Recently, Schlögl[7] obtained ether III in 71% yield from alcohol I and phosphorus trichloride, in which reaction the chloride corresponding to alcohol I was presumably an intermediate. Also, other workers[8] have reported the formation of ether III (54%) in an attempt to hydrogenate aldehyde II over Raney nickel.

Of the above methods for preparing ether III, only that involving the acid catalyzed reaction of alcohol I (see Equation 1) may be considered to follow an anticipated course.

With regard to the resistance of the iron in aldehyde II to oxidation, this aldehyde was recovered unchanged after heating a solution of it in an equal mixture of ethanol and water containing 2% potassium permanganate on the steam bath for 10 min. The aldehyde was also recovered after similar treatment employing a weakly acidic or weakly basic permanganate solution. This resistance to oxidation of the aldehyde group in II, as well as the iron, is of interest, since benzaldehyde undergoes oxidation to benzoic acid under similar conditions.[9]

However, aldehyde II was destroyed on heating an aqueous ethanolic solution of it containing alkaline permanganate for 2 hr. on the steam bath. These conditions produced a high melting material which was not the carboxylic acid corresponding to aldehyde II. As was anticipated, aldehyde II readily produced a colored (blue-green) ferricinium ion with 5% solutions of ceric sulfate, ferric chloride or ceric ammonium nitrate.

Also, aldehyde II in *n*-hexane evidently underwent oxidation on passing air through the solution, but the corresponding acid was not obtained. Instead, there was precipitated an unidentified brown[10] powder which had the properties of an "inner salt" or "zwitter ion." Thus, it did not melt at 320°, and it was soluble in both dilute aqueous hydrochloric acid and dilute aqueous sodium hydroxide, and reprecipitated on careful neutralization (to *p*H 7), followed by the addition of acetone.

EXPERIMENTAL

Ferrocenylmethyl alcohol II with potassium permanganate. To 200 ml. of 5% solution of potassium permanganate in ethanol-water (50-50) was added 5 g. (0.023 mole) of ferrocenylmethyl alcohol (II). After stirring until the solid had disappeared, the resulting solution was allowed to sit for 12 days at room temperature. During this time, there was a slow discoloration of the permanganate solution (to greenish brown) which may have been due to oxidation of the ethanol. The remaining oxidizing agent was destroyed by the addition of saturated sodium bisulfite solution. The mixture was extracted twice with 150 ml. portions of ethyl ether and the extracts combined. The ethereal solution was dried over magnesium sulfate and most of the solvent removed by heating on the steam bath. The last traces of the solvent were removed *in vacuo* (water aspirator) to give 4.1 g. (87%) of a yellow solid, m.p. 126–129°, which was apparently the bisferrocenylmethyl ether III. A portion of the product was recrystallized from *n*-hexane to form orange crystals, m.p. 132–134°.

Anal.[11] Calcd. for $C_{22}H_{22}OFe_2$: C, 63.81; H, 5.35; Fe, 26.99. Found: C, 63.35; H, 5.59; Fe, 25.86.

Ferrocenylmethyl alcohol II with dilute acetic acid. In 80 ml. of a 1% solution of acetic acid in ethanol-water (50-50) was dissolved 2.5 g. (0.023 mole) of ferrocenylmethyl alcohol II. This solution was refluxed for 5 hr., cooled, and poured into 300 ml. of water. The resulting mixture was extracted three times with 100 ml. portions of ether and the extracts were combined. After drying over magnesium sulfate the ethereal solution was concentrated to a volume of about 50 ml. Approximately 100 ml. of hot *n*-hexane was added and the solution allowed to cool in a refrigerator. The resulting yellow precipitate was collected on a funnel and washed with *n*-hexane. There was obtained 2.2 g. (88%) of bisferrocenylmethyl ether III, m.p. 126–130°. Recrystallization from *n*-hexane gave orange crystals of the ether III, m.p. 132–134°.

Anal.[11] Calcd. for $C_{22}H_{22}OFe_2$: C, 63.81; H, 5.35; Fe, 26.99. Found: C, 64.01; H, 5.48; Fe, 26.63.

Samples of this product and of the product from the oxidation experiment above were shown to be identical by mixture melting point and infrared spectra.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
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(7) K. Schlögl, *Monatsh. Chem.*, **88**, 601 (1957).

(8) P. J. Graham, R. V. Lindsay, G. W. Parshall, M. L. Peterson, and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

(9) See R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., 4th Edition, New York, N. Y., 1956, p. 133.

(10) In reference 8 the statement is made that aldehyde II is sensitive to oxidation in dilute aqueous or in concentrated anhydrous hydrocarbon solutions to produce an amorphous brown powder.

(11) Analyses by Galbraith Laboratories, Knoxville, Tenn.

Methiodide of *N*-(4-Benzyloxy-2,6-dimethylbenzyl)-*N*,*N*-dimethylamine. Attempted Rearrangement[1]

DANIEL LEDNICER AND CHARLES R. HAUSER

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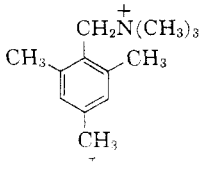
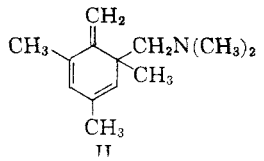
Recently[2] quarternary ammonium ion I has been shown to undergo with sodium amide in liquid ammonia the first phase of the ortho substitution rearrangement to form the *exo*-methyleneamine II, which exhibited certain interesting reactions.



I

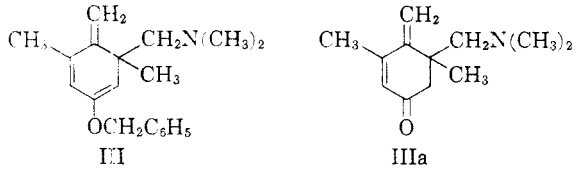


II

(1) Supported by the Office of Ordnance Research, U.S.A.

(2) C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, **78**, 5698 (1956).

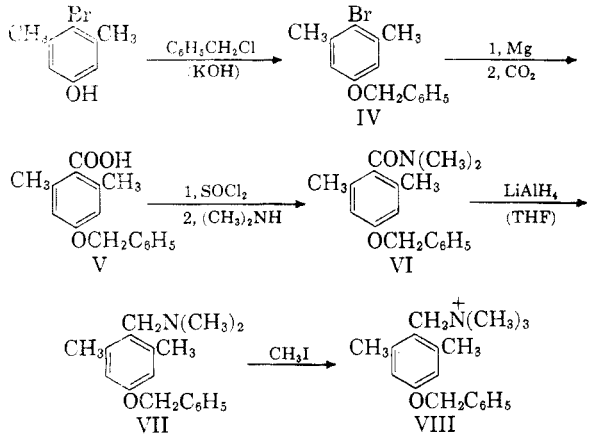
This type of rearrangement has now been employed in an attempt to prepare the corresponding 4-benzyloxy-*exo*-methyleneamine III, the benzyl group of which might be cleaved to form ketone IIIa.



III IIIa

Although the rearrangement was not realized satisfactorily, the synthesis of the starting quaternary ammonium ion VIII should be of some interest. The steps are indicated in Scheme A.

Scheme A



Compounds IV, V, and VI were prepared by well known procedures but refluxing an ethereal solution of the dimethylamide VI in the presence of lithium aluminum hydride for one hour failed to effect reduction to form amine VII. This amine was produced in 54% yield, however, by heating the amide VI with the same reducing agent for an extended time in tetrahydrofuran. Besides the amine there was obtained a high boiling fraction which, on the basis of an infrared absorption band at 3.0 μ and its partial solubility in strong base, was judged to contain some phenolic material. This product appears to have arisen from reductive cleavage of the benzyl ether group.

Quaternary ammonium ion VIII, which was readily obtained from the corresponding amine VII, produced on treatment with sodium amide in liquid ammonia a viscous oil that showed ultraviolet absorption maximum at 316 mμ (log ϵ = 3.22). Such a maximum is characteristic of *exo*-methyleneamines of type II.[2] However, the product was not isolated in pure condition.

Treatment of the crude product with hydrogen over palladium-on-charcoal or, alternately, with dilute acid apparently failed to produce any appreciable amount of the amino ketone IIIa, since the infrared spectrum of the total products failed to show even a trace of a band in the carbonyl region.

EXPERIMENTAL[3]

4-Benzyloxy-1-bromo-2,6-dimethylbenzene (IV). A solution of 32.8 g. of 4-bromo-2,5-dimethylphenol[4] (0.162 mole), 22 g. of benzyl chloride, and 10 g. of potassium hydroxide was refluxed with good stirring for 4 hr. At the end of 2 hr. an additional 2 g. of base was added to the now heterogeneous mixture. After cooling, the inorganic solid was removed by filtration and washed well with ether. The organic solution was washed with water and combined with the ether washes. The oil which remained when the solvent was removed from the extracts solidified to a waxy mass. Crystallization from methanol afforded 36.7 g. (77%) of the ether, m.p. 44–49°.

Conversion of IV *to the acid* V. A solution of 36.7 g. (0.126 mole) of the bromoether in 200 ml. of ether was added to a well-stirred suspension of 3.1 g. (0.128 mole) of magnesium in 100 ml. of ether. The reaction was started by adding a small amount of benzylmagnesium chloride to the suspension. After refluxing for 24 hr. most of the magnesium had been consumed. The Grignard reagent was then poured onto about 200 g. of Dry Ice snow with stirring. When the mixture had returned to room temperature, water was added, and the mixture was made strongly acidic with hydrochloric acid. The ethereal layer was separated and washed with water. The acid was extracted with saturated sodium carbonate and obtained from this solution, on acidification, as a solid, m.p. 87–106°. Crystallization from cyclohexane afforded 14.3 g. (44%) of fine needles, m.p. 103–110°.

A sample of the acid was recrystallized from aqueous ethanol to a constant m.p. of 114–115°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.02; H, 6.47.

Amide VI *from acid* V. Thionyl chloride (7.5 ml.) was added to a suspension of 12.8 g. (0.05 mole) of V in 50 ml. of benzene. The resulting solution was warmed at a gentle reflux until the evolution of gas had ceased (2 hr.). The excess reagent and solvent were removed *in vacuo*.

The oily acid chloride was then dissolved in 100 ml. of dry ether. Gaseous dimethylamine was bubbled through the solution. Almost immediately solid began to come out of solution. At the end of 2.5 hr. the reaction was stopped and 100 ml. of ether was added. The suspension was washed with water and the resulting clear solution dried by percolation through sodium sulfate. The solvent was removed to leave behind an oil which on scratching, crystallized. Recrystallization from cyclohexane afforded the amide (11.4 g. 80%) as needle-like prisms, m.p. 94–98°.

The analytical sample, m.p. 101–102.5°, was obtained by recrystallization from cyclohexane.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.40; H, 7.50; N, 5.16.

Reduction of the amide VI *to amine* VII. A solution of 10.2 g. (0.047 mole) of the amide in 150 ml. of dry tetrahydrofuran was added to a suspension of 1.52 g. of lithium aluminum hydride in the same solvent. The suspension was stirred and heated under reflux for 18 hr. At the end of this time, the mixture was cooled and 6 ml. of water was added, followed by 5 ml. of 20% sodium hydroxide. The resulting grayish solid was removed by filtration. The filtrate was taken to dryness and the residual oil distilled at 2.5 mm. The amine was obtained as 5.18 g. (54%) of an oil b.p. 178–180°; a second fraction (2.10 g.) was obtained b.p. 184–200°.

A small sample of the amine (0.25 g.) was treated with 5

(3) All melting points are recorded as obtained on a Fisher-Johns melting point block. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(4) R. C. Fuson, J. Corse, and P. B. Welldon, *J. Am. Chem. Soc.*, **63**, 2645 (1941).

ml. of saturated ethanolic picric acid to afford the picrate, m.p. 123–130°. This was recrystallized from ethanol to a constant m.p. of 133–134°.

Anal. Calcd. for $C_{24}H_{26}O_8N_4$: C, 57.82; H, 5.26; N, 11.24. Found: C, 57.95; H, 5.33; N, 10.72.

On treatment with aqueous potassium hydroxide part of the afterrun went into solution. Neutralization of the solution with carbon dioxide precipitated an oil.

Methiodide of the amine (VIII). To a solution of 5.5 g. of the tertiary amine VII in 40 ml. of acetonitrile there was added 10 ml. of methyl iodide. Within 20 min. the glistening crystals of the methiodide started to separate. After standing overnight, there was collected 6.5 g. of the salt (76%), m.p. 165–175.5°.[5] The analytical sample, m.p. 175–180°, was prepared by recrystallization from acetonitrile.

Anal. Calcd. for $C_{19}H_{28}NOI$: C, 55.47; H, 6.37; N, 3.41. Found: C, 55.61; H, 6.40; N, 3.30.

Attempted ortho substitution rearrangement of VIII. The solid quaternary salt (11.0 g., 0.027 mole) was added to a solution of 0.08 mole of sodium amide (prepared from 1.85 g. of sodium) in 200 ml. of liquid ammonia. On standing a dark gum separated from the light grey reaction mixture. At the end of 1 hr. ammonium chloride (6 g.) was added and the ammonia allowed to evaporate. The residue was then washed with a total of 250 ml. of ether. Concentration of the ethereal solution *in vacuo* at 30–40° afforded 6.71 g. of a yellow oil, λ_{max} 316 mμ (log ϵ = 3.22).

Catalytic hydrogenation of 1.0 g. of this oil led to the uptake of 72.6 ml. (0.92 equiv.) of hydrogen. The infrared spectrum of the product showed no bands in the C=O region. Similarly a small amount of the product was allowed to stand with glacial acetic acid; the oil which was obtained on working up the reaction mixture again showed no C=O absorption. Finally an attempt to prepare a picrate of the rearrangement product yielded only intractable gums.

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(5) This melting point is dependent on the rate of heating.

A Convenient Laboratory Synthesis of Certain 6-Hydroxypurines and 7-Hydroxy-*v*-triazolo-[*d*]pyrimidines

D. S. ACKER AND J. E. CASTLE

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The importance of purines in biological systems prompted an investigation of various routes which might make these compounds and their structural analogs more readily available. In the course of this work it was found that ethyl acetamidocyanoacetate is a convenient and versatile intermediate for the synthesis of a variety of 6-hydroxypurines and 7-hydroxy-*v*-triazolo[*d*]pyrimidines.

In 1948, Wilson[1] prepared 5-acetamido-2,4-diamino-6-hydroxypyrimidine by condensation of ethyl acetamidocyanoacetate with guanidine. This reaction was carried out to prove the structure of the product obtained by acetylation of 2,4,5-triamino-5-hydroxypyrimidine and apparently has not been recognized as a preparative method for purine intermediates.

In the present work ethyl acetamidocyanoacetate was condensed with acetamidine, urea, or guanidine as indicated in Fig. 1 to give 5-acetamidopyrimidines (I) in high yields. These pyrimidines were readily converted to 2-methylhypoxanthine (II-a), xanthine (II-b), or guanine (II-c), respectively, by brief treatment with boiling formamide. It has already been shown that 5-acetamido-4-amino-2,6-dihydroxypyrimidine gives xanthine when heated with formamide.[2] When the intermediate pyrimidines (I) were dehydrated with phosphorus oxychloride, the corresponding 6-hydroxy-8-methylpurines (III) were formed. 5-Acetamido-4-amino-6-hydroxy-2-methylpyrimidine (I-a) on hydrolysis with hot concentrated hydrochloric acid and treatment with aqueous sodium nitrite gave high yields of the corresponding *v*-triazolo[*d*]pyrimidine (IV-a). The experimental data are summarized in Table I.

Ethyl acetamidocyanoacetate is available from several suppliers or can be easily prepared in large quantities by nitrosation of ethyl cyanoacetate followed by reduction in the presence of acetic anhydride.[3] From this one intermediate a variety of substituted purines and purine analogs can be synthesized in only two steps.

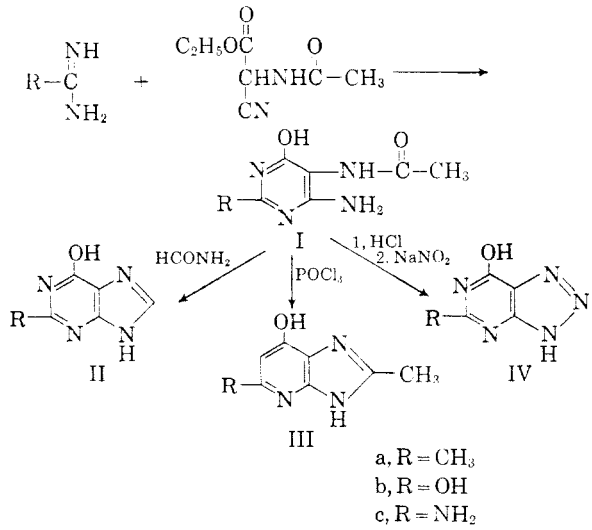

Figure 1

EXPERIMENTAL

Procedure A: 5-acetamido-4-amino-6-hydroxypyrimidines. A solution of 0.2 mole of acetamidine, guanidine, or urea and 34 g. (0.2 mole) of ethyl acetamidocyanoacetate in 125–200 ml. of absolute ethyl alcohol was treated with 10.8 g. (0.2 mole) of sodium methoxide and then heated under reflux for 2–3 hr. The reaction mixture was chilled and the precipitate collected. The free pyrimidines were obtained by dissolving this precipitate in a minimum of hot water, decolorizing with charcoal, and adjusting the solution to

(1) W. Wilson, *J. Chem. Soc.*, 1157 (1948).

(2) H. Bredereck, I. Hennig, W. Pfleiderer, and G. Weber, *Ber.*, **86**, 333 (1953).

(3) M. Fields, D. E. Walz, and S. Rothchild, *J. Am. Chem. Soc.*, **73**, 1000 (1951).