An Improved Synthesis of Willardiine and 1-(2′,2′-Diethoxyethyl)uracil[1]

ABELARDO P. MARTINEZ AND WILLIAM W. LEE

Life Sciences Research, Stanford Research Institute, Menlo Park, California

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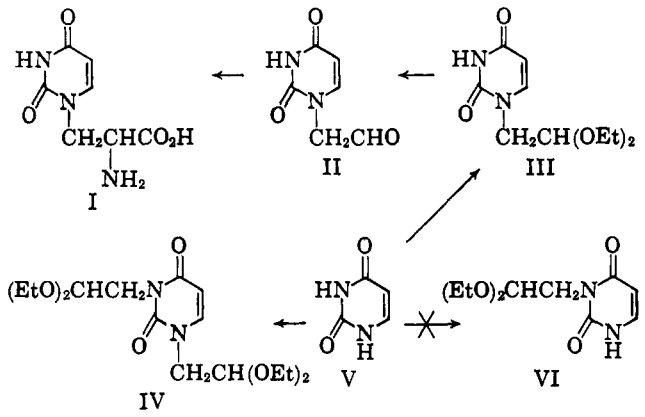
The structure of Willardiine, a new nonprotein L-amino acid containing uracil, was recently established as I by unambiguous synthesis.[2a,b] An additional synthesis of Willardiine has been recently achieved.[3] Because of the current interest in Willardiine and because none of the above methods could conveniently provide the large quantities of DL-Willardiine needed in another problem that will be reported later, we have devised a much shorter synthesis.

The method of Dewar and Shaw[2a] proceeded from ethyl bromoacetate by a number of steps to N-2,2-diethoxyethyl-N′-β-ethoxyacryloylurea which was cyclized to the acetal III. Hydrolysis to the aldehyde II followed by the Strecker reaction afforded I. We find that the key intermediate, 1-(2′,2′-diethoxyethyl)-uracil (III), can be prepared in one step from uracil in 40% yield (the yield from ethyl bromoacetate was below 4%[2a]).



Reaction of sodium hydride with uracil in N,N-dimethylformamide furnished the sodium salt. This reacted with 2-bromo-1,1-diethoxyethane, used in excess, to form III (40%) and some dialkylation product IV (18%) which did not interfere with the ready isolation of III. No 3-alkylated product VI was found. With a smaller excess of sodium hydride and the bromo acetal, the yield of III dropped and much unchanged uracil was left. The reaction did not proceed well at lower temperatures.

The above alkylation results are interesting since direct monalkylation of uracil generally fails. Thus, 1,3-dimethyluracil is obtained with diazomethane, methyl sulfate, or methyl iodide.[4] The N-monoalkylated uracils are generally made by less direct methods from 2-ethylthio-4-hydroxypyrimidine, which can only monoalkylate, or by construction of the uracil ring.[4] However, monoalkylation is possible; chloroacetic acid reacts with uracil in aqueous potassium hydroxide to give uracil-1-acetic acid.[5] Unfortunately, these conditions are not applicable when 2-bromo-1,1-diethoxyethane replaces chloroacetic acid. In another case of monoalkylation, uracil and ethyl acrylate (and other acrylic acid derivatives) react in liquid ammonia to give ethyl 3-(1-uracil)propionate.[6] We were unable to adapt this reaction to 2-(acetamido)acrylic acid.

An additional improvement in the DL-Willardiine synthesis resulted when the acetal III was hydrolyzed to the aldehyde II. Excellent yields were obtained by heating III in aqueous ammonium chloride and reusing the hydrolysis medium.

Experimental[7]

1-(2′,2′-Diethoxyethyl)uracil (III).—To a stirred suspension of 14.0 g. (0.125 mole) of uracil in 150 ml. of N,N-dimethylformamide (reagent grade, used without purification) was added 7.00 g. (0.158 mole) of a 54% sodium hydride suspension in oil (prewashed with petroleum ether, b.p. 30–60°, to remove the oil) in one portion. After stirring for 2 hr., protected from moisture, the mixture was treated with a solution of 50.0 g. (0.25 mole) of 2-bromo-1,1-diethoxyethane in 25 ml. of N,N-dimethylformamide and heated to 80° for 14 hr. An additional portion of 25.0 g. (0.125 mole) of the acetal was added. The temperature was then raised to 149–150° and maintained until all the solids had dissolved and fine crystals of sodium bromide had begun to precipitate (about 30 min.). The reaction mixture was cooled and evaporated at 60° and 1 mm. to leave a residue. This was extracted with 300 ml. of ethyl acetate; the extract was filtered, washed with two 200-ml. portions of water, dried over magnesium sulfate, and evaporated *in vacuo* to leave 20.8 g. of a yellow oil which crystallized on seeding. The crude product was triturated with 50 ml. of ether and 50 ml. of petroleum ether, b.p. 30–60°, to leave 10.5 g. (37%) of 1-(2′,2′-diethoxyethyl)-uracil (III), m.p. 93.0–93.5° (lit.[2a] 91°); it moved as a single spot in solvents A (R_f 0.67), B (R_f 0.79), and C (R_f 0.87). It was identical in all respects by comparison with an authentic sample of III prepared according to the literature.[2a]

Evaporation of the ether–petroleum ether solution left 9.2 g. of residue which was chromatographed on a 2.4 × 15.5 cm. column of neutral alumina (Woelm, activity grade I). Elution with chloroform afforded 7.68 g. (18%) of IV as a yellow oil, moving as one spot in solvent B (R_f 0.90) A portion of this oil was rechromatographed, and shown to be 1,3-bis(2′,2′-diethoxyethyl)uracil (IV) by nuclear magnetic resonance as well as analysis.

Anal. Calcd. for $C_{16}H_{28}N_2O_6$: C, 55.8; H, 8.20; N, 8.13. Found: C, 55.4; H, 8.48; N, 7.89.

Further elution of the column with methanol afforded an additional 1.21 g. (4%) of III, m.p. 90–92°, homogeneous on paper chromatograms. No 3-(2′,2′-diethoxyethyl)uracil (VI) was found.

Uracil-1-acetaldehyde (II).—A mixture of 18.0 g. of the acetal III, 35.0 g. of ammonium chloride, and 150 ml. of water was heated on a steam bath for 3.5 hr. The resultant clear light yellow solution was cooled in ice to afford 9.3 g. of the aldehyde II monohydrate, m.p. 206.5–208.5°. Reusing the same hydrolysis liquors, 18.3 g. of III similarly afforded 10.5 g. of II

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(2) (a) J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 583 (1962); (b) A. Kjaer, A. Knudsen, and P. O. Larsen, *Acta Chem. Scand.*, **15**, 1193 (1961).

(3) Yu P. Shvachkin and M. T. Azarova, *Zh. Obshch. Khim.*, **34**, 407 (1964).

(4) D. J. Brown ("The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, p. 360) has summarized the N-alkylation of uracils.

(5) H. L. Wheeler and L. M. Liddle, *J. Am. Chem. Soc.*, **30**, 1152 (1908).

(6) Yu P. Shvachkin, M. T. Azarova, and I. I. Rapanovich, *Vestn. Mosk. Univ., Ser. II, Khim.*, **18**, 68 (1963).

(7) Melting points were taken on a Fischer-Johns apparatus and are corrected. Paper chromatography was done by the descending technique on Whatman No. 1 paper (except solvent A), and the spots were detected under ultraviolet light. The solvent systems were A, benzene–methanol–water (2:6:1), run on Schleicher and Schuell No. 2496 acetylated paper; B, *n*-butyl alcohol–water (saturated); and C, 5% aqueous disodium hydrogen phosphate, pH 8.9.

monohydrate, m.p. 213.5–214.5°. Repeating with 14.0 g. of III afforded 11.5 g. of II monohydrate, m.p. 213–214°. The total yield of II monohydrate was 31.3 g. (83%) from 50.3 g. of III. The samples of II were all homogeneous on paper in solvents A (R_f 0.70), B (R_f 0.51, streaky), and C (R_f 0.65), and were identical in all respects to authentic II.[2a]

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The Organic Chemistry of a New Weak Field Tridentate Chelating Agent. 3,5-Di(2-pyridyl)-1,2,4-triazole

JOHN F. GELDARD[1] AND FRANCIS LIONS

Department of Organic Chemistry, University of Sydney, Sydney, Australia

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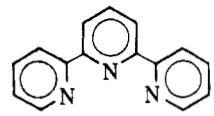
As a result of an interest in tridentate chelating agents of the terpyridine [2,6-di(2-pyridyl)pyridine, I] type, we have synthesized a new ligand, 3,5-di(2-



I

pyridyl)-1,2,4-triazole (II), by the methods shown in Chart I. Hydrazine hydrate and 2-cyanopyridine were heated together under reflux; the product was 3,6-di(2-pyridyl)-1,2-dihydro-1,2,4,5-tetrazine (III).[2] III was rearranged to 3,5-di(2-pyridyl)-4-amino-1,2,4-triazole (VI) essentially by the method of Dallacker[2] but again without Raney nickel. We were unable to convert VI to bis(2-picolinoyl)hydrazide to any appreciable degree by further treatment with acid.[2,3]

Nitrous acid attacked VI with difficulty giving the desired triazole II. The infrared spectrum of VI shows substantial hydrogen bonding of the amine protons. VI does not form a stable salicylidene derivative and its resistance to attack by nitrous acid appears to be a consequence of this bonding.

Treatment of III with nitrous acid gives one of two products depending of the pH of the reaction medium. In almost neutral solutions, nitrous acid oxidizes III to 3,5-di(2-pyridyl)-1,2,4,5-tetrazine (IV). The same reaction has been reported using nitric acid as the oxidant.[2] In acidic media, nitrous acid converts III to 2,5-di(2-pyridyl)-1,3,4-oxadiazole (V). Elemental analysis, the mass spectrum, and spectroscopic data establish unambiguously the identity of V. V and VI are probably produced *via* a common intermediate. It is obvious that III does not first rearrange to VI

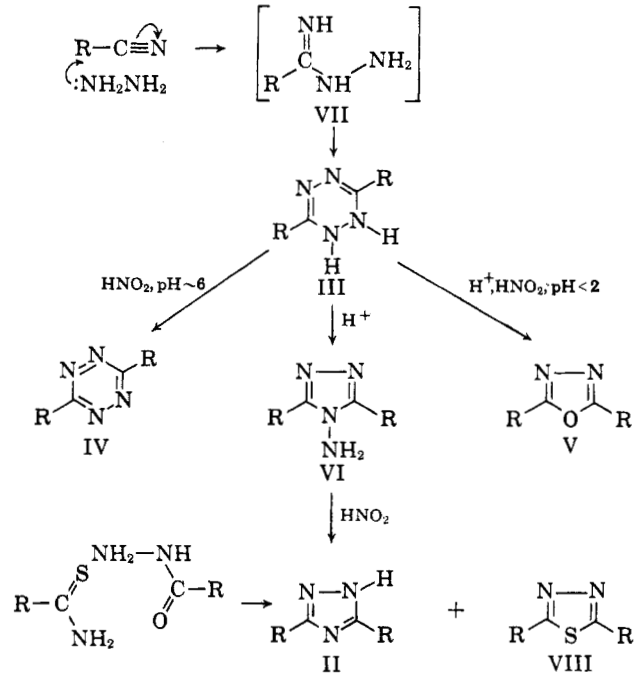
(1) Petroleum Research Fund Fellow of the University of Sydney; Department of Chemistry, University of Illinois, Urbana, Ill.

(2) F. Dallacker [*Monatsh.*, **91**, 294 (1960)] reports the use of Raney nickel in this condensation.

(3) D. D. Libman and R. Slack, *J. Chem. Soc.*, 2253 (1956).

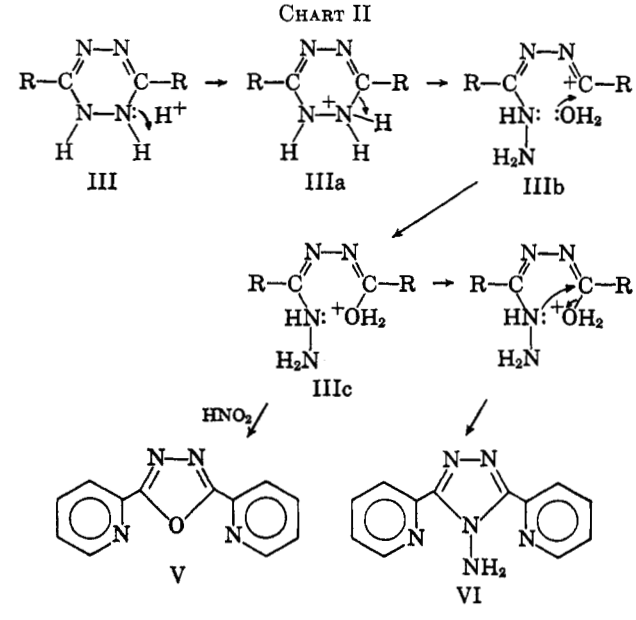
CHART I

(R = $2C_5H_4N$)



during formation of V because nitrous acid attack on VI gives the triazole II. A suggested mechanism is given by the scheme shown in Chart II.

CHART II



It is reasonable to postulate the conversion of III to IIIc by acid attack. IIIc can then cyclize to VI by elimination of water or to V by the attack of nitrous acid. IIIc is constituted similarly to compounds known to give oxadiazoles when treated with nitrous acid.[4]

The triazole II was also prepared by heating together equimolecular amounts of 2-picolinthionamide and 2-picolinoylhydrazide at 160°. Sodium hydroxide extracted II from the mixture of products. The alkali-insoluble material proved to be 2,5-di(2-pyridyl)-1,3,4-thiadiazole (VIII).

(4) A. Pinner, *Ann.*, **297**, 221 (1897); **298**, 16 (1897); A. Pinner and N. Caro, *Chem. Ber.*, **27**, 3288 (1894).