[CONTRIBUTION FROM THE CLAYTON FOUNDATION FOR RESEARCH, THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of 1-Deazaguanine[1]

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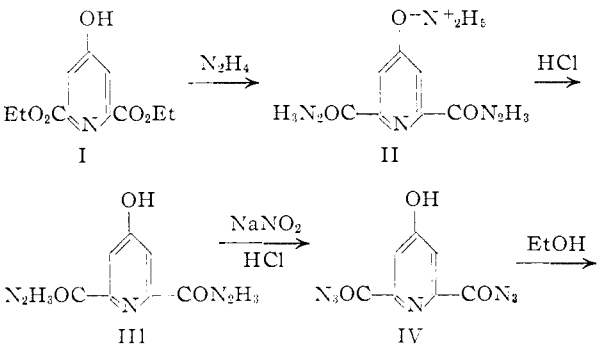
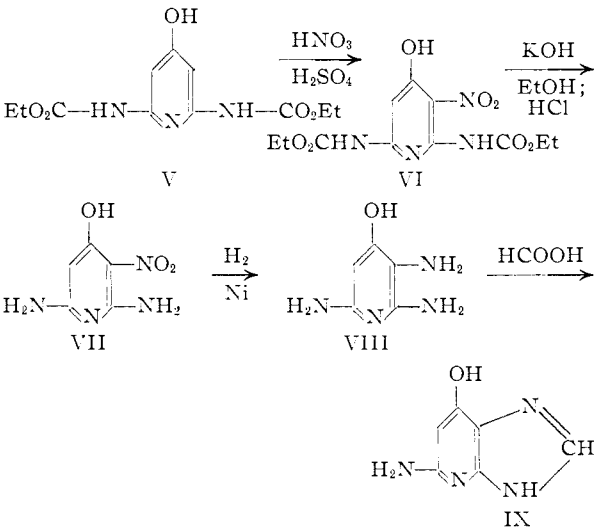
The synthesis of 5-amino-7-hydroxyimidazo[b]pyridine (1-deazaguanine), a potential antagonist for guanine, from chelidamic acid is reported. Chelidamic acid dihydrazide was converted to the diazide and then to 4-hydroxy-2,6-pyridinedicarbamate *via* a Curtius reaction. Nitration of the latter product followed by hydrolysis and reduction yielded 2,3,6-triamino-4-pyridinol which was finally formylated and cyclized to produce 1-deazaguanine.

Analogs of naturally occurring purines are of interest as potential antagonists in biological systems, particularly in malignant cells. Several compounds possessing such biological activity have altered ring structures in which carbon and nitrogen are interchanged or substituted for one another, *i.e.*, benzimidazole,[2a] 8-azapurines[2b] and 4-aminopyrazolo[3,4,-d]pyrimidine.[3] Several imidazopyridines (deazapurines) have been reported, but were found to be inactive as growth inhibitors for several organisms.[4-9] However, the analog corresponding to guanine (5-amino-7-hydroxyimidazo-[b]pyridine or 1-deazaguanine) (IX) has not been reported. This compound having two functional groups, amino and hydroxyl, on the imidazopyridine nucleus in positions corresponding to these groups in guanine would have greater opportunities than some of the previously reported imidazopyridines for complexing with enzymes involved in utilization of guanine. The intermediate VIII for the preparation of 1-deazaguanine, 2,3,6-triamino-4-pyridinol, is of further interest as an intermediate in the preparation of analogs of other metabolites, *e.g.*, folic acid.

The synthesis of 1-deazaguanine was accomplished by the steps





On treating diethyl chelidamate (I) with hydrazine in ethanol, the hydrazonium salt of the ester separated out of solution initially, but on prolonged refluxing of the mixture, the ester groups were replaced in sequence to form a monohydrazide and finally the dihydrazide of the hydrazonium salt II. On neutralization with acid, the dihydrazide of chelidamic acid (III) could be isolated; however, for the preparation of chelidamyl diazide, the hydrazonium salt of the dihydrazide was dissolved in hydrochloric acid and treated with nitrous acid. The precipitated diazide was immediately dissolved in ethanol, and the mixture heated to reflux temperatures to form diethyl 4-hydroxy-2,6-pyridinedicarbamate (V). Nitration of this compound V occurred so readily that the dinitro derivative was initially obtained; however, by using milder conditions, diethyl 4-hydroxy-3-nitro-2,6-pyridinedicarbamate (VI) could be obtained in good yield. This nitro derivative of the dicarbamate was quite resistant to acid hydrolysis, and to hydrolyze the carbamate groups it was necessary to reflux the compound in alcoholic potassium hydroxide for several days to obtain the potassium salt of 2,6-diamino-3-nitro-4-pyridinol (VII). In contrast to the nitro derivative of the dicarbamate VI which reduced readily to the corresponding amine, the catalytic reduction of the nitro group of VII proceeded slowly. However, shaking several hours with Raney nickel in ethanol and hydrogen at 50 lb./sq. in. pressure reduced the nitro compound to 2,3,5-triamino-4-pyridinol (VIII). On removing the solvent under vacuum, a white crystalline solid was obtained, but was

(1) After this report had been submitted for publication, the preparation of 1-deazaguanine from chelidamic acid by another route was reported by D. G. Markees and G. W. Kidder, THIS JOURNAL, **78**, 4130 (1956).

(2) (a) D. W. Woolley, *J. Biol. Chem.*, **152**, 225 (1944); (b) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

(3) R. K. Robins, *ibid.*, **78**, 784 (1956).

(4) R. Weidenhagen and U. Weeden, *Chem. Ber.*, **71**, 2347 (1938).

(5) F. Kogl, G. M. van der Want and C. A. Salemink, *Rec. trav. chim.*, **67**, 29 (1948).

(6) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

(7) C. A. Salemink and G. M. van der Want, *Rec. trav. chim.*, **68**, 1013 (1949).

(8) J. R. Vaughn, Jr., J. Krapcho and J. P. English, THIS JOURNAL, **71**, 1885 (1949).

(9) F. Korte, *Chem. Ber.*, **85**, 1012 (1952).

rapidly oxidized so that within a few minutes after opening the flask, the solid had turned a deep purple. Hence, in practice, VIII was prepared from VII just prior to its use in other reactions. Attempts to prepare a picrate of VIII were unsuccessful under the usual conditions.

Variable results have been reported by different workers in attempting to form imidazoles from diaminopyridines with formic acid. Petrow and Saper[6] claimed to have prepared imidazo[b]pyridine by refluxing 2,3-diaminopyridine in 98% formic acid. Korte[9] obtained only 2-amino-3-formamidopyridine on using the same procedure; he found it necessary to heat the formamido derivative to 120° at 1 mm. pressure for ring closure. Similarly, formation of the imidazole from 2,3,6-triamino-4-pyridinol by refluxing with formic acid failed. Intermediate derivatives could be isolated depending on the length of time that the triaminopyridinol (VIII) was refluxed with formic acid. If the formic acid reaction mixture was evaporated to dryness and the crude residue heated to 270° under reduced pressure, cyclization of the formamido derivative gave 5-amino-7-hydroxyimidazo[b]pyridine (IX) (1-deazaguanine). That ring closure occurred between the amines in the 2- and 3-position rather than between the 3-amino and 4-hydroxy group was confirmed by the presence of an acidic group in the compound isolated.

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Experimental[10]

Diethyl Chelidamate (I).—Chelidonic acid was prepared by the method of Riegel and Zwilgmeyer[11] and was converted to chelidamic acid by the method of Riegel and Reinhard.[12] Attempts to esterify chelidamic acid with an ethanol–sulfuric acid mixture[13] were not particularly successful; however, esterification could be effected readily with ethanol–hydrogen chloride. Chelidamic acid, 57 g., was refluxed for 3 hours in 1 l. of absolute ethanol containing 5% hydrogen chloride by weight. The solution was cooled and poured into 3 l. of cold water. The slow separation of crystals of I was facilitated by vigorous stirring. The mixture was filtered and the cake washed with cold water until free of acid. The filtrate was evaporated to dryness, giving a solid which could be re-esterified to increase the yield of 34 g., m.p. 68–73°. Recrystallization of the product from water and drying in vacuum over anhydrous calcium chloride gave white crystals, m.p. 112–113°. A hydrate was previously reported to melt at 80–81°.[13]

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.2; H, 5.47. Found: C, 55.2; H, 5.43.

Trisodium Chelidamate.—During early attempts to isolate diethyl chelidamate from its ethanol–hydrogen chloride solution, a sample of the reaction mixture containing the ester was poured into 1 *N* sodium hydroxide. A white powder immediately separated which was analyzed without further purification after washing and drying. The compound was insoluble in water and soluble in 1 *N* hydrochloric acid. On burning a sample of the compound, a white basic ash was left. Analysis of a sample dried at 100° for 2 hours indicated that the compound was apparently the trihydrate of trisodium chelidamate. The substance did not melt below 300°.

Anal. Calcd. for $C_7H_2NO_5Na_3 \cdot 3H_2O$: C, 27.7; H, 2.66; N, 4.62; Na, 22.8. Found: C, 27.4; H, 3.15; N, 4.74; Na, 23.2.

Chelidamic Acid Dihydrazide (III).—Diethyl chelidamate (34 g.) in 500 ml. of absolute ethanol was heated under reflux for 6 hours with 15 g. of 95% hydrazine. The mixture was cooled and filtered, and the solid was then washed with 95% ethanol and allowed to air dry. The crude yield of the hydrazonium salt of chelidamic acid dihydrazide (II) was 34 g. The chelidamic acid dihydrazide could be liberated by neutralizing a water solution of the salt with 4 *N* hydrochloric acid. For analysis, the dihydrazide was recrystallized from water and dried at 100° for 3 hours. The crystalline material did not melt below 300°.

Anal. Calcd. for $C_7H_9N_5O_3 \cdot {}^1/_2H_2O$: C, 38.2; H, 4.57. Found: C, 38.4; H, 4.46.

Hydrazonium Salt of Diethyl Chelidamate.—On addition of 95% hydrazine to an ethanol solution of diethyl chelidamate, the solution became warm and in 5 minutes a crystalline precipitate formed. The precipitate was recovered by filtration and washed with ethanol to give a white powder, m.p. 128–130°. An analytical sample was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{17}N_5O_5$: N, 15.5. Found: N, 15.8.

Hydrazonium Salt of the Monohydrazide of Diethyl Chelidamate.—After heating to reflux an ethanol–hydrazine solution with the hydrazonium salt of diethyl chelidamate for 15 minutes, a solution formed. The solution was filtered and cooled. Colorless, light crystals separated which were filtered and washed with ethanol. The crystals did not melt below 300°. A sample suitable for analysis was obtained by recrystallization from pyridine.

Anal. Calcd. for $C_9H_{15}N_5O_4$: N, 27.2. Found: N, 27.4.

Chelidamyl Diazide (IV).—Sufficient 4 *N* hydrochloric acid to effect solution was added to 34 g. of II. The solution was cooled to 5° with cracked ice and 20 g. of sodium nitrite in 100 ml. of water was added slowly. The precipitate was filtered and dissolved in 200 ml. of ethanol. The solution was then dried with anhydrous sodium sulfate. A white powder, obtained by evaporating the solvent under vacuum, exploded at 100° on heating. No attempt was made to analyze the compound.

4-Hydroxy-2,6-pyridinedicarbamate (V).—The ethanol solution of chelidamyl diazide (IV) prepared by the above procedure was refluxed for 6 hours. The solvent was evaporated on a steam-bath to obtain a viscous liquid which was redissolved in 100 ml. of absolute ethanol and decolorized with Darco G-60. The solvent was removed under vacuum to give 22.5 g. of crystalline product. The material was triturated with hot water to yield white crystals, m.p. 201–203°. The sample was dried at 100° for analysis.

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 49.1; H, 5.61; N, 15.6. Found: C, 48.9; H, 5.43; N, 15.5.

Diethyl 4-Hydroxy-3,5-dinitro-2,6-pyridinedicarbamate.—Two grams of V was stirred with 2 ml. of concentrated sulfuric acid (sp. gr. 1.84). To the mixture was added 2 ml. of fuming nitric acid (sp. gr. 1.5) with cooling. After the reaction had subsided, the mixture was heated on the steam-bath for 20 hours. The solution was cooled and poured into ice-water. The light yellow precipitate which formed was recovered by filtration and washed with water to give 1.5 g. of crude product. Recrystallization from water gave pale yellow, long, fine needles, m.p. 173–176°.

Anal. Calcd. for $C_{11}H_{13}N_5O_9$: C, 36.8; H, 3.65. Found: C, 36.9; H, 3.51.

Diethyl 4-Hydroxy-3-nitro-2,6-pyridinedicarbamate (VI).—Twenty-two grams of V was slurried in 25 ml. of concentrated sulfuric acid (sp. gr. 1.84) with cooling. The mixture was slowly poured into 100 ml. of fuming nitric acid (sp. gr. 1.5) and allowed to stand at room temperature for 2 hours. The nitration mixture was then poured into an ice–water mixture and allowed to warm to room temperature. The acid solution was neutralized with 10% sodium hydroxide to give a bright yellow precipitate which was filtered and washed with ice-water. The crude yield of VI was 15.5 g. An analytical sample was obtained by recrystallization of

(10) All melting points were determined on a Fisher–Johns melting point block and are uncorrected.

(11) E. R. Riegel and F. Zwilgmeyer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 126.

(12) E. R. Riegel and M. C. Reinhard, THIS JOURNAL, **48**, 1334 (1926).

(13) J. U. Lerch, *Monatsh.*, **5**, 388 (1884).

the crude product from water to give bright yellow platelets, m.p. 164–167°.

Anal. Calcd. for $C_{11}H_{14}N_4O_7$: C, 42.0; H, 4.49; N, 17.8. Found: C, 42.0; H, 4.14; N, 18.1.

2,6-Diamino-3-nitro-4-pyridinol (VII).—Fifteen grams of VI was added to 100 ml. of absolute ethanol saturated with potassium hydroxide. The mixture was refluxed on a steam-bath for 3 days. An insoluble red potassium salt was formed as soon as the dicarbamate VI was added to the alcoholic alkali solution but, as the reaction proceeded, the color of the precipitate slowly changed to a yellowish-orange. The cooled mixture was filtered, and the precipitate dissolved in water. On neutralization with concentrated hydrochloric acid, a yellowish-orange precipitate was formed. After filtering and washing with water, the product weighed 5.7 g. A sample recrystallized from water gave fine yellowish-orange platelets which decomposed at 256–258°.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.3; H, 3.55; N, 32.9. Found: C, 35.0; H, 3.70; N, 32.8.

2,3,6-Triamino-4-pyridinol (VIII).—2,6-Diamino-3-nitro-4-pyridinol (VII), 0.5 g., was dissolved in 25 ml. of 95% ethanol and shaken for 3 hours with Raney nickel and hydrogen under 50 lb./sq. in. pressure. After the catalyst had been removed, the solvent was evaporated under vacuum to give solid 2,3,6-triamino-4-pyridinol (VIII) which colored rapidly on exposure to air. No attempt was made to analyze the material.

5-Amino-7-hydroxy-imidazo[b]pyridine (IX).—To the 2,3,6-triamino-4-pyridinol (VIII) obtained by the above procedure was added 20 ml. of 98% formic acid. The solution was refluxed for 4 hours and then evaporated to dryness on the steam-bath. The solid residue was then heated to 270° for 3 hours at 1 mm. pressure. The residue from this pyrolysis was extracted with boiling water. The solution was decolorized with Darco G-60, filtered and allowed to cool. The 5-amino-7-hydroxy-imidazo[b]pyridine (IX) separated as feathery needles which did not melt below 300°; λ_{max} (in 95% ethanol), 264 mμ, log ε, 4.15; 282 mμ, log ε, 4.15. The product was dried at 110° for 4 hours for analysis.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.02; N, 37.3. Found: C, 47.6; H, 3.98; N, 37.1.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

The Preparation of Polymeric and Cyclic Urethans and Ureas from Ethylene Carbonate and Amines

BY ELIZABETH DYER AND HARVEY SCOTT[1]

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2-(Hydroxyethyl)-carbamates, obtained from primary amines and ethylene carbonate, lose ethylene glycol when subjected to vacuum distillation with an alcohol in the presence of barium oxide or zinc borate as catalysts. The alcohol group may be part of the 2-(hydroxyethyl)-carbamate or of a diol. Polyurethans were obtained from the reaction products of ethylene carbonate with 1,6-hexanediamine, 1,10-aminodecanol and 4-aminomethylbenzyl alcohol and also from the reaction of bis-(2-hydroxyethyl)-1,6-hexanedicarbamate with two high-boiling diols. Cyclic urethans were prepared from the reaction of ethylene carbonate with 2-aminoethanol, the N-ethyl- and N-butyl-2-aminoethanols, 1,3-aminopropanol and 4-amino-butan-2-ol. A polyurea was obtained from ethylene carbonate and N-isobutyl-1,6-hexanediamine. A cyclic urea resulted from ethylene carbonate and N-isopropyl-1,3-propanediamine.

In the last few years the preparation of various 2-hydroxyethyl carbamates from ethylene carbonate and amines has been reported[2]

$$RNH_2 + \underbrace{OCH_2CH_2OCO} \rightarrow RNHCOOCH_2CH_2OH$$

It occurred to the authors that polyurethans might be prepared from 2-(hydroxyethyl)-carbamates by elimination of ethylene glycol as is done in the commercial preparation of polyethylene terephthalate.[3] Such a procedure would avoid the need for chemically sensitive diisocyanates, which are the most common starting materials for the preparation of polyurethans.[4]

The following types of reactions were investigated

$$\underset{\text{I}}{HOCH_2CH_2OCONH(CH_2)_6NHCOOCH_2CH_2OH} \longrightarrow \underset{\text{II}}{HOCH_2CH_2OH} + \underset{\text{III}}{[\text{—}OCH_2CH_2OCONH(CH_2)_6NHCO\text{—}]_n} \quad (1)$$

$$\text{I} + HOROH \longrightarrow \underset{\text{IV}}{2\ \text{II}} + \underset{\text{V}}{[\text{—}OROCONH(CH_2)_6NHCO\text{—}]_n} \quad (2)$$

IVa and Va, R = $(CH_2CH_2OC_6H_4)_2C(CH_3)_2$-*p*
IVb and Vb, R = $(CH_2CH_2OC_6H_4)_2SO_2$-*p*

$$\underset{\text{VI}}{HOR'NH_2 + \underbrace{OCH_2CH_2OCO}} \longrightarrow [HOR'NHCOOCH_2CH_2OH] \quad (3)$$

$$[HOR'NHCOOCH_2CH_2OH] \longrightarrow \underset{\text{VII}}{\text{II} + [\text{—}OR'NHCO\text{—}]_n}$$

VIa and VIIa, R′ = $(CH_2)_{10}$
VIb and VIIb, R′ = $CH_2C_6H_4CH_2$-*p*

A polyurethan III was obtained readily by subjecting bis-(2-hydroxyethyl)-1,6-hexanedicarbamate[2d] (I), to vacuum distillation at 150° in the presence of a catalytic amount of barium oxide. This polymer was shown by analysis and infrared absorption to have the same composition as the polyurethan obtained by Brewster[4c] from 1,6-hexane diisocyanate and ethylene glycol. Attempts to apply this synthesis to the preparation of N-substituted polyurethans, by starting with secondary diamines, were unsuccessful.

In order to extend this type of reaction to the preparation of polyurethans other than those derived from ethylene glycol, reaction 2 was investigated. Appreciable transesterification was not accomplished by the reaction of I with 1,4-butanediol, *p*-xylylenediol, 1,4-bis-(2-hydroxyethoxy)-benzene or 1,5-bis-(2-hydroxyethoxy)-naphthalene, be-

(1) From the Ph.D. Thesis, 1956, of Harvey Scott, Armstrong Cork Co. Research Fellow, 1953–1955.

(2) (a) F. Strain, U. S. Patent 2,441,298 (May 11, 1948); (b) R. Delaby, A. Sekera, P. Chabrier and P. Piganiol, *Bull. soc. chim. France*, 392 (1951); (c) R. Delaby, P. Chabrier and H. Najer, *Compt. rend.*, **234**, 2374 (1952); (d) R. Delaby, P. Chabrier and H. Najer, *ibid.*, **235**, 376 (1952); (e) M. J. Viard, British Patent 689,705 (April 1, 1953); (f) W. Kern and W. Thoma, *Makromol. Chem.*, 11, 10 (1953).

(3) J. R. Whinfield and J. T. Dickson, British Patent 578,079 (June 14, 1946).

(4) (a) O. Bayer, *Angew. Chem.*, **59**, 257 (1947); (b) C. S. Marvel and J. H. Johnson, THIS JOURNAL, **72**, 1674 (1950); (c) J. H. Brewster, *ibid.*, **78**, 368 (1951); (d) E. Dyer and G. W. Bartels, *ibid.*, **76**, 591 (1954).