EXPERIMENTAL

The Nitration of 2-Fluoro-anthraquinone

2-Fluoro-anthraquinone (10 g) was dissolved in concentrated sulphuric acid (100 ml). The solution was cooled to 0° and a quantity of well ground, dry sodium nitrate (3.8 g) was added while the solution was well stirred. After 12 hours the solution was heated to 40–45° for 2 hours and then poured onto ice. During the reaction a noticeable change in color to grey-yellow was observed. The grey-yellow precipitate was recrystallized from chlorobenzene to give *1-nitro-6 or 7-fluoro-anthraquinone* (8.2 g, 66.2%), m.p. 222–223°. Anal. Found: C, 62.15; H, 2.2; F, 6.9; N, 5.15%. $C_{14}H_6FNO_4$ requires: C, 62.1; H, 2.25; F, 6.9; N, 5.15%.

Similarly, 2,6-difluoro-anthraquinone (10 g) was nitrated to give *1-nitro-2,6-difluoro-anthraquinone* which on recrystallization from chlorobenzene (7.75 g, 66.3%), had m.p. 207–209°. Anal. Found: F, 13.00; N, 4.9%. $C_{14}H_5F_2NO_4$ requires: F, 13.15; N, 4.85%.

The Nitration of 1-Fluoro-anthraquinone

1-Fluoro-anthraquinone (10 g) was dissolved in sulphuric acid (100 ml) and to the red solution maintained at 0° was added sodium nitrate (3.7 g) with stirring. The reaction mixture was kept at 0° (12 hours) and then poured onto ice to precipitate the grey nitration product (6.7 g, 55.7%), which was recrystallized from chlorobenzene, m.p. 213–214°. Anal. Found: F, 6.95; N, 5.15%. $C_{14}H_6FNO_4$ requires: F, 6.9; N, 5.15%.

Similarly, 1,5-difluoro-anthraquinone (10 g) was nitrated to *1-nitro-4,8-difluoro-anthraquinone.* Recrystallization from chlorobenzene gave a grey product (6.65 g, 60.8%), of m.p. 235–240°. Anal. Found: F, 11.9; N, 4.9%. $C_{14}H_5F_2NO_4$ requires: F, 13.15; N, 4.85%.

1-Fluoro-4-nitro-anthraquinone

1-Amino-4-nitro-anthraquinone (50 g) was converted by treatment with nitrosyl – sulphuric acid solution to *1-diazonium fluoroborate-4-nitro-anthraquinone* (1) (yield, 60.9 g, 89%), decomposition temperature 171-173°. The well dried salt was heated to decomposition in a round-bottomed flask equipped with a reflux condenser. The decomposition was followed by sublimation of the product which was recrystallized from chlorobenzene and further purified by sublimation, m.p. 226–227°. Anal. Found: F, 6.95; N, 5.15%. $C_{14}H_6FNO_4$ requires: F, 6.9; N, 5.15%.

1-Amino-6 or 7-Fluoro-anthraquinone

The nitration product of 2-fluoro-anthraquinone (5 g) was ground to a paste with sodium sulphide nonahydrate (10 g), suspended in hot water at 70–80°, and stirred. The complete reaction occurred in 40 minutes. The solution turned to violet and was filtered hot. The red product recrystallized from anisole gave red needles (yield 4.2 g, 94.2%), m.p. 199–201°. Reduction with sodium hydrosulphide in benzene in the presence of calcium chloride (7) gave similar results; from 5 g of starting material, 4.4 g (98.5%) of amine were obtained which on recrystallization from anisole had m.p. 203–204°. Found: C, 69.6; H, 3.3; F, 7.55; N, 5.8%. Calc. for $C_{14}H_8FNO_2$: C, 69.7; H, 3.3; F, 7.9; N, 5.8%.

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Received May 13, 1963.
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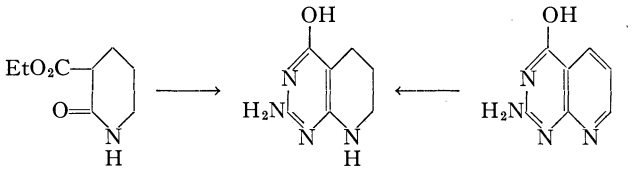
CONVERSION OF A β-AMIDOESTER TO A PYRIMIDINE: 2-AMINO-4-HYDROXY-5,6,7,8-TETRAHYDRO-1,3,8-TRIAZANAPHTHALENE

Joseph DeGraw and Leon Goodman

As an extension of previous work on the synthesis of folic acid analogs (1), the preparation of 5-deazatetrahydrofolic acid is being investigated. Initially, a study of the preparation of the basic heterocyclic portion of this folic acid analog, 2-amino-4-hydroxy-5,6,7,8-tetrahydro-1,3,8-triazanaphthalene (II), was undertaken. It is hoped that the best general

method for preparing II can be elaborated to provide 6-substituted derivatives of II useful for the synthesis of 5-deazatetrahydrofolic acid.

The condensation of guanidine with a β-keto ester represents probably the most useful general method for preparing 2-amino-4-hydroxypyrimidines. As an extension of this method the condensation of guanidine with 3-carbethoxy-2-piperidone (I) (2) was



I II III

investigated for the synthesis of II. The reaction, carried out at 150° in methanol with sodium methoxide, afforded the pyrimidopiperideine (II) in 38% yield. This appears to be the first such example of the condensation of guanidine with a β-amidoester to form a pyrimidine ring.

In order to provide a proof of structure for the condensation product and as a second preparative method for II, the catalytic reduction of 2-amino-4-hydroxypyrido[2,3-*d*]-pyrimidine (III) (3) was investigated. When an aqueous suspension of III was treated with hydrogen at atmospheric pressure over platinum oxide, approximately 2 moles of hydrogen were absorbed. The product (II) was identical with that prepared by the condensation method with respect to infrared and ultraviolet spectra and paper chromatographic behavior.

The further utility of these methods for the ultimate synthesis of 5-deazatetrahydrofolic acid is currently under investigation.

EXPERIMENTAL

3-Carbethoxy-2-piperidone (I) was prepared in a two-step reaction sequence as follows. Malonic ester was reacted with acrylonitrile to afford ethyl 2-carbethoxy-4-cyanobutyrate in a 56% yield according to the procedure of Mikeska (4). The cyano ester was catalytically reduced over platinum oxide at atmospheric pressure to yield 3-carbethoxy-2-piperidone (I), essentially following the method described by Koelsch (2). 2-Amino-4-hydroxypyrido [2,3-*d*]pyrimidine (III) was prepared in 51% yield by the procedure of Price *et al.* (3).

2-Amino-5,6,7,8-tetrahydro-4-hydroxypyrido[2,3-d]pyrimidine (II)

A. Condensation of Guanidine and 3-Carbethoxy-2-piperidone

A 1-liter autoclave was charged with 14.4 g (84 mmoles) of 3-carbethoxy-2-piperidone (I), 15.7 g (0.29 mole) of sodium methoxide, 16.4 g (0.172 mole) of guanidine hydrochloride, and 200 ml of absolute methanol. The mixture was stirred at 150° for 8 hours and allowed to cool for another 15 hours. The mixture was evaporated to dryness *in vacuo* and the residue was triturated with 100 ml of water. The insoluble material was collected, washed with water, and dried to leave 5.3 g (38%), m.p. 245–255°. An analytical sample, m.p. 260–270°, was obtained by recrystallization from water; $\lambda_{max(m\mu)}^{pH\,1}$ 280 (ϵ 16150), $\lambda_{max(m\mu)}^{pH\,13}$ 274 (ϵ 8900), R_f 0.70 in *n*-butanol/acetic acid/water, 5/2/3.

Anal. Calc. for $C_7H_{10}N_4O \cdot \frac{1}{4}H_2O$: C, 49.3; H, 6.20; N, 32.8. Found: C, 49.3; H, 6.60; N, 32.6. The material was quite hygroscopic and samples showing various degrees of hydration were encountered; the samples were dried *in vacuo* at 120° for 15 hours prior to analysis.

B. Hydrogenation of 2-Amino-4-hydroxypyrido[2,3-d]pyrimidine

To 10 ml of water were added 0.50 g (2.8 mmoles) of 2-amino-4-hydroxypyrido[2,3-*d*]pyrimidine (III) and 50 mg of platinum oxide. The mixture was stirred under an atmosphere of hydrogen for 21 hours. An uptake of 1.91 moles of gas was observed and the product deposited from solution. The mixture was heated to 95–100° and quickly filtered by suction. The residue was retreated with 5 ml of hot water, filtered, and the combined filtrates were chilled for 30 minutes. The white crystals which formed were collected, washed

with water, and dried to leave 0.12 g (24%), m.p. 262–273°. This material was identical with that obtained in procedure A with respect to infrared and ultraviolet spectra and paper chromatographic behavior.

ACKNOWLEDGMENTS

This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

The authors are indebted to Dr. Peter Lim for infrared interpretations, to his staff for ultraviolet and paper chromatographic data, and to Mr. O. P. Crews for the large-scale preparation of intermediates.

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Received July 15, 1963.
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THE EFFECT OF ALKYL GROUP VARIATION ON THE RATES OF SOLVOLYSIS OF ALKYL SULPHONIUM HALIDES

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Tertiary butyl and amyl dimethylsulphonium salts have been the standard examples of the sulphonium salt series used in neutral solvolytic rate studies of this type of compound in the past (1). Apart from these cases the apparent hygroscopic nature of the sulphonium salts has limited the study of their solvolytic behavior. In the course of our studies of sulphonium salt solvolysis we have prepared and characterized α-phenethyldimethylsulphonium and benzyldimethylsulphonium bromides. The solvolytic rate behavior of these two compounds together with comparative data on the *t*-butyldimethylsulphonium salt are reported here.

RESULTS

Approximately 10^{-3} *M* solutions of the various sulphonium salts in the desired solvent media were prepared by weight. Solvolytic kinetics were followed using the conductimetric technique described previously (2) and due to Robertson (3). While the iodide salt was used in the *t*-butyl case the bromides of both the α-phenethyl and benzyl sulphonium ions were employed. Since 0.325 mole fraction ethanol in water was the lowest polarity solvent used the anion does not enter the rate determining step as was shown previously (2, 4). Consequently the change from iodide to bromide does not invalidate the comparison of rates. In both the α-phenethyl and benzyl cases difficulty was encountered in obtaining reproducible results in pure water. In the benzyl case only those rates measured in higher ethanolic compositions were of satisfactory reproducibility. In Table I the rates for the