Fractional distillation of the combined filtrate and washings, after removal of the solvents, gave 2,4-diethoxy-6-bromopyrimidine, b.p. 132–133° (10 mm.), 35.7 g. (89% yield), used in subsequent experiments. The analytical sample was recrystallized twice from ethanol at −80° and redistilled, m.p. 17–19°, $n^{20}D$ 1.5248, d^{26}_{20} 1.380.

Anal. Calcd. for $C_8H_{11}N_2BrO_2$: N, 11.33; Br, 32.38. Found: N, 11.1; Br, 32.3.

2,4-Diethoxy-6-pyrimidinecarboxylic Acid. (a) **From 2,4-Diethoxy-6-pyrimidylmagnesium Bromide.**—A minute crystal of iodine was added to a stirred mixture of 2,4-di-

(13) H. Gilman, *et al.*, *ibid.*, **71**, 1499 (1949).

(14) H. Gilman, E. A. Zoellner and W. M. Selby, *ibid.*, **54**, 1957 (1932).

(15) H. Gilman and A. H. Haubein, *ibid.*, **66**, 1515 (1944).

(16) H. Gilman, E. A. Zoellner and W. M. Selby, *ibid.*, **55**, 1252 (1933).

(17) E. Berger, *Bull. soc. chim.*, [5] **3**, 721 (1908).

(18) Dimethylaniline facilitates the preparation of 2,4,6-trichloropyrimidine from barbituric acid and phosphorus oxychloride; J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944).

(19) D. R. V. Golding and E. A. Senear, *J. Org. Chem.*, **12**, 293 (1947).

(20) Private communication from Dr. S. B. Greenbaum.

(21) E. Büttner, *Ber.*, **36**, 2227 (1903); S. Gabriel and J. Colman, *ibid.*, **36**, 3379 (1903); T. B. Johnson and H. J. Fisher, THIS JOURNAL, **54**, 727 (1932).

(22) S. B. Greenbaum and W. L. Holmes, *ibid.*, **76**, 2899 (1954).

ethoxy-6-bromopyrimidine (444 mg., 1.8 mmoles), tetrahydrofuran (5 ml.) and magnesium filings (43 mg., 1.8 matom). Within a few minutes the yellow iodine color suddenly faded. One minute later the reaction vessel was placed in a bath maintained at −30° and kept there for 40 minutes. The mixture, which then was red and fluorescent, was cooled to −80° and treated with an excess of finely powdered solid CO_2. The cooling bath was removed and the mixture allowed to attain room temperature. After removal of the tetrahydrofuran *in vacuo* the product was shaken with a mixture of ether (10 ml.) and 4 *N* sulfuric acid (5 ml.). The aqueous layer was separated and extracted with ether (2 portions of 5 ml.). The combined extract was shaken with 5% aqueous sodium bicarbonate (5 ml.) and the latter separated, washed with ether (2 ml.) and acidified with 12 *N* hydrochloric acid (0.5 ml.). An oil separated which was extracted with ether (4 portions of 5 ml.). Evaporation of the washed and dried extract gave 2,4-diethoxy-6-pyrimidinecarboxylic acid (132 mg., 35% yield) which crystallized from benzene as colorless needles, m.p. 115–117°.

Anal. Calcd. for $C_9H_{12}N_2O_4$: N, 13.21. Found: N, 13.15, 13.25.

When this experiment was repeated on a larger scale (0.02 mole) much lower yields resulted, apparently because the reagent decomposed during the longer periods then required for substantial dissolution of the magnesium. Attempts to hasten[23] the latter process by using magnesium–copper alloy (88:12)[24] were unsuccessful.

(b) **From 2,4-Diethoxy-6-pyrimidyllithium.**—This lithium compound is extremely unstable, even at −80°; success in experiments using it demands extremely rapid working and the use of efficient cooling baths, *e.g.*, continuously stirred mixtures of powdered solid CO_2 and 2-ethoxyethanol. Halide and alkyllithium solutions should be allowed to remain in these cooling baths at least 15 minutes before mixing.

An ethereal solution of *n*-butyllithium (1.19 *M*, 38 ml., 0.045 mole) was cooled to −80° and added during 5 minutes to a stirred solution of 2,4-diethoxy-6-bromopyrimidine (10 g., 0.0405 mole) in ether (250 ml.) or tetrahydrofuran (150 ml.) at −80°. One minute later powdered solid CO_2 (*ca.* 150 g.) was added to the mixture and the cooling bath removed. When the whole had reached room temperature, ether (250 ml.) and 4 *N* sulfuric acid (50 ml.) were added, and the aqueous layer was separated and extracted with ether (2 portions of 50 ml. each). The combined solvent extract was washed with water (20 ml.), dried over sodium sulfate and evaporated. The crystalline residue was ground with ice-cold petroleum ether (b.p. 30–60°, 2 portions of 10 ml. each) to remove traces of oil and valeric acid. Nearly pure 2,4-diethoxy-6-pyrimidinecarboxylic acid (3.7–4.4 g., 43–51% yield), m.p. 114–116°, remained.

Higher yields would probably be obtained with improved methods[25] of carbonation.

Hydrolysis of 2,4-Diethoxy-6-pyrimidinecarboxylic Acid to Orotic Acid.—A mixture of this diethoxyacid (270 mg.) and 6 *N* hydrochloric acid (20 ml.) was heated under reflux for 2 hours and then evaporated under reduced pressure. After grinding the resulting product with water (2 ml.) nearly pure orotic acid monohydrate (212 mg., 96%) was obtained. Two recrystallizations of this from water gave the analytical sample.

Anal. Calcd. for $C_5H_4N_2O_4 \cdot H_2O$: N, 16.09. Found: N, 16.3.

This analytical sample when heated *in vacuo* (140°, 0.1 mm., 24 hours) gave anhydrous orotic acid, the paper chromatogram,[26] ultraviolet spectra[27] and infrared spectrum (Nujol mull)[28] of which were identical with those of a sample of anhydrous orotic acid prepared by the method of Johnson and Schroeder.[6b]

Anal. Calcd. for $C_5H_4N_2O_4$: C, 38.46; H, 2.56; N, 17.94. Found: C, 38.5; H, 2.67; N, 17.97.

Orotic Acid-$C^{14}O_2H$.—Murray, Foreman and Langham[29] have described the carbonation of 3-pyridyllithium and *p*-aminophenyllithium with millimolar quantities of $C^{14}O_2$. Their method is not readily applicable to the carbonation of 2,4-diethoxy-6-pyrimidyllithium (I) because of the extreme instability of this compound, which is even greater in the presence of the excess of 2,4-diethoxy-6-bromopyrimidine required to ensure substantial interconversion of the *n*-butyllithium.

The apparatus used consisted of a cylinder A from which a stream of purified nitrogen passed through an ascarite tube B into a $C^{14}O_2$ generator. In the latter, acid in a pressure-equalized dropping funnel D could fall onto $BaC^{14}O_3$ contained in a r.b. flask C. The gas from C passed through a magnesium perchlorate tube E into the reaction vessel F (described below) and from there *via* another magnesium perchlorate tube G into a sodium hydroxide bubbler H which was protected from atmospheric CO_2 by an ascarite tube K. (The tubes B, E, G and K measured 18 mm. by 30 cm.; the reagents in these tubes were "microanalytical grade" and 8–20 mesh.)

The reaction vessel is shown in detail in Fig. 1 and consisted of a glass tube L 20 mm. diam. and 85 mm. long with a coarse sintered disc M near its base, through which the nitrogen stream passed from N. (L was conveniently made from a sintered glass funnel, Corning code No. 416310.) The ground-joint stopper of the tube carried an exit tube O, a serum cap P and a stout movable plunger Q for breaking an ampule R placed on the sintered disc.

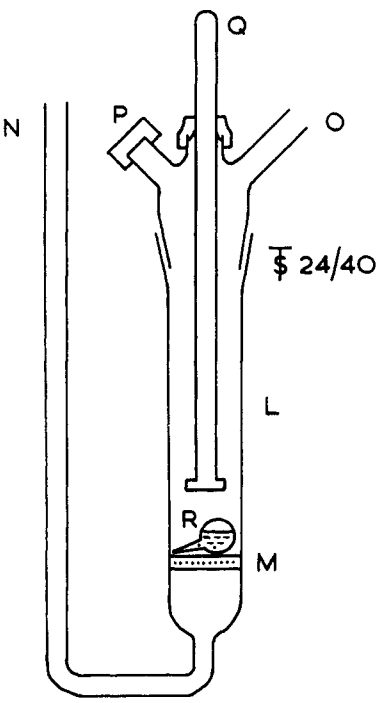

Fig. 1.

The carbonation was conducted as follows. Barium carbonate-C^{14} (Oak Ridge National Laboratories, 177 mg., 0.89 mmole, 5.9 mc.) was placed in C and covered with water (1 ml.). Perchloric acid (4 *N*, 1 ml.) was placed in D, and an ampule R (approx. 13 mm. diam., from 8 mm. Pyrex tubing), containing freshly prepared ethereal *n*-butyllithium[13] (1.35 *M*, 1 ml., introduced into the ice-cooled ampule with a calibrated hypodermic syringe) was carefully placed, bulb uppermost, in L. The whole apparatus was then assembled and all connections were wired together. Nitrogen from A was allowed to flow through the apparatus at approx. 150 ml. per minute for 10 minutes to expel air. Tetrahydrofuran (10 ml.) and 2,4-diethoxy-6-bromopyrimidine (0.5

(23) H. Gilman, J. M. Peterson and F. Schultze, *Rec. trav. chim.*, **47**, 19 (1928).

(24) Generously provided by the Dow Chemical Corporation, Midland, Mich.

(25) H. Gilman and P. R. Van Ess, THIS JOURNAL, **55**, 1258 (1933).

(26) E. Leone and E. Scale, *Boll. Soc., ital. biol. sper.*, **26**, 1223 (1950).

(27) J. J. Fox and D. Shugar, *Biochem. Biophys. Acta*, **9**, 199 (1952).

(28) Kindly determined by Dr. Nettie Coy and Miss Barbara Keeler of the Squibb Institute for Medical Research.

(29) A. Murray III, W. W. Foreman and W. Langham, THIS JOURNAL, **70**, 1037 (1948).

ml., 2.8 mmoles) were then introduced into L with hypodermic syringes and the bubbler H was filled with carbonate-free 3 *N* sodium hydroxide. The nitrogen flow was then readjusted to 150 ml. per minute and L was gradually introduced into a bath at −80°. After 10 minutes the ampule of *n*-butyllithium, R, was broken with the plunger Q and immediately afterward the perchloric acid in D was allowed to flow onto the $BaC^{14}O_3$ in C. When effervescence had ceased, the contents of C were boiled for 1 minute to expel the last traces of $C^{14}O_2$. Ten minutes later the excess organometallic compounds in L were destroyed by the injection of methanol (0.5 ml.) and the cooling bath was removed. When L had attained room temperature, inorganically combined $C^{14}O_2$ in the reaction mixture was released by the injection of 4 *N* sulfuric acid (1 ml.). The nitrogen flow was continued for 5 minutes. The reaction mixture was then removed from L and worked up as described below.

The mixture was made alkaline with 3 *N* sodium hydroxide and the tetrahydrofuran and ether were removed *in vacuo*. Water was added to bring the volume of the residue to 4 ml. Non-acidic organic substances were largely removed by ether extraction (4 portions of 5 ml. each; this extract contains a considerable amount of radioactivity); the aqueous residue was brought to *p*H 1 with 18 *N* sulfuric acid and then extracted with ether (4 portions of 10 ml. each). Evaporation of the washed and dried extract gave crude crystalline 2,4-diethoxy-6-pyrimidinecarboxylic acid-$C^{14}O_2H$ (II) (82 mg.) which was heated under reflux with 8 *N* hydrochloric acid (3 ml.) for 1 hour. Evaporation of the product gave crude orotic acid-$C^{14}O_2H$ together with traces of barbituric acid (the latter arose from the hydrolysis of a small quantity of 2,4-diethoxy-6-bromopyrimidine which was not removed in the above extractions) which were separated by ion exchange chromatography as follows. The solution of this crude acid in water (30 ml.) was brought to *p*H 10 with *N* sodium hydroxide and poured onto a column of Dowex 1 (10 cm. by 1 cm.^{2}, 200–400 mesh, chloride form). The development of the column was followed by examining the ultraviolet absorption of alkalinized portions of the eluate. Successive elution with 0.005 *N* hydrochloric acid (820 ml.) and 0.1 *N* hydrochloric acid (220 ml.) yielded barbituric acid (2.8 mg.) and pure orotic acid-$C^{14}O_2H$ (36.9 mg., estimated as anhydrous acid spectrophotometrically, 26.3% yield calcd. on $BaC^{14}O_3$ used). The high specific activity of this acid (approx. 70×10^6 counts/minute/mg., counted directly with a windowless counter) and the presence of this activity in the carboxyl group probably increased the risk of radiation-decomposition[30] in the solid state. Therefore, the eluate was not evaporated but stored as such. Paper chromatograms made with this material using *n*-butyl alcohol–acetic acid–water and isopropyl alcohol–ammonium hydroxide as solvents showed the presence of only one radioactive spot in each case (R_f 0.39 and 0.32, respectively), each spot was found to be coincident with that revealed by ultraviolet scanning and was identical in position with that shown by authentic orotic acid run concurrently.

Unreacted $C^{14}O_2$ in the above carbonation was recovered as $BaC^{14}O_3$ (58 mg.) from the contents of the bubbler H. Consequently, the yield of orotic acid-$C^{14}O_2H$, based on $BaC^{14}O_3$ unrecovered, was 39.2%.

2,4-Diethoxy-6-pyrimidyl Secondary Alcohols.—Solutions of 2,4-diethoxy-6-pyrimidyllithium were prepared from the corresponding bromide (0.05 mole) and *n*-butyllithium (0.055 mole) as described above for the preparation of 2,4-diethoxy-6-pyrimidinecarboxylic acid. Addition to these solutions at −80° of 30% ethereal solutions of acetaldehyde (0.075 mole), propionaldehyde (0.07 mole) and benzaldehyde (0.06 mole) over 1 minute (the aldehyde solutions were not pre-cooled) followed by stirring periods of 10 minutes at −80° gave reaction mixtures containing the secondary alcohols IV (R = CH_3, C_2H_5 and C_6H_5, respectively). These mixtures were shaken with 2 *N* sulfuric acid (60 ml.; larger amounts impeded the ether extraction of the somewhat basic alcohols) at room temperature. Evaporation of the washed and dried ether layers gave products from which the desired alcohols were obtained as described below.

(a) **2,4-Diethoxy-6-pyrimidylmethylcarbinol** (IV, R = CH_3).—Traces of solvent and volatile by-products (notably hexanol-2) were removed by heating the evaporated reaction product *in vacuo* (100°, 10 mm., 30 minutes). The residual crude alcohol (70% yield) crystallized on cooling. Recrystallization of this from petroleum ether (b.p. 30–60°) gave pure material, m.p. 72° (49% yield).

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: N, 13.21. Found: N, 13.3.

(b) **2,4-Diethoxy-6-pyrimidylethylcarbinol** (IV, R = C_2H_5).—Distillation of the evaporated reaction mixture gave a fraction, b.p. 140–155° (7 mm.), composed largely of the crude alcohol (38% yield) which when dissolved in a small volume of petroleum ether (b.p. 30–60°) and allowed to stand at 0° overnight deposited crystals of pure material, m.p. 49° (29% yield).

Anal. Calcd. for $C_{11}H_{18}N_2O_3$: N, 12.39. Found: N, 12.1, 12.2.

This alcohol was converted to the corresponding **chloride**, b.p. 146° (8 mm.), $n^{18}D$ 1.4997 (71% yield), with thionyl chloride. *Anal.* Calcd. for $C_{11}H_{17}N_2O_2Cl$: Cl, 14.52. Found: Cl, 14.7.

A ***p*-toluenesulfonate**, m.p. 62°, was also obtained from this alcohol by reaction with *p*-toluenesulfonyl chloride in pyridine at 0°. *Anal.* Calcd. for $C_{18}H_{24}N_2O_5S$: N, 7.37. Found: N, 7.4, 7.4.

Attempts to prepare 2,4-diethoxy-6-propenylpyrimidine, required in connection with other work, by treating these last two compounds with various bases, were largely unsuccessful.

(c) **2,4-Diethoxy-6-pyrimidylphenylcarbinol** (IV, R = C_6H_5).—In this case the evaporated reaction mixture crystallized directly. Recrystallization of the product from petroleum ether (b.p. 30–60°) gave the pure alcohol, m.p. 113° (77% yield).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: N, 10.22. Found: N, 10.1.

Reaction of 2,4-Diethoxy-6-pyrimidyl Secondary Alcohols with Acids. (1) Aliphatic Alcohols IV (R = CH_3 and C_2H_5). —A solution of 2,4-diethoxy-6-pyrimidylethylcarbinol (200 mg.) in 8 *N* hydrochloric acid (10 ml.) was heated under reflux. Aliquots of the solution were withdrawn at intervals, diluted with 0.1 *N* hydrochloric acid and their ultraviolet absorption measured. After 3 hours refluxing the intense absorption band due to the pyrimidine carbinol (λ_{max} 258–260 mμ, ϵ_{max} 10,000, in 0.1 *N* HCl) had been replaced by a spectrum showing only end-absorption. Evaporation of the reaction mixture gave a hygroscopic oil. When this oil was mixed with 3 *N* sodium hydroxide a crystalline precipitate formed (70 mg.). After recrystallization from water this darkened at 220° and melted, with considerable decomposition, at 265–270°. Gabriel and Posner[31] report that 4-methyl-5-ethylimidazolone-2 behaved similarly when heated. The ultraviolet spectrum of this product showed only end-absorption in acid. This spectrum and behavior on heating were identical with those shown by an authentic sample of 4-methyl-5-ethylimidazolone-2.[31]

A parallel experiment with 2,4-diethoxy-6-pyrimidylmethylcarbinol gave a basic substance, dec. 280–330°, again showing only end-absorption in the ultraviolet, presumably 4,5-dimethylimidazolone-2 (lit. dec. 290–355°,[32a] 210–280°[32b]).

When these hydrolyses were interrupted after short reaction periods (10–30 minutes), considerable quantities of unchanged diethoxy-alcohols could be recovered by extracting the diluted reaction mixtures with ether. Imidazolones again were isolated after evaporation of the aqueous layers.

(2) **2,4-Diethoxy-6-pyrimidylphenylcarbinol** (IV, R = C_6H_5). (a) **8 *N* HCl at Reflux.**—This alcohol (360 mg.) was heated under reflux with 8 *N* hydrochloric acid (6 ml.) for 1 hour. The product was evaporated to small bulk, diluted with water (10 ml.) and kept at 5° overnight. The crystals which separated when recrystallized from water gave 6-uracil phenylcarbinol (V, R = C_6H_5), 215 mg. (75% yield), m.p. 224–226° (slight decomp.); ultraviolet absorption: λ_{max} 283–285 mμ, ϵ_{max} 9,110 (in 0.1 *N* NaOH); λ_{max} 260 mμ, ϵ_{max} 9,600 (in 0.1 *N* HCl).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.59. Found: C, 60.3; H, 4.4.

Proof of the structure of this product is given by its oxidation to 6-benzoyluracil and its synthesis from the latter by reduction, *vide infra*.

(30) M. Calvin, *et al.*, THIS JOURNAL, **75**, 1867 (1953).

(31) S. Gabriel and T. Posner, *Ber.*, **27**, 1037 (1894).

(32) (a) H. Biltz, *ibid.*, **40**, 4801 (1907); (b) H. Künne, *ibid.*, **28**, 2040 (1895).

(b) **Fuming HCl at 140°.**—A solution of the alcohol (141 mg.) in fuming hydrochloric acid (2 ml., d. 1.20), was heated in a sealed tube at 140° for 4 hours. The contents of the tube, in which a considerable pressure had developed, were diluted with water (20 ml.) and kept overnight at 5°. The crude 4-methyl-5-phenylimidazolone-2 (64 mg., 71% yield) which separated was removed by filtration. The filtrate, when kept at 5° for several days, deposited more crystalline material (20 mg., 18% yield) which was shown by its m.p., ultraviolet absorption and alkaline solubility, to be 6-uracilphenylcarbinol. The crude imidazolone after two recrystallizations from aqueous ethanol darkened above 240° and melted with decomposition at 265–290°, behavior typical of aliphatic imidazolones (*vide supra*) and identical with that shown by authentic 4-methyl-5-phenylimidazolone-2 prepared by the method of Dakin and West,[33] although these authors and others[34] have described the m.p. of this substance as 287–289° and 285–286°, respectively. with no mention of decomposition. Our product and authentic material showed identical ultraviolet absorption: λ_{max}^{EtOH} 282–284 mμ, ϵ_{max} 12,800.

Oxidation of 2,4-Diethoxy-6-pyrimidylphenylcarbinol (V, R = C_6H_5).—A solution of this carbinol (3 g.) in pyridine (30 ml.) was added slowly to the complex[8] prepared from chromium trioxide (3 g.) and pyridine (30 ml.), the whole being cooled in a bath at 20° during the addition. After standing at room temperature overnight the reaction product was poured into water (600 ml.) and extracted with ether (5 portions of 60 ml. each; emulsions which formed were broken by adding methanol). The ethereal extract was washed successively with water (3 portions of 50 ml. each), 3 *N* hydrochloric acid (3 portions of 30 ml.) and water (50 ml.) and dried with sodium sulfate. Evaporation of the product gave 2,4-diethoxy-6-benzoylpyrimidine, m.p. 51° (2.7 g., 91% yield). The analytical sample, m.p. 53°, was recrystallized from petroleum ether (b.p. 30–60°) and sublimed *in vacuo* (100°, 0.5 mm.).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: N, 10.29. Found: N, 10.5.

Oxidation of 2,4-Diethoxy-6-pyrimidylmethylcarbinol (IV, R = CH_3).—The alcohol (270 mg.) was stirred with a suspension of activated manganese dioxide[9a] (448 mg.) in benzene (3 ml.) for 24 hours at room temperature. Cautious evaporation of the filtered benzene solution *in vacuo* (the product is appreciably volatile at room temperature) gave 2,4-diethoxy-6-acetylpyrimidine, m.p. 36° (228 mg., 85% yield). The analytical sample, m.p. 37°, was recrystallized from petroleum ether (b.p. 30–60°) and sublimed *in vacuo* (130°, 10 mm.).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.15; H, 6.67; N, 13.34. Found: C, 56.8; H, 6.5; N, 13.5.

This ketone gave a **2,4-dinitrophenylhydrazone**, m.p. 203°, in the usual manner. *Anal.* Calcd. for $C_{16}H_{18}N_6O_6$: N, 22.70. Found: N, 22.8.

A **phenylhydrazone**, m.p. 141°, was also prepared. *Anal.* Calcd. for $C_{16}H_{20}N_4O_2$: C, 64.00; H, 6.67; N, 18.67. Found: C, 63.5; H, 6.5; N, 18.6.

Oxidation of secondary alcohols with manganese dioxide is relatively recent.[9b] Before this method was applied in the present case various other modes of oxidation of this alcohol IV (R = CH_3) had been tried as follows: acetone–aluminum isopropoxide (no oxidation), benzophenone–aluminum isopropoxide (no oxidation), copper powder dehydrogenation (tar produced + 10% ketone), *t*-butyl chromate (tar produced + 7% ketone), CrO_3–acetic acid (30% ketone), CrO_3–pyridine (10% ketone + 70% unchanged alcohol).

6-Benzoyluracil (VIII, R = C_6H_5).—The ketone VII (R = C_6H_5) (2.7 g.) was heated under reflux with 8 *N* hydrochloric acid (40 ml.) for 1 hour. Evaporation of the mixture *in vacuo* and recrystallization of the residue from water (350 ml.) gave pure 6-benzoyluracil (VIII, R = C_6H_5) (1.6 g., 74%) as long needles, m.p. 252–253°; ultraviolet absorption: λ_{max} 275 mμ, ϵ_{max} 6,640 (in 0.1 *N* HCl); λ_{max} 257 mμ, ϵ_{max} 14,620, λ_{max} 323 mμ, ϵ_{max} 338 (in 0.1 *N* NaOH).

Anal. Calcd. for $C_{11}H_8N_2O_3$: N, 12.96. Found: N, 13.1.

This ketone gave an **oxime**, m.p. 260–270° dec., when heated with hydroxylamine hydrochloride in pyridine. *Anal.* Calcd. for $C_{11}H_9N_3O_3$: N, 18.18. Found: N, 18.2.

6-Acetyluracil (VIII, R = CH_3).—De-ethylation of the ketone VII (R = CH_3) by the method employed with VII, R = C_6H_5, gave crude 6-acetyluracil (85%), which after recrystallization from a small volume of water (7 ml. per g.) and vacuum sublimation (160°, 0.01 mm.) gave the analytical sample, m.p. 255–260° dec.; ultraviolet absorption: λ_{max} 293–295 mμ, ϵ_{max} 6,670 (in 0.1 *N* HCl); λ_{max} 325–330 mμ, ϵ_{max} 3,910 (in 0.1 *N* NaOH).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.76; H, 3.90. Found: C, 46.6; H, 3.9.

This ketone gave a **2,4-dinitrophenylhydrazone**, decomp. over 330°, on warming with a solution of the hydrazine in 2 *N* hydrochloric acid. *Anal.* Calcd. for $C_{12}H_{10}N_6O_6$: C, 43.11; H, 2.99; N, 25.15. Found: C, 43.3; H, 3.2; N, 24.7.

This derivative was also prepared by the partial hydrolysis of 2,4-diethoxy-6-acetylpyrimidine 2,4-dinitrophenylhydrazone. The latter was heated under reflux with a mixture of equal volumes of glacial acetic acid and 12 *N* hydrochloric acid for 18 hours and the evaporated product recrystallized from glacial acetic acid.

Stability of 6-Benzoyluracil (VIII, R = C_6H_5) **and 6-Acetyluracil** (VIII, R = CH_3) **to Acid and Alkali.**—Solutions of these ketones (1%) in 3 *N* sodium hydroxide and in 8 *N* hydrochloric acid were heated under reflux for 1 hour. There was no change in the ultraviolet absorption of acidified, diluted aliquots withdrawn before and after heating in each case. The resulting products were acidified (where necessary) and concentrated to small bulk. 6-Benzoyluracil, m.p. 252°, separated unchanged from the solutions which contained it. 6-Acetyluracil was isolated from the remaining two solutions as its 2,4-dinitrophenylhydrazone.

Oxidation of 6-Uracilphenylcarbinol (V, R = C_6H_5).—To a boiling solution of this alcohol (25.7 mg.) in glacial acetic acid (1 ml.) was added a solution of chromium trioxide (9.4 mg., 20% excess) in glacial acetic acid (0.2 ml.). The resulting green solution was cooled rapidly and evaporated to small bulk *in vacuo*. The product was dissolved in hot water (5 ml.) and the solution placed in an ice-bath for 1 hour. Crystals of nearly pure 6-benzoyluracil separated, m.p. 251–252°, undepressed on admixture with a sample prepared from VII, R = C_6H_5 (15.5 mg., 61% yield).

Reduction of 6-Benzoyluracil (VIII, R = C_6H_5).—The ketone (54 mg.) was added to a solution of sodium borohydride (23 mg.) in water (1 ml.). The mixture was stirred for 10 minutes at room temperature and then for a further 5 minutes at 100°. Acidification of the chilled reaction product gave 6-uracilphenylcarbinol (V, R = C_6H_5) (52 mg., 96% yield), which after one recrystallization from water had m.p. 223–224° undepressed on admixture with a sample prepared by direct de-ethylation of IV, R = C_6H_5.

Preparation of 2,4-Diethoxy-6-acetylpyrimidine (VII, R = CH_3) **from Methyllithium and 2,4-Diethoxy-6-pyrimidinecarboxylic Acid.**—A solution of this acid (212 mg., 1 mmole) in tetrahydrofuran (5 ml.) was added during 5 minutes to a stirred ethereal solution of methyllithium (0.6 *M*, 4 ml.), the mixture being cooled in ice throughout. After being stirred for a further 10 minutes the mixture was diluted with ether (15 ml.), washed with water (4 ml.), dried with sodium sulfate and evaporated cautiously under reduced pressure. The crude ketone VII (R = CH_3) remained as a yellow oil which crystallized slowly in an ice-bath. The yield of product was estimated approximately by mixing this oil with an ice-cold saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. When kept at 0° for 24 hours this mixture deposited pure 2,4-diethoxy-6-acetylpyrimidine 2,4-dinitrophenylhydrazone, m.p. 203°, undepressed on admixture with material described above (234 mg., 60% yield).

In another experiment the crude ketone VII (R = CH_3) was hydrolyzed in the usual way. 6-Acetyluracil was then obtained by vacuum sublimation of the evaporated hydrolysis product (45% yield).

2,4-Dimethoxy-5-pyrimidinecarboxylic Acid.—An ethereal solution of *n*-butyllithium (1.14 *M*, 2 ml.) was added dropwise during 5 minutes to a stirred solution of 2,4-dimethoxy-5-bromopyrimidine[11] (463 mg., 2.11 mmoles) in tetrahydrofuran (8 ml.) maintained at −80°. One minute after the addition was complete the mixture was carbonated with an excess of finely powdered solid CO_2. The solvent was re-

(33) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 759 (1928).

(34) L. Behr-Bregowski, *Ber.*, **30**, 1515 (1897).

moved *in vacuo* at room temperature and the residue dissolved in water (3 ml.). The resulting solution was adjusted to *p*H 2–3 with 4 *N* sulfuric acid and cooled in ice for 1 hour. The crystalline 2,4-dimethoxy-5-pyrimidinecarboxylic acid which separated was removed and washed with ice-water (1 ml.) and cold ether (3 ml.) (213–290 mg., 55–75% yield). The analytical sample, m.p. 167–168°, was recrystallized from ethyl acetate.

Anal. Calcd. for $C_7H_8N_2O_4$: N, 15.22. Found: N, 15.1, 15.3.

The 2,4-dialkoxy-5-pyrimidyllithium intermediate in this reaction is somewhat more thermostable than the 6-substituted analog. Longer reaction times (up to 15 minutes) and higher working temperatures (up to −50°) do not noticeably affect the yield in the above reaction, nor is it necessary to cool the alkyllithium solution before addition to the halide.

Hydrolysis of 2,4-Dimethoxy-5-pyrimidinecarboxylic Acid to 5-Uracilcarboxylic Acid.—A solution of this dimethoxy acid (188 mg.) in 8 *N* hydrochloric acid (2 ml.) was heated in a steam-bath for 30 minutes and then diluted with water (2 ml.). The crude 5-uracilcarboxylic acid monohydrate (130 mg., 73% yield) which crystallized from this solution was removed, washed with water (2 ml.) and recrystallized from hot water. The product, when dried at 140° (0.01 mm.) for 24 hours, gave an analytical sample of anhydrous 5-uracilcarboxylic acid.

Anal. Calcd. for $C_5H_4N_2O_4$: C, 38.46; H, 2.56; N, 17.94. Found: C, 38.8; H, 2.7; N, 17.8.

The ultraviolet absorption of this acid was identical with that shown by 5-uracilcarboxylic acid[12b]: λ_{max} 272–274 mμ, ϵ_{max} 10,800 (in 0.1 *N* HCl); λ_{max} 291 mμ, ϵ_{max} 13,300 (in 0.1 *N* NaOH) for which Stimson[35] quotes λ_{max} 270 mμ, ϵ_{max} 11,200 (at *p*H 3.0); λ_{max} 290 mμ, ϵ_{max} 12,800 (at *p*H 11.0). A paper chromatogram made with this acid using *n*-propyl alcohol–water as the solvent[26] showed only one spot, R_f 0.37, identical with that shown by 5-uracilcarboxylic acid.

(35) M. M. Stimson, THIS JOURNAL, **71**, 1470 (1949).

NEW HAVEN, CONNECTICUT
LEEDS, YORKSHIRE, ENGLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

2-Bromopyrazines, 2-Cyanopyrazines and their Derivatives

BY GEORGE KARMAS[1] AND PAUL E. SPOERRI

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A variety of 2-bromopyrazines has been synthesized by reaction of hydroxypyrazines with phosphorus tribromide or phosphorus oxybromide. The corresponding 2-cyanopyrazines are formed on heating the bromides with cuprous cyanide in γ-picoline. A few nitrile derivatives, such as carboxamides, methyl ketones and amidines have been prepared.

After 2-hydroxypyrazines had become readily accessible,[2,3] our interest in this field centered on the conversion of these compounds to useful derivatives. A previous publication[3] discussed the synthesis of 2-chloropyrazines by reaction of hydroxypyrazines with phosphorus oxychloride. When it was found that displacement of chlorine by the cyano group could not be satisfactorily accomplished the conversion of hydroxypyrazines to bromopyrazines was studied in anticipation of a greater reactivity for the latter class of compounds.

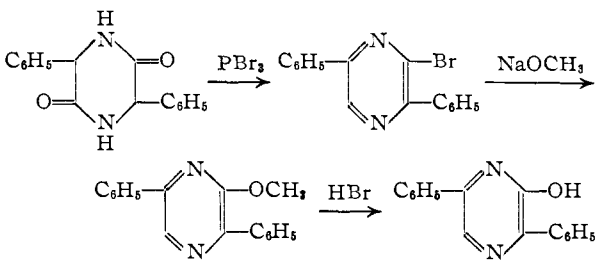
The only known example of such a reaction was the finding of Erickson and Spoerri[4] that a mixture of phosphorus oxybromide and phosphorus pentabromide converted 2-hydroxypyrazine to a mixture of 2-bromopyrazine and 2,6-dibromopyrazine.

In this investigation such displacements were first attempted using phosphorus tribromide alone. It was found that all phenylsubstituted 2-hydroxypyrazines were transformed to the corresponding 2-bromopyrazines in good yield by refluxing with this reagent. This simple procedure was not satisfactory when applied to alkylhydroxypyrazines; the latter formed complexes insoluble in phosphorus tribromide and the yields of bromopyrazines were poor.

Phosphorus oxybromide alone, or with tribromide as diluent, proved to be a useful reagent for the synthesis of alkylated 2-bromopyrazines. However, it complicated the reaction by yielding polybromides as by-products, presumably as a result of free radical bromination of alkyl substituents and of the pyrazine nucleus. This behavior prohibited forcing conditions as a means of improving the yields of monobromopyrazines.

The displacement of chlorine by bromine was considered as an obvious synthesis of 2-bromopyrazines, and it was observed that such a reaction occurred readily when 2-chloro-5,6-diphenylpyrazine and 2-chloro-3-ethyl-5,6-diphenylpyrazine were refluxed in phosphorus tribromide. However, this offered no advantage over direct synthesis from the phenylhydroxypyrazines. Very little displacement occurred when *alkyl*monochloropyrazines were heated in phosphorus tribomide, and so the general synthesis of 2-bromopyrazines started with hydroxypyrazines and is summarized in Table I.

In connection with the work on bromopyrazines, a decided improvement was effected in the synthesis of 2-hydroxy-3,6-diphenylpyrazine. The report[5] that *dl*-phenylglycine anhydride reacts with phosphorus oxychloride to give small amounts of this hydroxypyrazine and its 2-chloro analog in addition to 2,5-dichloro-3,6-diphenylpyrazine suggested an investigation of the reaction of the anhydride with phosphorus tribromide. This was found to yield



(1) Ortho Pharmaceutical Corporation, Raritan, New Jersey.

(2) R. G. Jones, THIS JOURNAL, **71**, 78 (1949); R. G. Jones, U. S. Patent 2,520,088 (1950).

(3) G. Karmas and P. E. Spoerri, THIS JOURNAL, **74**, 1580 (1952).

(4) A. E. Erickson and P. E. Spoerri, *ibid.*, **68**, 400 (1946).

(5) J. J. Gallagher, G. T. Newbold, F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 910 (1949).