film) showed peaks at 2.93 (NH), 6.04 (olefinic C=C), and 6.20 μ (aromatic C=C).

The **hydrochloride salt** VI·HCl was prepared and purified for analysis in the same way as IVa·HCl. The twice-crystallized small colorless prisms were dried *in vacuo* at 85° for 72 hr. over phosphorus pentoxide in a closed drying pistol (some sublimation of the sample); m.p. 210–211° dec.

Anal. Calcd. for $C_{18}H_{17}N \cdot HCl$: C, 69.78; H, 8.09; Cl, 15.87; N, 6.26. Found: C, 69.77; H, 8.20; Cl, 15.79; N, 6.18.

Acknowledgment.—The assistance of Mr. Michael Botchan in obtaining infrared and quantitative ultraviolet absorption spectra is gratefully acknowledged.

2,4-Diaminopyrimidines from Dicyandiamide. III. Reaction with Monocyclic Ketones*[1-4]

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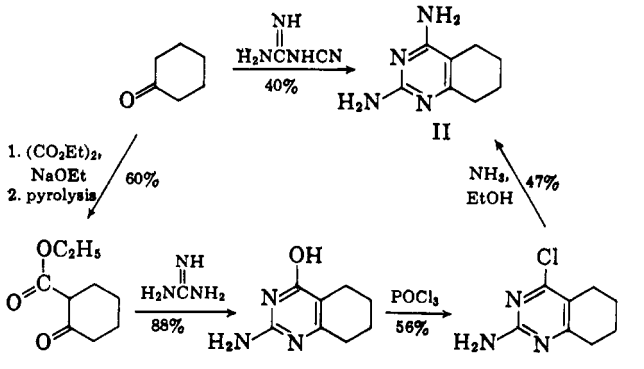
A novel, one-step synthesis of a variety of 2,4-diaminopyrimidine derivatives by condensation of dicyandiamide with monofunctional ketones is reported. The method, which represents a new pyrimidine ring-forming reaction, is general for α-unsubstituted ketones and dicyandiamide or substituted dicyandiamides. This article deals with the preparation of bicyclic 2,4-diaminopyrimido systems from monocyclic ketones. The scope of the reaction is outlined and a reaction mechanism is proposed.

Derivatives of 2,4-diaminopyrimidine are of interest in these laboratories because of the various growth-inhibitory properties, especially antifolic activity, of compounds possessing this biologically versatile ring system.[5-7] In his exhaustive analysis of pyrimidine chemistry, Brown cites three methods of direct synthesis of 2,4-diaminopyrimidines by pyrimidine ring-forming reactions: condensation of guanidine with cyano esters, with malononitriles, and with α-aryl- (or α-alkyl-) β-alkoxyacrylonitriles.[8] The latter route requires the synthesis of an α-cyanocarbonyl compound, alkylation to the enol ether, and condensation with guanidine.[9-11] Another route to 2,4-diaminopyrimidines involves the synthesis of 2-amino-4-hydroxy- or 2,4-dihydroxypyrimidines and subsequent chlorination and amination.[12] Of the foregoing synthetic methods, only the routes from β-alkoxyacrylonitriles and from 4-chloropyrimidines are generally useful for the preparation of 2,4-diaminopyrimidines likely to act as folic acid antagonists, namely, derivatives with carbon substitution at position 5 and, preferably, with carbon or hydrogen substitution at position 6.[6,7] Since each of these two methods is indirect and frequently inefficient, a simpler and more direct route to the requisite 2,4-diaminopyrimidine derivatives would be of obvious importance.

We envisioned a potentially useful, direct route to these compounds in a patent reference[13] in which reaction of dicyandiamide and cyclohexanone was assumed, on the basis of elementary analysis only, to have given 2,4-diamino-5,6,7,8-tetrahydroquinazoline (II). We obtained the same product in 40% yield from dicyandiamide and cyclohexanone and confirmed the structure as 2,4-diamino-5,6,7,8-tetrahydroquinazoline (II) by an independent synthesis.[14] The reaction of guanidine carbonate and 2-carbethoxycyclohexanone gave 2-amino-4-hydroxy-5,6,7,8-tetrahydroquinazoline,[15,16] which was chlorinated to the 4-chloro derivative.[16] Amination of the latter compound afforded the diamine



* To Professor Louis F. Fieser.

(1) This investigation was supported in part by Research Grants CY3335 and C6516 and Research Career Development Award K3-CA-22,151 form the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) (a) E. J. Modest, S. Chatterjee, H. Kangur, and D. M. Brun, Abstracts of Papers, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960, p. 4-N; (b) E. J. Modest, H. Kangur, and S. Chatterjee, Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, p. 26-N.

(3) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962); paper I of this series.

(4) E. J. Modest, S. Chatterjee, G. E. Foley, and S. Farber, *Acta, Unio Intern. Contra Cancrum*, **20**, 112 (1964); paper II of this series.

(5) E. J. Modest, G. E. Foley, and S. Farber, *ibid.*, **16**, 702 (1960).

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(8) D. J. Brown, "The Pyrimidines," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp. 64–74.

(9) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(10) B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951).

(11) B. H. Chase and J. Walker *ibid.*, 3518 (1953).

(12) See ref. 8, pp. 187–198.

(13) In U. S. Patent 2,517, 824 (Aug. 8, 1950) on production of aminoformaldehyde resins as surface coating and molding compositions, A. J. Appelquest describes a condensation product obtained by reaction of dicyandiamide and cyclohexanone for 3 hr. at 150–160°. No evidence for the proposed structure is given other than questionable microanalytical values. *Anal.* Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 57.56, 57.83; H, 7.16, 7.33; N, 35.53, 35.71.

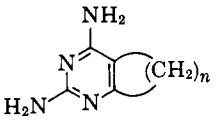
(14) S. Chatterjee, H. N. Schlein, D. M. Brun, and E. J. Modest, Abstracts of Papers, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959, p. 9-N.

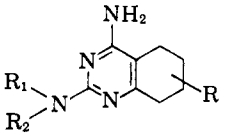
(15) P. C. Mitter and A. Bhattacharya, *Quart. J. Indian Chem. Soc.*, **4**, 149 (1927).

(16) R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 357 (1946).

II[17] in 14% over-all yield from cyclohexanone. Dehydrogenation of II with palladium on carbon at 280–300° for 3 hr. afforded the fully aromatic 2,4-diaminoquinazoline XIII, obtained by Vopicka and Lange *via* amination of 2,4-dichloroquinazoline.[19]

The formation of 2,4-diaminopyrimidine derivatives by reaction with dicyandiamide has been extended to a number of monocyclic ketones, including cyclopentanone, cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, cycloheptanone, cyclooctanone, cyclononanone, cyclodecanone, and cyclopentadecanone. Cyclohexanone has also been found to undergo cyclization with N^1-methyl-, N^1-(*n*-dodecyl)-, and N^1,N^1-dimethyldicyandiamide.





	n
I	3
II	4
VIII	5
IX	6
X	7
XI	8
XII	13

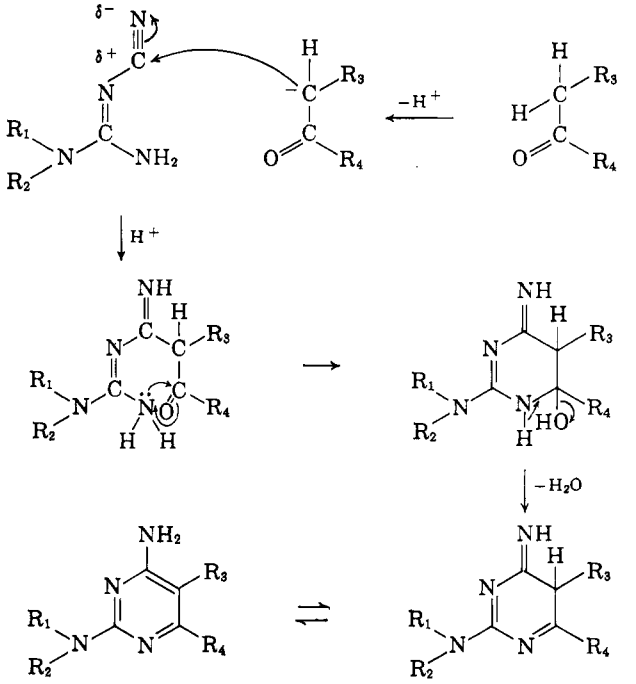
	R_1	R_2	R
III	H	H	6-CH_3
IV	H	H	7 (or 5)-CH_2
V	CH_3	H	H
VI	CH_3	CH_3	H
VII	*n*-$C_{12}H_{25}$	H	H

The general reaction conditions require maintenance of an internal temperature in the range 155–205° for 2–44 hr., the usual reaction time being 3–6 hr. Where possible, water is removed from the reaction as it is formed, by use of an air condenser to permit evaporation (V–XII) (procedures C and D) or by employment of a water-cooled condenser and water trap (II–IV) (procedure B). Most of the condensations were carried out with an excess of ketone as solvent and the reaction temperature was maintained below 200°. The employment of 2-(2-ethoxyethoxy)ethanol as solvent has been found to be superior in certain instances to the original conditions without solvent. An excess of dicyandiamide was employed when the internal reaction temperature was maintained at or slightly above 200° and 2-(2-ethoxyethoxy)ethanol was used as a solvent (IX–XII) (procedure D, for higher boiling ketones), because polymerization and decomposition of dicyandiamide (m.p. 209° dec.) takes place to a greater extent at higher temperatures; in the latter four reactions small amounts of melamine and some unidentified, high-melting, insoluble by-products, which are now under investigation, were found. The slow generation of ammonia was consistently detected in the reactions reported. In the condensation of dicyandiamide with cyclohexanone, an equimolar ratio of reactants gave the maximum yield of II.

Because of the relatively low boiling point of cyclopentanone (130°), no condensation with dicyandiamide occurred at atmospheric pressure, even at a bath temperature of 210°. The reaction was successful in an autoclave at an internal temperature of 185–200°

CHART I

PROPOSED REACTION MECHANISM



(procedure A). Identification of the product as 2,6-diamino-4,5-trimethylenepyrimidine (I) by comparison with authentic samples, synthesized in these laboratories[14] by amination of 2-amino-6-chloro-4,5-trimethylenepyrimidine[16,20] or 2,6-dichloro-4,5-trimethylenepyrimidine,[21] afforded additional proof of the course of the reaction.

The diaminopyrimidines reported are pure, single substances, and all structures are unequivocal, except for IV, the product from 3-methylcyclohexanone. In this instance, cyclization can occur theoretically on either side of the carbonyl group of the unsymmetrical ketone and therefore IV may be either the 5-methyl or the 7-methyl homolog of II; on steric grounds, IV is probably 2,4-diamino-7-methyl-5,6,7,8-tetrahydroquinazoline.

A mechanism is proposed in Chart I for the general reaction of dicyandiamide with a ketone. Loss of a proton affords the α carbanion of the ketone, which attacks the positively polarized nitrile carbon atom. The terminal primary amino group of the resulting biguanide intermediate is then sufficiently basic to undergo cyclization with the carbonyl group *via* nucleophilic attack of the nitrogen electron pair on the carbonyl carbon atom. Dehydration of the carbinolamine and tautomerization yield the 2,4-diaminopyrimidine. This mechanism is supported by several considerations. It is unlikely that the first step is carbon–nitrogen bond formation because dicyandiamide is an amphoteric, neutral molecule and the primary amino group is weakly basic. The steady evolution of ammonia during the reaction (presumably due to slow decomposition of dicyandiamide) provides a reaction medium sufficiently basic for the proposed carbon-

(17) Two other preparations of II have been described. Chase and Walker[11] synthesized II in 6% yield from 1-isobutoxy-2-cyanocyclohexene (2-cyanocyclohexanone enol ether) by condensation with guanidine. DeGraw and co-workers[18] obtained II in 48% yield from this enol ether by prolonged heating under the same reaction conditions, the over-all yield of II from cyclohexanone being 12% in five steps.

(18) J. DeGraw, L. Goodman, B. Weinstein, and B. R. Baker, *J. Org. Chem.*, **27**, 576 (1962).

(19) E. Vopicka and N. A. Lange, *J. Am. Chem. Soc.*, **57**, 1068 (1935).

(20) W. Braker, E. J. Pribyl, J. T. Sheehan, E. R. Spitzmiller, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 3072 (1947).

(21) L. O. Ross, L. Goodman, and B. R. Baker, *ibid.*, **81**, 3108 (1959). Prior to the appearance of this publication, we had completed the syntheses of the indicated 4,5-trimethylenepyrimidines by similar methods.[14]

carbon bond formation in the first step.[22] Finally, although the reaction requires heating for several hours, it is complete when the evolution of water stops; therefore, the final step seems to be cyclization and dehydration. In order to accommodate the formation of VI from N^1,N^1-dimethyldicyandiamide by this mechanism, dicyandiamide is written in the diaminomethylenimine form advocated by Jones and Orville-Thomas[23] on the basis of a detailed spectral analysis.

Dicyandiamide is known to react with 1,3-difunctional reagents, such as acetylacetone, acetoacetic ester, and ethyl cyanoacetate, with the formation of 2-cyanamino-4-hydroxy-6-substituted pyrimidines (or possibly the N^1-cyano isomers)[24]; in this kind of cyclization, dicyandiamide functions as a substituted guanidine derivative and the reaction, which does not afford 2,4-diaminopyrimidine derivatives, approximates a standard pyrimidine synthesis.

This new reaction is a distinct improvement over the previously discussed, presently available routes to 2,4-diaminopyrimidines and is the method of choice, where it can be used, for the one-step synthesis of these biologically active substances.[25] Further studies are in progress on various aspects of this synthetic method.

Experimental[26]

The ultraviolet absorption spectra were measured at pH 1 (0.1 *N* hydrochloric acid) and at pH 10 (0.05 *M* sodium carbonate–sodium borate buffer) with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 137B double-beam spectrophotometer. Melting points are corrected and were taken by the capillary method at a heating rate of 2°/min. in a modified Wagner–Meyer melting point apparatus.[27] Decomposition points are not reproducible unless conditions are rigidly controlled. If not otherwise specified, analytical samples were dried at 70–100° for 17 hr. *in vacuo* over phosphorus pentoxide. All dicyandiamide–ketone condensations were carried out with an internal thermometer or thermocouple in the reaction mixture; all reaction temperatures given are *internal* temperatures, not *bath* temperatures.

2,6-Diamino-4,5-trimethylenepyrimidine (I). Procedure A.—A mixture of 100 g. (1.19 moles) of dicyandiamide and 150 g. (1.79 moles) of cyclopentanone was heated in an autoclave for 3.5 hr. at 185–200° (internal thermocouple). After being cooled, the reaction mixture, containing a yellow solid in a nonviscous liquid, was triturated with 100 ml. of acetone, and the product was collected; yield 85.8 g. of crude material. Crystallization of 40.0 g. of this product from 300 ml. of dimethylformamide gave 7.08 g. (8.5% yield). Three further crystallizations of 500 mg. of this solid from water, the first being with Darco,[28] afforded 150 mg. of analytically pure, colorless crystalline solid: m.p. 231–232° (lit.[21] m.p. 230–232°); λ_{max}^{KBr} 2.89, 3.02, 3.19, 3.39, 3.50, 6.08, 6.20, 6.30, 6.81, 6.97 μ; λ_{max} in mμ (ϵ), at pH 1, 278 (8150), at pH 10, 232 (7970), 285 (9600) [lit.[21] at pH 1, 277 (7110), at pH 13, 286 (6910)].

Anal. Calcd. for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.32. Found: C, 55.9; H, 6.7; N, 37.2.

This compound was identical with samples prepared by amination of 2-amino-4-chloro- and 2,4-dichloro-4,5-pentamethylenepyrimidine,[14] having the same ultraviolet and infrared spectrum; mixture melting points were undepressed.

2,4-Diamino-5,6,7,8-tetrahydroquinazoline (II). Procedure B.—A mixture of dicyandiamide (25.2 g., 0.3 mole) and cyclohexanone (29.4 g., 0.3 mole) was heated for 5.5 hr. at 158–170° (internal temperature) in an oil bath in a flask equipped with a water-cooled condenser, a Dean–Stark water trap, and an immersion thermometer. A complete solution was obtained in 2 hr. and solid started to deposit 1 hr. later. The water collected amounted to 4.1 ml. (76% of theory); the reaction was considered complete when water no longer accumulated in the water trap. The reaction mixture was cooled and triturated with 50 ml. of acetone and the resulting solid (45.2 g.) was collected. Crystallization from 300 ml. of dimethyl sulfoxide at 100° gave 19.5 g. (40% yield) of II. For analysis 1 g. was crystallized twice from 95% ethanol. The colorless prismatic rods, m.p. 243–245°, were dried for 17 hr. at 50° (lit. m.p. 241–243°,[11] 240–242°[18]): λ_{max}^{KBr} 2.91, 3.00, 3.21, 3.41, 6.02, 6.15, 6.30, 6.96 μ; λ_{max} in mμ (ϵ), at pH 1, 275 (7850), at pH 10, 226 infl. (10,360), 284 (7620) [lit.[18] at pH 1, 275 (6850), in EtOH, 285 (6575)].

Anal. Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.5; H, 7.5; N, 33.9.

This sample and the one obtained by amination of 2-amino-4-chloro-5,6,7,8-tetrahydroquinazoline[14] had identical ultraviolet and infrared absorption spectra and a mixture melting point was not depressed.

2,4-Diamino-6-methyl-5,6,7,8-tetrahydroquinazoline (III) was prepared by procedure B by reaction of dicyandiamide (0.2 mole) and 4-methylcyclohexanone (0.3 mole) for 2.5 hr. at 170–185°; a 67% yield of water was collected. The reaction mixture was triturated with ether. Crystalline product was obtained in 48% yield from methanol after concentration, and the analytical sample was crystallized from the same solvent: colorless prismatic rods; m.p. 232–234°; λ_{max} in mμ (ϵ), at pH 1, 274 (7330), at pH 10, 231 (9040), 284 (7050).

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 60.70; H, 7.83; N, 31.10.

2,4-Diamino-7(or 5)-methyl-5,6,7,8-tetrahydroquinazoline (IV) was synthesized by procedure B from dicyandiamide (0.2 mole) and 3-methylcyclohexanone (0.3 mole) for 2.5 hr. at 169–179°; a 50% yield of water was collected. The reaction mixture was triturated with petroleum ether. Crystallization from absolute ethanol gave a 63% yield of IV after concentration. Two further crystallizations from absolute ethanol afforded colorless laminated prisms (m.p. 199–203°) which were dried for 55 hr. at 50°: λ_{max} in mμ (ϵ), at pH 1, 274.5 (7780), at pH 10, 229 (10,080), 285 (7550).

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 60.46; H, 7.99; N, 31.62.

4-Amino-2-methylamino-5,6,7,8-tetrahydroquinazoline (V). Procedure C.—A mixture of N^1-methyldicyandiamide (29.4 g., 0.3 mole) and cyclohexanone (44.2 g., 0.45 mole) was heated for 24 hr. at 166–174° in a flask fitted with an immersion thermometer and an air condenser to permit escape of water vapor. A complete solution occurred in 5 min. The reaction solution solidified completely on being cooled to room temperature. After refrigeration for 1 hr. the solid was triturated with acetone and collected: pale yellow prismatic rods; yield 44.3 g. (83%). Crystallization from 1200 ml. of absolute ethanol, with Darco, gave 27.9 g. (52% yield). Two further crystallizations from absolute ethanol afforded colorless prismatic plates, m.p. 204–205°, dried for 48 hr. at 50°: λ_{max} in mμ (ϵ), at pH 1, 225 (22,490), 281 (6280), at pH 10, 231 (13,710), 292 (6390).

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 60.55; H, 7.91; N, 31.40.

4-Amino-2-dimethylamino-5,6,7,8-tetrahydroquinazoline (VI), prepared by procedure C from N^1,N^1-dimethyldicyandiamide and cyclohexanone at 166–174° for 44 hr., crystallized from 50% ethanol (Darco) in 24% yield. One more crystallization from 50% ethanol afforded colorless prismatic plates, m.p. 135–136°, dried for 17 hr. at 45°: λ_{max} in mμ (ϵ), at pH 1, 231 (28,490), 283 (5250) at pH 10, 236 (18,690), 298 (5530).

(22) Further support for this argument is that higher yields of 2,4-diamino-5,6-dihydrobenzo[*h*]quinazoline from dicyandiamide and 1-tetralone were obtained with basic catalysts, such as Triton B.[8] The mechanism of the general reaction is currently under investigation.

(23) W. J. Jones and W. J. Orville-Thomas, *Trans. Faraday Soc.*, **55**, 193 (1959).

(24) See ref. 8, pp. 34, 37, 340, 343.

(25) For example, DeGraw and co-workers,[18] on the basis of information that we supplied them during the early stages of this work, reported a 17% yield of 2,4-diamino 5,6,7,8-tetrahydro-6-quinazolinecarboxaldehyde dimethyl acetal by reaction of 4-oxocyclohexanecarboxaldehyde dimethyl acetal with dicyandiamide at 180–185° for 2 hr., as opposed to an over-all yield of 11% in three steps by the α-cyano ketone enol ether route.

(26) Analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark; Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England; and Dr. Carol K. Fitz, Needham Heights, Mass.

(27) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938).

(28) Darco G-60 activated carbon, Atlas Chemical Industries, Inc., Wilmington, Del.

Anal. Calcd. for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.7; H, 8.3; N, 29.0.

4-Amino-2-(*n*-dodecylamino)-5,6,7,8-tetrahydroquinazoline (**VII**) was synthesized according to procedure C from N^1-(*n*-dodecyl)dicyandiamide[29] and cyclohexanone at 166–178° for 24 hr. Crystallization from ethanol (Darco) afforded a 61% yield after reduction of solvent volume. Two more crystallizations from 95% ethanol gave colorless prismatic needles, m.p. 98–100°, dried for 24 hr. at room temperature: λ_{max} in mμ (ϵ), at pH 1, 227 (20,490), 283 (5480), at pH 10, 235 (13,790), 294 (6330).

Anal. Calcd. for $C_{20}H_{36}N_4$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.76; H, 10.70; N, 16.76.

2,6-Diamino-4,5-pentamethylenepyrimidine (**VIII**) was prepared by procedure C from dicyandiamide and cycloheptanone for 4 hr. at 175–190°; the reaction mixture was triturated with petroleum ether. Crystallization from methanol gave a 51% yield and three further crystallizations from methanol afforded the analytical sample: m.p. 216–217°; λ_{max} in mμ (ϵ), at pH 1, 280 (7630), at pH 10, 235 (9880), 289.5 (7640).

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 60.40; H, 8.10; N, 31.60.

2,6-Diamino-4,5-hexamethylenepyrimidine (**IX**). **Procedure D.**—Dicyandiamide (0.63 g., 7.5 mmoles) and cyclooctanone (0.63 g., 5 mmoles) in 2.5 ml. of 2-(2-ethoxyethoxy)ethanol was heated for 5 hr. at 180–202° in a V-shaped flask equipped with an air condenser and an immersion thermometer. A clear solution was obtained in 5 min. and solid started to deposit 1 hr. later. The reaction mixture was cooled to room temperature, dissolved in 50 ml. of acetone, and filtered. The filtrate was evaporated to dryness and the residue was triturated with a mixture of acetone and ether. The off-white crystalline solid that resulted was collected; yield 0.83 g. (87%). A solution of 0.69 g. of the crude solid in 35 ml. of absolute methanol was treated with Darco and concentrated to 2 ml. After overnight refrigeration, the crystalline solid was collected and washed with benzene; yield 0.33 g. (42%). For analysis this solid was crystallized once more from absolute methanol and twice from a minimal volume of 50% ethanol: colorless prismatic plates; m.p. 191–193°; λ_{max} in mμ (ϵ) at pH 1, 221 (16,820), 278 (7690), at pH 10, 233 (9760), 287 (7820).

Anal. Calcd. for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.40; H, 8.40; N, 29.08.

2,6-Diamino-4,5-heptamethylenepyrimidine (**X**), prepared by procedure D from cyclononanone and dicyandiamide for 5 hr. at 192–203°, crystallized in 49% yield from 95% ethanol (Darco) after concentration. For analysis this product was crystallized three more times from 95% ethanol and twice from 50% ethanol; the colorless prismatic plates, dried for 17 hr. at 50°, had m.p. 189–192°; λ_{max} in mμ (ϵ), at pH 1, 277 (6640), at pH 10, 232 (8620), 287 (6500).

Anal. Calcd. for $C_{11}H_{18}N_4$: C, 64.04; H, 8.79; N, 27.16. Found: C, 63.75; H, 8.72; N, 27.04.

2,6-Diamino-4,5-octamethylenepyrimidine (**XI**), synthesized by procedure D from cyclodecanone and dicyandiamide for 17 hr. at 190–202°, was obtained in 49% yield on crystallization from 50% ethanol (Darco) after concentration. Two more crystallizations from 50% ethanol afforded prismatic plates, m.p. 207–210°, dried for 65 hr. at 50°: λ_{max} in mμ (ϵ), at pH 1, 277 (7770), at pH 10, 230 (9810), 287 (7790).

Anal. Calcd. for $C_{12}H_{20}N_4$: C, 65.42; H, 9.15; N, 25.43. Found: C, 64.98; H, 9.18; N, 25.24.

2,6-Diamino-4,5-tridecamethylenepyrimidine (**XII**) was obtained by procedure D from cyclopentadecanone and dicyandiamide for 8 hr. at 196–203°. Crystallization from 95% ethanol (Darco) gave a 24% yield after concentration. Two more crystallizations from 95% ethanol afforded colorless prismatic plates, m.p. 235–236°, dried for 24 hr. at 45°: λ_{max} in mμ (ϵ), at pH 1, 278 (8230), at pH 10, 232 (10,430), 289 (8170).

Anal. Calcd. for $C_{17}H_{30}N_4$: C, 70.30; H, 10.41; N, 19.29. Found: C, 70.08; H, 10.49; N, 19.15.

2,4-Diaminoquinazoline (**XIII**) **by Dehydrogenation of II.**—An intimate mixture of 2,4-diamino-5,6,7,8-tetrahydroquinazoline (1 g., 6.1 mmoles) and 10% palladium on carbon (1 g.) was heated in a metal bath at 280–300° (bath temperature) for 3 hr. During the reaction a slow stream of nitrogen was passed continuously through the reaction vessel. The cooled reaction mixture was transferred directly to a sublimation apparatus and fractionally sublimed. The light yellow fraction subliming at 140–160° (0.5 mm.) was collected. Resublimation at 140–160° (0.05 mm.) afforded light yellow prismatic crystals: yield 150 mg. (15%); m.p. 250–252° (lit.[19] m.p. 259°); λ_{max} in mμ (ϵ) at pH 1, 226 (39,010), 230 infl. (37,350) 247 infl. (13,000), 315 (4860), 322 infl. (4010), at pH 10, 231 (44,740), 266 (8770), 273 sh (7800), 332 (4470).

Anal. Calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.14; H, 5.15; N, 34.79.

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Hexahydro-1-methyl-4-phenyl-4-acetoxyazepine and the Demjanov Rearrangement of 1-Methyl-4-phenylpiperidine-4-methylamine*

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The preparation of hexahydro-1-methyl-4-phenyl-4-acetoxyazepine has been accomplished by the lead tetraacetate acetoxylation of hexahydro-1-methyl-4-phenylazepine. Three other possible methods of preparation were explored, including the Ziegler method, the amide degradation, and the Demjanov rearrangement of 1-methyl-4-phenylpiperidine-4-methylamine. The latter method did not yield the desired product, but gave instead, without ring enlargement, a mixture of 1-methyl-4-benzylpiperidinol and 1-methyl-4-benzyl-1,2,5,6-tetrahydropyridine.

The potent hexahydroazepine analgesic proheptazine was made from a hexahydroazepinone which was secured by ring closure of the appropriate cyano ester.[2] Attempts to use this route to make the corresponding hexahydroazepine IV without the 3-methyl group were unsuccessful. We have, however, obtained this hexahydroazepinone in low yield by the Ziegler method and found it to be unstable, darkening rapidly at room

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