washed, and dried; weight, 0.68 g.; m.p. 137–173°; Beilstein halogen test, negative. The infrared spectrum showed peaks at 2.93 (hydroxyl), 5.89 (carbonyl), 6.03 (conjugated carbonyl), and 6.19 μ (carbon–carbon double bond), but no acetate bands. Numerous variations in the above procedure gave similar poor results.

(b) *By chromous chloride.* To a solution of 500 mg. of VII in 100 ml. of acetone at room temperature was slowly added 40 ml. of chromous chloride solution. Reduction was virtually instantaneous, as judged by color. Water (200 ml.) was added and the acetone was removed under reduced pressure. The resulting suspension of crystals was chilled and filtered, yielding 400 mg. (98%) of material giving a negative Beilstein halogen test and melting at 140–155° after softening at 115°.[13] To complete the isomerization of the double bond, 100 mg. of the material was dissolved in 2 ml. of ethanol and 6 drops of *N* sulfuric acid in ethanol was added. The solution was refluxed for 6 min., then diluted with water. The progesterone was collected, washed, and dried; yield, 90 mg.; m.p. 120.5–122°, undepressed on admixture with authentic material; infrared spectrum identical with that of authentic material.

17α-Hydroxyprogesterone (X). The oxidation of 5α,6β-dichloro-3β,17α-dihydroxypregnan-20-one (I) was carried out essentially as described for the preparation of IV. The yield of crude 5α,6β-dichloro-17α-hydroxypregnane-3,20-dione (IX) was 60–70%, and the material decomposed unsharply in the range 145–170°. Chromous chloride reduction in refluxing acetone gave a halogen-free product whose infrared spectrum showed at peak at 5.78 μ, indicating that the oxidation product had contained a considerable amount of 17-ketone due to cleavage of the side chain. Isomerization with a trace of acid followed by recrystallization from methanol gave 17α-hydroxyprogesterone, m.p. 219–222° (lit.,[14] 222–223°). The yield from I was about 30%.

3β,17α-Dihydroxy-5-pregnen-20-one (XI) was prepared in 80% yield by the reduction of 5 g. of I in 500 ml. of acetone with 400 ml. of chromous chloride solution. Recrystallized from methanol, the material melted at 262–268° (lit.,[15] 271–273°).

3β,17α,21-Trihydroxy-5-pregnen-20-one 21-acetate (XII). Reduction of 10 g. of III in 250 ml. of acetone with 500 ml. of chromous chloride solution by heating for 5 min. at the reflux temperature afforded 8.0 g. (94%) of crude XII. This was recrystallized twice from acetonitrile, the first time involving a charcoal treatment, then from methanol, and finally again from acetonitrile to give 3.96 g. of XII, m.p. 209–213° (lit.,[16] 211–213°). Acetylation of XII with acetic anhydride in pyridine gave the 3,21-diacetate, m.p. 196–199° (lit.,[16] 195°).

Acknowledgment. We wish to thank the staff of the Physical and Inorganic Research Department for microanalyses and for spectral determinations.

RAHWAY, N. J.

(13) 5-Pregnene-3,20-dione is reported[9] to melt at 158–160°.

(14) J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

(15) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).

(16) J. Heer and K. Miescher, *Helv. Chim. Acta*, **34**, 359 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXIV. Tetrahydroquinazoline Analogs of Tetrahydrofolic Acid. II.

JOSEPH DEGRAW, LEON GOODMAN, RUTH KOEHLER, AND B. R. BAKER

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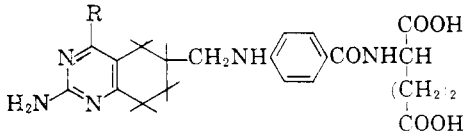
A variety of 6-substituted 5,6,7,8-tetrahydroquinazolines were prepared in which the substituents at 2 and 4 were mercaptohydroxy, dihydroxy, dichloro, diamino, and bis(benzylamino). The use of the dichloro-, diamino-, and bis(benzylamino)-5,6,7,8-tetrahydroquinazolines in synthetic schemes designed to prepare intermediates for the synthesis of 5,8-dideaza-5,6,7,8-tetrahydroaminopterin, is described.

In a preceding work of this series[2] the synthesis of 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (I) was described. The key compound in the synthesis of I was 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxylic acid (VIII). In the course of that work a number of other substituted 5,6,7,8-tetrahydroquinazolines were prepared and, subsequent to that work, many more such compounds have been synthesized as part of an attempted synthesis of 5,8-dideaza-5,6,7,8-tetrahydroaminopterin (II), the 4-amino analog of I. Although the work has not achieved the synthesis of II, the interesting chemistry involved prompts a description of the observations.



I. R = OH
II. R = NH_2

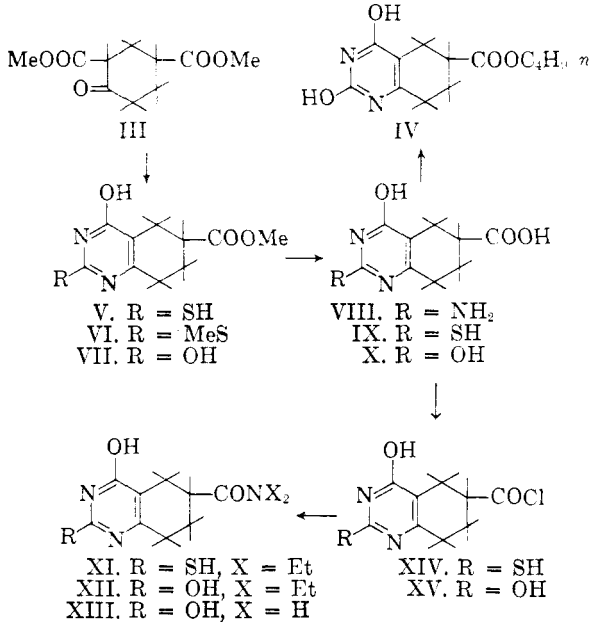
Condensation of dimethyl 4-oxo-1,3-cyclohexanedicarboxylate (III)[2] with thiourea proceeded readily in the presence of sodium methoxide to give a good yield of methyl 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylate (V). In contrast with the condensation of III with

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 5176 (1959).

(2) R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5779 (1958).

guanidine, there was no evidence for the presence of the 6-carboxylic acid (IX) in the product. When the crude product from the condensation of III and thiourea was saponified, the acid IX was isolated as a chromatographically homogeneous solid in 87% over-all yield. The acid (IX) was converted to the acid chloride (XIV) with thionyl chloride and a trace of pyridine and XIV, in turn, was converted in low yield to the diethylamide (XI).

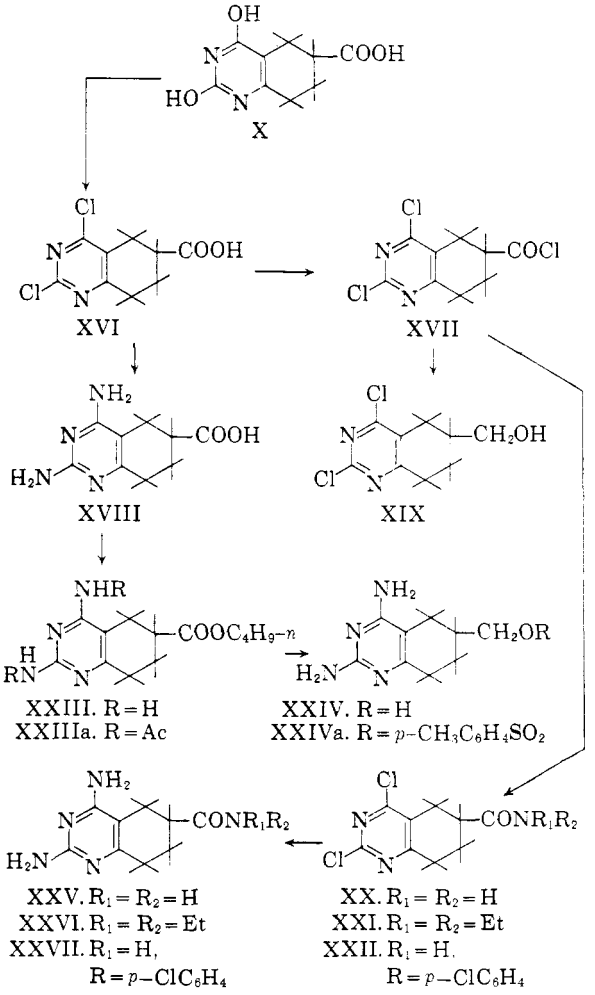
The ester (V) was converted to the 2-methylthio derivative (VI) by means of dimethyl sulfate in methanolic sodium methoxide. Compound VI was unstable in 0.1 *M* hydrochloric acid and slowly changed to, presumably, the 2,4-dihydroxytetrahydroquinazoline ester (VII). This was shown by the coincidence of the ultraviolet absorption spectra of VI and the 2,4-dihydroxy acid (X) after the dilute acid solution of VI had stood for about 20 hr.



Although it is known that 2-alkylthio groups on a pyrimidine ring are hydrolyzed in hot acid,[3] the mildness of the hydrolytic conditions for VI is surprising.

The condensation of III with urea in the presence of sodium methoxide gave a mixture of products which was converted to the 2,4-dihydroxy acid (X) in fair yield by a further treatment with aqueous alkali. Attempted isolation of the direct product of the urea condensation, the methyl ester (VII), from the condensation mixture was unsuccessful. However, the acid (X) was converted to the crystalline *n*-butyl ester (IV) in high yield. Conversion of the acid (X) to the acid chloride (XV) was accomplished with thionyl chloride and a trace of pyridine. The crude acid chloride was converted to the diethylamide (XII) and to the carboxamide (XIII).

Two routes leading to the diaminotetrahydroquinazoline ring system, of which II was the desired end product, were visualized. Chlorination of the aminohydroxy acid (VIII) to the 2-amino-4-chloro acid, followed by amination to the diamino acid (XVIII), appeared to be one practical sequence, and chlorination of the dihydroxy acid (X) to the dichloro acid (XVI), followed by amination to XVIII, seemed to represent a second method. However, attempts to achieve the chlorination of VIII using phosphoryl chloride and a variety of conditions gave heterogeneous products, while chlorination of X with phosphoryl chloride proceeded smoothly and gave a good yield of the crystalline dichloro acid (XVI). Amination of XVI with ethanolic ammonia at 150° gave the diamino acid (XVIII) as a chromatographically homogeneous solid. The acid (XVIII) could be converted to the *n*-butyl ester (XXIII) in good yield, but a number of attempts to convert the ester (XXIII) to amides were unsuccessful. The ester (XXIII) was smoothly acetylated with acetic



(3) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **29**, 492 (1903); H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 349 (1904); T. B. Johnson and A. W. Joyce, *J. Am. Chem. Soc.*, **37**, 2151 (1915).

(4) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955).

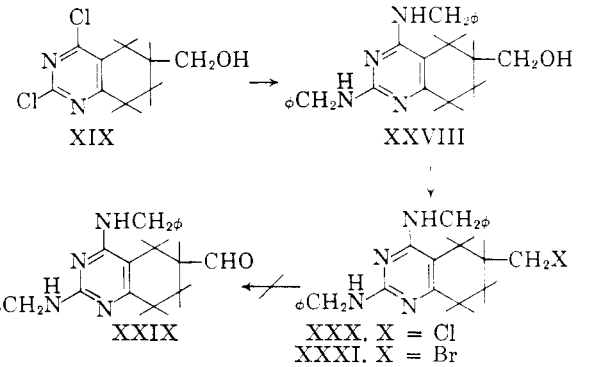
anhydride to the diacetamido ester (XXIIIa); the *N*-acetyl groups represented, possibly, blocking groups for some other contemplated transformations using diaminotetrahydroquinazoline derivatives. The butyl ester (XXIII), either as the free base or as the *p*-toluenesulfonic acid salt, was reduced to the diamino-6-hydroxymethyl compound (XXIV) by means of the sodium borohydride–aluminum chloride reagent first reported by Brown and Subba Rao[4] and used previously in the reduction of butyl 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinecarboxylate.[2] However, compound XXIV was not useful as a precursor for II. A number of attempts to convert XXIV to the 6-chloromethyl compound by means of thionyl chloride were unsuccessful, as were a variety of attempts to form the 6-bromomethyl compound with hydrogen bromide and hydrogen bromide-sulfuric acid combinations. The *p*-toluenesulfonate ester (XXIVa) of XXIV could be prepared but in such low yield that the approach to II through the tosylate was not practical. This same situation also was true for the preparation of the 6-*p*-toluenesulfonate ester of 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-quinazolinemethanol.[2]

The diamino acid (XVIII) could not be converted to an acid chloride by means of thionyl chloride under a variety of conditions. Alternately, however, a number of amides were prepared in good yield from the acid chloride (XVII) of the dichloroacid (XVI). The carboxamide (XX) was prepared from XVII in ammonia-saturated acetonitrile at 0°, the diethylamide (XXI) was prepared in refluxing methylene chloride, and the *p*-chloroanilide (XXII) was prepared in methylene chloride in the presence of pyridine at room temperature. Under these conditions there was no tendency for replacement of the ring chlorines of XVII. Ammonolysis of the amides (XX, XXI, and XXII) in ethanol at 150° gave good yields of the diamino amides (XXV, XXVI, and XXVII, respectively). As expected, no amide interchange occurred.

The lability of the ring chlorines of XVI under acid conditions was demonstrated in several attempts to prepare esters of XVI. The use of ethanesulfonic acid and butyl alcohol gave the dihydroxy butyl ester (IV) and the reaction of the acid chloride (XVII) with methanol gave replacement of the ring chlorines by methoxyl. When pyridine was used as an acid acceptor in the reaction of XVII with methanol, the product could not be purified.

The acid chloride (XVII) was reduced to the 6-hydroxymethyl compound (XIX) with sodium borohydride in diglyme[5] at −20°. At this temperature ring dechlorination and reduction of the pyrimidine ring were minimized and fair yields of XIX could be isolated. The reduction of the dichloro acid (XVI) with the sodium borohydride–aluminum chloride combination was unsuccessful. A number of attempts were made to oxidize XIX to the 6-aldehyde, which, in turn, could probably be ammonolyzed to 2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxaldehyde, a probable precursor for II. The chromic acid-pyridine reagent of Poos,[6] *et al.*, gave only tars and no reaction was observed with the sodium dichromate–acetic acid method of Friedman.[7] Attempts to reduce the acid chloride (XVII) to the dichloro aldehyde by the Rosenmund method or with lithium tri-*t*-butoxyaluminum hydride[8] were unsuccessful. The latter method gave mostly alcohol (XIX), even at −75°.

The utility of 2,4-bis-(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinemethanol (XXVIII) in the preparation of precursors of II was next investigated on the assumption that the benzyl groups could be removed at a later step in the synthesis. The alcohol (XXVIII) was prepared in high yield by the treatment of dichloro alcohol (XIX) with benzylamine at 150°. Thionyl chloride readily converted the alcohol (XXVIII) to the chloromethyl compound (XXX) and phosphorus tribromide converted XXVIII to the bromomethyl compound (XXXI). Reaction of the bromomethyl derivative (XXXI) with *N*-(*p*-aminobenzoyl) glutamic acid (PABGA) or the dimethyl ester of PABGA gave crude products which did not contain the desired precursors of II and which could not be purified to any well-defined compounds. Reaction of XXXI with *p*-aminobenzoic acid (PABA) gave a product which was insoluble in both acid and base and therefore could not have been the simple product of alkylation of PABA.



Two attempts were made to prepare 2,4-bis(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinecarboxaldehyde (XXIX), whose reductive coupling with PABGA might be expected to give the dibenzyl precursor of II.[9] Reaction of the bromo compound (XXXI) with pyridine *N*-oxide and treatment of

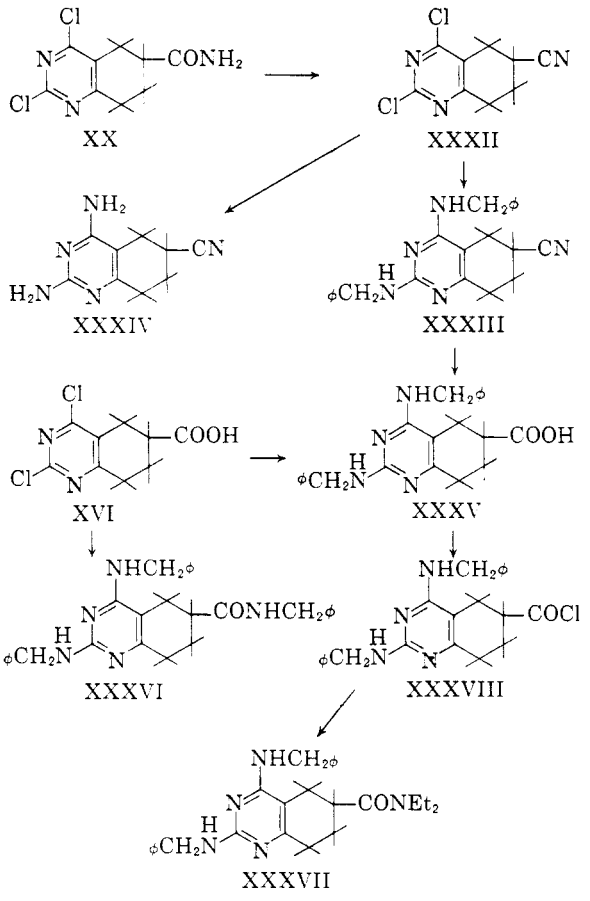
(5) The dimethyl ether of diethylene glycol.

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(7) Dr. L. Friedman, New York University, private communication.

(8) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **78**, 252 (1956).

(9) M. Sletzinger, D. Rheinhold, J. Grier, M. Beachem, and M. Tischler, *J. Am. Chem. Soc.*, **77**, 6365 (1955).



the crude product with aqueous sodium hydroxide[10] failed to give any aldehyde. Hydrogenation of the bis(benzylamino) nitrile (XXXIII) in the presence of *N,N'*-diphenylethylenediamine according to the method of Plieninger[11] resulted in the uptake of about 80% of the theoretical amount of hydrogen but acid treatment of the residue, the supposed imidazolidine, gave no aldehyde. The nitrile (XXXIII) was prepared by conversion of the dichloro amide (XX) to the dichloro nitrile (XXXII) with phosphoryl chloride and reaction of the nitrile (XXXII) with ethanolic benzylamine at 150°. Reaction of the dichloro nitrile (XXXII) with alcoholic ammonia at 150° gave the diamino nitrile (XXXIV). However, the synthesis of 2,4-diamino-5,6,7,8-tetrahydro-6-carboxaldehyde has been successful and will be reported in a future paper.

In order to investigate the utility of the benzyl group as a blocking group in reactions directed toward the synthesis of II, the bis(benzylamino) acid (XXXV) was prepared by mild treatment of the dichloro acid (XVI) with benzylamine, or by hydrolysis of the dibenzyl nitrile (XXXIII). Extended treatment of the dichloro acid (XVI) with benzylamine gave another compound whose infrared spectrum suggested it to be the bis(benzylamino) benzylamide (XXXVI). The bis(benzylamino) acid (XXXV) with thionyl chloride gave the acid chloride (XXXVIII) which, without purification, was converted to the diethylamide (XXXVII). Attempts to remove the benzyl groups from XXXVII by hydrogenation to give the diamino amide (XXV) were unsuccessful; there was no hydrogenolysis of the benzyl groups but only reduction of the pyrimidine ring when platinum oxide was used as the catalyst. A number of cases have been reported where benzylamino groups do not undergo hydrogenolysis.[12]

(10) W. Feeley, W. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(11) H. Plieninger and B. Kiefer, *Ber.*, **90**, 617 (1957).

EXPERIMENTAL[13]

Methyl 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylate (V). A mixture of 2.14 g. (10 mmoles) of dimethyl 4-oxo-1,3-cyclohexanedicarboxylate (III), 1.20 g. (16 mmoles) of thiourea, and 16 ml. of methanolic 1 *M* sodium methoxide was heated under reflux for 3 hr. Water (40 ml.) was added, the solution was acidified with acetic acid, and the resulting precipitate was collected, washed with water, and air-dried to give 1.75 g. (73%) of product, m.p. 273–274°. A portion of the crude product was recrystallized from ethyl alcohol-*N,N*-dimethylformamide and again from *N,N*-dimethylformamide to give white crystals, m.p. 269–271°; $\lambda_{max(\mu)}^{KBr}$ 2.94 and 3.15 (NH, OH), 5.78 (ester C=O), 6.05 and 6.42 (pyrimidine ring), 8.25 (ester C—O—C); $\lambda_{max(m\mu)}^{pH\ 1}$ 275 (ϵ 25,200). On paper chromatography in either solvent A or C the product showed a single spot with R_{Ad} 1.67 and R_{Ad} 1.59, respectively.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: C, 50.0; H, 5.00. Found: C, 49.6; H, 5.13.

5,6,7,8-Tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylic acid (IX). A mixture containing double the amounts of reagents used in the preparation of V was heated under reflux for 3 hr., then allowed to stand overnight. After 5 ml. of 50% aqueous sodium hydroxide had been added, the mixture was refluxed 1.5 hr. The heavy precipitate that formed

(12) J. A. Carbon, *J. Am. Chem. Soc.*, **80**, 6083 (1958); R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949); V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(13) Boiling and melting points are uncorrected; the latter were obtained with the Fisher-Johns Apparatus. Paper chromatography was done by the descending technique, usually on Whatman No. 1 paper, and the spots were detected by visual examination under ultraviolet light. Adenine was used as a standard and the spots were located relative to R_{Ad} 1.00. These solvent systems were used: A,[14] methyl Cellosolve-H_2O (9:1); B,[15] 5% aqueous Na_2HPO_4 (no organic phase); C,[16] *n*-BuOH—HOAc—H_2O (5:2:3); D, *n*-BuOH—2*N*NH_4OH; E,[17] H_2O sat'd. *n*-BuOH; F,[18] benzene-Skellysolve C—MeOH—H_2O (3.3:6.7:8:2); when Schleicher & Schuell acetylated paper was used, solvent system G,[19] benzene-MeOH-H_2O (2:6:1) was employed.

Infrared absorption assignments for the common functional groups were made in accordance with the data of Bellamy;[23] those of the substituted pyrimidine rings were made according to the consistent bands noted in a given series (*i.e.*, diamino, dihydroxy, dichloro, etc.) in this and in the previous paper.[2]

(14) A. E. Bender, *Biochem. J.*, **48**, xv (1951) (Proc. Biochemical Society).

(15) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1835 (1950).

(16) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(17) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(18) I. E. Bush, *Biochem. J.*, **50**, 370 (1952).

(19) T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

dissolved upon the addition of 30 ml. of water. The cooled solution was adjusted to *p*H 4 with concentrated hydrochloric acid; the odor of hydrogen sulfide was noticeable. The precipitate was collected, washed with water, and dried to give 3.94 g. (87%) of product, m.p. >300°. A portion of this product (0.20 g.) was dissolved in 4 ml. of saturated aqueous sodium bicarbonate and the solution filtered. The filtrate was acidified with acetic acid to give 0.14 g. (61%) of product, m.p. >300°; $\lambda^{KBr}_{max(\mu)}$ 2.94 and 3.15 (NH, OH), 3.75–3.85 (OH of COOH, SH), 5.77 (shoulder, C=O of carboxyl), 5.95 and 6.40 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 217 (ε 13,700), 278 (ε 19,700). On paper chromatography in solvent A the product showed a single spot with R_{Ad} 1.24.

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.8; H, 4.42; N, 13.3. Found: C, 47.4; H, 4.53; N, 12.4, 12.3.

N,N-Diethyl-5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxamide (XI). A suspension of 0.23 g. (1 mmole) of 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylic acid (IX) in 4 ml. of anhydrous ether, 1.46 ml. (0.02 mole) of thionyl chloride, and 0.02 ml. of pyridine was stirred overnight. After addition of 20 ml. of anhydrous ether, the precipitate was collected and washed with two 5-ml. portions of ether. The crude acid chloride (XIV) was added to a solution of 0.32 g. (4.2 mmoles) of diethylamine in 6 ml. of reagent acetone and the resulting suspension was stirred for 2.5 hr. The mixture was evaporated to dryness *in vacuo* and the residue was washed with 10 ml. of water and air-dried to give 0.11 g. (40%) of a dark brown solid, m.p. 272–276°. Both paper chromatography and infrared spectrum indicated this material to be essentially the same as the purified product described below. The crude product (0.10 g.) was recrystallized from ethyl alcohol and water to give 0.09 g. of a tan solid which, in turn, was dissolved in 15 ml. of saturated sodium bicarbonate solution, decolorized with Norit, and reprecipitated with 0.1 *M* hydrochloric acid to yield 0.04 g. (16% over-all yield) of solid, m.p. 286.5–287°; $\lambda^{KBr}_{max(\mu)}$ 2.90 and 3.19 (NH, OH), 6.12 (amide C=O and pyrimidine ring). On paper chromatography in solvent A the product showed a single spot with R_{Ad} 1.37.

Anal. Calcd. for $C_{13}H_{19}N_3O_2S$: C, 55.5; H, 6.76; N, 14.9. Found: C, 55.3; H, 6.90; N, 14.9.

Methyl 5,6,7,8-tetrahydro-4-hydroxy-2-(methylthio)-6-quinazolinecarboxylate (VI). To a stirred solution of 0.25 g. (1.0 mmole) of methyl 5,6,7,8-tetrahydro-4-hydroxy-2-mercapto-6-quinazolinecarboxylate (V) in 1.05 ml. of methanolic 1 *M* sodium methoxide was added dropwise 0.13 g. (1.0 mmole) of dimethyl sulfate. After the solution had stood 10 minutes the white solid which had precipitated was collected and washed. The crude product was treated with hot aqueous sodium bicarbonate solution to remove unchanged V and there remained 0.10 g. (40%) of crude VI, m.p. 271–274°. The analytical sample was obtained by recrystallization from methanol-*N,N*-dimethylformamide (2:3), m.p. 277–280°; $\lambda^{KBr}_{max(\mu)}$ 2.95 (OH), 5.78 (ester C=O), 6.11 and 6.50 (pyrimidine ring), 8.18 (ester C—O—C). In the ultraviolet, fresh solutions of VI gave the following results: $\lambda^{pH\ 1}_{max(m\mu)}$ 230 (ε 9590), 253 (ε 10,600), 270–275 (ε 9670); and $\lambda^{pH\ 3}_{max(m\mu)}$ 218 (ε 16,100), 252 (ε 9750), 270–275 (ε 7050). After standing 3 days the acid solution gave $\lambda^{pH\ 1}_{max(m\mu)}$ 207 (ε 9840), 266 (ε 8440), which is in good agreement with the acid spectrum of X (*vide infra*); there was essentially no change in the alkaline solution. On paper chromatography in solvents A or C, the product showed a single spot with R_{Ad} 1.65 or 1.72, respectively.

Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 52.0; H, 5.51; N, 11.0. Found: C, 52.3; H, 5.63; N, 11.0.

5,6,7,8-Tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X). A mixture of 4.28 g. (0.02 mole) of dimethyl 4-oxo-1,3-cyclohexanedicarboxylate (III), 1.92 g. (0.032 mole) of urea, and 32 ml. of 1 *M* sodium methoxide was refluxed 3-2/3 hr., then allowed to stand overnight. After the addition of 5 ml. of 50% sodium hydroxide, the reaction mixture was refluxed for 2 hr. Then 30 ml. of water was added and the solution was acidified with 6 *M* hydrochloric acid with cooling. The resulting white precipitate was filtered and washed with water to give 2.34 g. (55.7%) of product, m.p. >300°. An analytical sample was obtained by solution of the crude product in saturated aqueous sodium bicarbonate filtration, and reprecipitation with acetic acid (over-all yield 31%), m.p. >300°; $\lambda^{KBr}_{max(\mu)}$ 2.90 and 3.15 (NH, OH), 5.79 (carboxyl C=O and pyrimidine C=O), 6.05 (pyrimidine C=O); $\lambda^{pH\ 1}_{max(m\mu)}$ 207 (ε 10,700), 267 (ε 9300); $\lambda^{pH\ 13}_{max(m\mu)}$ 217 (ε 12,700), 275 (ε 6300). On paper chromatography in solvents A or C, the product showed a single spot at R_{Ad} 1.02 or 1.00, respectively.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.4; H, 4.76; N, 13.3. Found: C, 51.9; H, 4.78; N, 13.3.

A large-scale run employing 500 g. of ketone (III) gave 270 g. (55.4%) of dihydroxyacid (X).

Butyl 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylate (IV). A mixture of 0.5 g. (2.4 mmoles) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X), 0.57 g. (3 mmoles) of *p*-toluenesulfonic acid monohydrate, and 25 ml. of butyl alcohol was refluxed 3.25 hr., then allowed to stand overnight at room temperature. The addition of 20 ml. of saturated aqueous sodium bicarbonate gave 2 layers and a suspended solid. The solid was filtered from the liquid phases, washed with 5 ml. of aqueous sodium bicarbonate solution and with water, and air-dried to give 0.13 g. of product, m.p. 260–265°. The two layers in the filtrate were separated. The upper layer was washed with 10 ml. of saturated aqueous sodium bicarbonate, then with 10 ml. of water, then concentrated to dryness *in vacuo*. The residue was suspended in 10 ml. of water and filtered to give 0.36 g. of product, m.p. 265° (total yield 78%). An analytical sample was obtained by heating 0.30 g. of crude product in 3 ml. of saturated aqueous sodium bicarbonate solution. The solid was removed by filtration, washed with 10 ml. of water, then recrystallized from *N,N*-dimethylformamide–water to give white crystals, m.p. 273–274°; $\lambda^{KBr}_{max(\mu)}$ 2.89 and 3.15 (NH, OH), 5.76 (ester C=O), 5.87 and 6.00 (pyrimidine C=O), 8.43 (ester C—O—C). On paper chromatography in solvent A, the product gave a single spot at R_{Ad} 1.51.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.6; H, 6.76; N, 10.5. Found: C, 58.4; H, 6.90; N, 10.5.

N,N-Diethyl-5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxamide (XII). To a suspension of 0.21 g. (1 mmole) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X) in 4 ml. of anhydrous ether containing 0.02 ml. of pyridine was added 1.46 ml. (0.02 mole) of thionyl chloride. The mixture, protected from moisture, was stirred 5 hr., then 10 ml. of ether was added. The solid was collected on a filter, washed 2 times with 10-ml. portions of ether, and added immediately to 6 ml. of acetone containing 0.45 ml. (4.2 mmoles) of diethylamine. After being stirred for 1.5 hr. and standing overnight, the reaction mixture was concentrated *in vacuo*. To the residue was added 10 ml. of water. The insoluble solid was collected on a filter, washed with water, and air-dried; yield 0.21 g. (81%), m.p. >300°. The crude product was washed with 3 ml. of saturated sodium bicarbonate solution and with 5 ml. of cold water, then recrystallized from 35 ml. of hot water to give 0.12 g. (48%) of white crystals.

Anal. Calcd. for $C_{13}H_{19}N_3O_3 \cdot H_2O$: C, 55.1; H, 7.42. Found: C, 55.3; H, 7.16.

When the material was redried at 140° in high vacuum, the anhydrous amide was obtained, $\lambda^{KBr}_{max(\mu)}$ 2.90 and 3.19 (NH, OH), 5.80 and 6.12 (amide C=O and pyrimidine C=O). On paper chromatography in solvents A or C, the product showed a single spot at R_{Ad} 1.35 and 1.44, respectively.

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.9; H, 7.17; N, 15.9. Found: C, 59.0; H, 7.38; N, 16.1.

5,6,7,8-Tetrahydro-2,4-dihydroxy-6-quinazolinecarboxamide (XIII). The acid chloride (XV) was prepared from 0.50 g. (2.4 mmoles) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quin-

azolinecarboxylic acid (X), 5 ml. of thionyl chloride, and 0.27 ml. of pyridine according to the procedure detailed for the preparation of XII. The crude acid chloride was suspended in 12 ml. of reagent acetone and the suspension was saturated with dry ammonia during 20 min. The mixture was concentrated to dryness *in vacuo* and the residue was washed with 10 ml. of water and air-dried to yield 0.47 g. (94%) of a solid which failed to melt at 300°. Paper chromatography indicated that the crude product was contaminated with the 6-carboxylic acid (X). The crude product was extracted with 15 ml. of saturated sodium bicarbonate solution and the residue, which was insoluble in organic solvents, was dissolved in 3 ml. of cold 10% aqueous sodium hydroxide, decolorized with Norit, and reprecipitated with 6 *M* hydrochloric acid. The solid was extracted with 3 ml. of hot saturated aqueous sodium bicarbonate solution, filtered, washed with water, and air-dried to yield 0.24 g. (48%) of solid, m.p. >300°; $\lambda^{KBr}_{max(\mu)}$ 2.90 and 3.15 (NH, OH), 5.86 and 6.05 (amide C=O and pyrimidine C=O). On paper chromatography in solvent C the product gave a single spot with R_{Ad} 0.52 but with some streaking from the origin.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.7; H, 5.26; N, 20.1. Found: C, 51.5; H, 5.45; N, 19.9.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid (XVI). A mixture of 10.0 g. (48 mmoles) of 5,6,7,8-tetrahydro-2,4-dihydroxy-6-quinazolinecarboxylic acid (X) and 200 ml. of phosphoryl chloride was heated under reflux for 2.5 hr. Most of the phosphoryl chloride was evaporated at 50° using a water pump vacuum and the sirupy residue was poured, with stirring, over 250 g. of ice and water. Stirring was continued for 30 min. to hydrolyze any acid chloride and the resulting fine suspension was filtered. The filtrate was extracted with 50 ml. of chloroform and the filtered solid was extracted with two 50-ml. portions of chloroform, filtering each time. The combined chloroform extracts were combined, dried over magnesium sulfate, and evaporated to leave 7.0 g. (61%) of crude product. This was recrystallized from 50 ml. of benzene-chloroform (2:1) to give 5.52 g. (47%) of product, m.p. 158–160, and a second crop of 0.54 g. (5%) of product, m.p. 161–164°. The analytical sample was obtained by further recrystallization, m.p. 159–160°; $\lambda^{KBr}_{max(\mu)}$ 5.77 and 5.90 (carboxyl C=O), 6.45 and 6.55 (aromatic pyrimidine); $\lambda^{95\%\ EtOH}_{max(m\mu)}$ 218 (ε 8000), 267 (ε 5100); $\lambda^{pH\ 13}_{max(m\mu)}$ 218 (ε 8500), 268 (ε 6000). On paper chromatography in solvent D, the product showed a single spot at R_{Ad} 0.97.

Anal. Calcd. for $C_9H_8Cl_2N_2O_2$: C, 43.7; H, 3.26; N, 11.3. Found: C, 43.9; H, 3.09; N, 11.3.

A large-scale run employing 270 g. of the dihydroxy acid (X) gave 284 g. (88.5%) of dichloro acid (XVI).

2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid (XVIII). To 10 ml. of absolute ethyl alcohol, previously saturated with dry ammonia at 0°, was added 1.00 g. (4.0 mmoles) of dichloro acid (XVI) and the solution was heated at 150° for 15 hr. in a stainless steel bomb. The bomb was cooled and the solution was transferred and evaporated *in vacuo*. The residue was dissolved in 35 ml. of water, the solution was extracted with 5 ml. of chloroform, and the *p*H of the solution was adjusted to 6–7 with 6 *M* hydrochloric acid. Upon standing, 0.49 g. (58%) of crystals deposited and were collected. These were redissolved in 1 *M* hydrochloric acid, the solution was decolorized with Norit, and, after filtration and neutralization of the filtrate, 0.15 g. (18%) of pure XVIII, m.p. >300°, was obtained as a crystalline solid; $\lambda^{KBr}_{max(\mu)}$ 2.98 and 3.12 (NH_2, NH), 6.00 (carboxyl C=O and NH_2), 6.35 (pyrimidine ring); $\lambda^{pH1}_{max(m\mu)}$ 273 (ε 7000); $\lambda^{pH\ 13}_{max(m\mu)}$ 285 (ε 6400). On paper chromatography in solvent D, the product moved as a single spot with R_{Ad} 0.40.

Anal. Calcd. for $C_9H_{12}N_4O_2 \cdot 1/2H_2O$: C, 49.8; H, 6.04; N, 25.8. Found: C, 49.9; H, 5.67; N, 25.8.

A large-scale run employing 100 g. of dichloro acid (XVI) gave 67.8 g. (80.4%) of diamino acid (XVIII).

Butyl 2,4-diamino-5,6,7,8-tetrahydro-6-quinazolinecarboxylate (XXIII). A mixture of 1.00 g. (4.8 mmoles) of diamino acid (XVIII), 1.3 g. (12 mmoles) of ethanesulfonic acid, and 32 ml. of butyl alcohol was heated to boiling and 20 ml. of distillate was collected during 1.5 hr. The solution was cooled to 50° and poured into 25 ml. of saturated sodium bicarbonate solution. The butyl alcohol layer was separated, washed with an equal volume of water, and dried over magnesium sulfate. The filtrate was evaporated *in vacuo* to leave 0.90 g. of residue, which was extracted with 20 ml. of benzene leaving 0.71 g. (56%) of XXIII, m.p. 160–163°. Previously, by using *p*-toluenesulfonic acid, an analytical sample had been obtained after recrystallization from ethyl alcohol, m.p. 162–163°; $\lambda^{KBr}_{max(\mu)}$ 2.87, 2.98, and 3.15 (NH), 5.75 (ester C=O), 6.15 (NH_2), 6.30 and 6.93 (pyrimidine ring), 8.55 (ester C—O—C); $\lambda^{95\%\ EtOH}_{max(m\mu)}$ 286 (ε 7100), $\lambda^{pH\ 1}_{max(m\mu)}$ 274 (ε 7100).

Anal. Calcd. for $C_{13}H_{20}N_4O_2$: C, 59.1; H, 7.63; N, 21.2. Found: C, 58.7; H, 7.54; N, 21.5.

A mixture of 10.0 g. (48 mmoles) of diamino acid (XVIII), 21.9 g. (0.11 mole) of *p*-toluenesulfonic acid (monohydrate), and 350 ml. of butyl alcohol was heated to boiling and 235 ml. of distillate collected. The solution, upon chilling, deposited 21.4 g. (100%) of product, which was recrystallized from 200 ml. of 95% ethyl alcohol to give 14 g. (66%) of the *p*-toluenesulfonic acid salt of XXIII, m.p. 203–206°. The analytical sample had m.p. 204–206°; $\lambda^{KBr}_{max(\mu)}$ 2.95 and 3.15 (NH), 5.76 (ester C=O), 5.95–6.10 and 6.60 (pyrimidine ring), 8.2–8.5 (ester C—O—C and sulfonate ion), 9.65 and 9.85 (sulfonate ion).

Anal. Calcd. for $C_{20}H_{28}N_4O_5S$: C, 55.1; H, 6.46; S, 7.35. Found: C, 55.2; H, 6.40; S, 7.37.

Butyl 2,4-diacetamido-5,6,7,8-tetrahydro-6-quinazolinecarboxylate (XXIIIa). A mixture of 0.50 g. (1.9 mmoles) of butyl ester (XXIII) and 4.0 ml. of acetic anhydride was heated for 10 minutes on the steam bath, complete solution resulting. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in 10 ml. of chloroform. The chloroform solution was washed with 5 ml. of saturated sodium bicarbonate solution and 10 ml. of water and was dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* gave a white residue which was recrystallized from 5 ml. of benzene to yield 0.55 g. (83%) of product, m.p. 160–162°. A second recrystallization from benzene gave the analytical sample, m.p. 163–165°; $\lambda^{KBr}_{max(\mu)}$ 3.05–3.15 (NH), 5.80 (ester C=O), 6.00 (amide C=O), 6.30 and 6.70 (pyrimidine ring), 8.30 and 8.45 (ester and amide C—O); $\lambda^{95\%\ EtOH}_{max(m\mu)}$ 230 (ε 23,800), 282 (ε 7530).

Anal. Calcd. for $C_{17}H_{24}N_4O_4$: C, 58.6; H, 6.94; N, 16.1. Found: C, 58.9; H, 7.11; N, 16.3.

2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinemethanol (XXIV). To 13.0 ml. of diglyme,[6] previously dried by distillation over lithium aluminum hydride, cooled to 0–5°, was 1.0 g. (7.5 mmoles) of anhydrous aluminum chloride and the mixture was stirred until the salt had dissolved. Sodium borohydride (0.85 g., 23.6 mmoles) was added and the mixture was stirred until almost all the hydride had dissolved. A suspension of 1.0 g. (3.8 mmoles) of butyl ester (XXIII) in 10 ml. of dry diglyme was added dropwise and with good stirring over a period of 15 minutes, while the temperature was maintained below 20°. The resulting solution was stirred at room temperature for 50 minutes and was poured over 50 g. of ice. The aqueous solution was acidified with 1.0 ml. of concentrated sulfuric acid, adjusted to *p*H 5 with 5.0 ml. of 10% aqueous sodium hydroxide, and evaporated to dryness *in vacuo* at about 60°. The residue was powdered and extracted with boiling methanol for 4 hr. in a Soxhlet apparatus. The methanol extract was evaporated to dryness *in vacuo* and the residue (2.0 g.) was dissolved in 15 ml. of water, the solution filtered, and the filtrate adjusted to *p*H 10 with saturated sodium carbonate solution. The solution was chilled and the crystalline product, 0.49 g. (67%), was collected and recrystallized from water to give the analytical sample, m.p. 260–270° (dec.); $\lambda^{KBr}_{max(\mu)}$ 2.95 (NH, OH), 6.15 and 6.30 (pyrimidine ring), 9.55 (alcohol C—O); $\lambda^{pH\ 1}_{max(m\mu)}$ 274 (ε 7580), $\lambda^{pH\ 13}_{max(m\mu)}$ 285 (ε 7500). On paper

chromatography in solvent C, the product showed a single spot at R_{Ad} 0.83.

Anal. Calcd. for $C_9H_{14}NO$: C, 55.6; H, 7.27; N, 28.8. Found: C, 55.7; H, 7.29; N, 28.2.

2,4-Diamino-5,6,7,8-tetrahydro-6-quinazolinylmethyl p-toluenesulfonate (XXIVa). To a suspension of 0.50 g. (2.6 mmoles) of diamino alcohol (XXIV) in 3 ml. of dry pyridine was added dropwise and with stirring a solution of 0.60 g. (3.2 mmoles) of *p*-toluenesulfonyl chloride in 2 ml. of dry pyridine. The solution was stirred 10 minutes more until complete solution was attained, the temperature reaching 35°, and was cooled and poured into 30 ml. of water. To the aqueous solution was added 10% aqueous sodium hydroxide until the color changed from yellow to pink (*p*H 9–10). On chilling, 0.06 g. (6.7%) of product precipitated, m.p. 186–188°. It was recrystallized from 4 ml. of absolute ethanol to give the analytical sample, m.p. 188–193°; $\lambda_{max(\mu)}^{KBr}$ 2.91–3.06 and 6.19 (NH_2), 6.35–6.40 and 6.95 (pyrimidine ring), 7.41, 8.43 and 8.53 (O-sulfonate), 12.30 (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{16}H_{20}N_4O_3S$: C, 55.2; H, 5.78; S, 9.21. Found: C, 55.1; H, 6.82; S, 8.28.

There was insufficient sample for further purification.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXIX). A mixture of 0.50 g. (2.0 mmoles) of dichloro acid (XVI) and 3.0 ml. of phosphoryl chloride was heated under reflux for 1.8 hr. The solution was evaporated *in vacuo* and the residue was dissolved in 4.0 ml. of dry acetonitrile. This solution was added dropwise, with stirring, to 3.0 ml. of acetonitrile which had been saturated with ammonia at 0°. The solution was allowed to stand at room temperature for 15 hr. and was evaporated *in vacuo*. The residue was dissolved in 15 ml. of water and the *p*H adjusted to 9 with 10% aqueous sodium hydroxide. The precipitate, 0.44 g. (88%), m.p. 210–225°, was collected, washed with water, and dried.[20] After several recrystallizations from ethyl alcohol–methanol (7:1), the analytical sample was obtained, m.p. 220–225°; $\lambda_{max(\mu)}^{KBr}$ 2.95, 3.00, 3.15 and 6.17 (NH), 6.00 (amide C=O), 6.43–6.50 (pyrimidine ring); $\lambda_{max(m\mu)}^{95\%\ EtOH}$ 218 (ϵ 9800), 267 (ϵ 6230). On paper chromatography in solvent E, the product showed a single spot with R_{Ad} 2.0.

Anal. Calcd. for $C_9H_4Cl_2N_3O$: C, 43.9; H, 3.69; Cl, 28.8. Found: C, 44.2; H, 3.89; Cl, 28.6.

2,4-Dichloro-N,N-diethyl-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXI). The dichloro acid chloride (XVII) was prepared as in the preparation of XX from 1.05 g. (4.1 mmoles) of XVI and 6.0 ml. of phosphoryl chloride. It was dissolved in 5 ml. of dry methylene chloride and the solution was cooled to 0–5°. A solution of 2.0 ml. (27 mmoles) of diethylamine in 2 ml. of methylene chloride was added dropwise during 5 minutes and the resulting solution was heated at reflux for 1 hr., allowed to stand at room temperature for 15 hr., and evaporated to dryness *in vacuo*. Water (15 ml.) was added to the gummy residue, which then solidified on standing. The aqueous mixture was adjusted to *p*H 9 with 10% aqueous sodium hydroxide and the precipitate was collected and washed with water to give 1.27 g. (100%), m.p. 108–109°. Recrystallization from benzene-hexane (1:1) gave the analytical sample, m.p. 109–110°; $\lambda_{max(\mu)}^{KBr}$ 6.10 (amide C=O), 6.45–6.50 (pyrimidine ring); $\lambda_{max(m\mu)}^{95\%\ EtOH}$ 267 (ϵ 5300). On paper chromatography in solvent F, the product moved as a single spot with R_f[21] 0.85.

Anal. Calcd. for $C_{13}H_{17}Cl_2N_3O$: C, 51.7; H, 5.68; Cl, 23.5. Found: C, 51.5; H, 5.67; Cl, 23.4.

2,4,4'-Trichloro-5,6,7,8-tetrahydro-6-quinazolinecarboxanilide (XXII). The dichloro acid chloride (XVII) was prepared in the usual way from 0.50 g. (2.0 mmoles) of XVI and was dissolved in 2 ml. of methylene chloride. This solution was added dropwise to an ice-cold solution of 0.50 g. (3.9 mmoles) of *p*-chloroaniline in 2 ml. of dry pyridine, the resulting solution was allowed to stand 15 hr. at room temperature and was poured over 20 g. of ice. The aqueous mixture was extracted with 15 ml. of chloroform and the chloroform solution was washed with 10 ml. of saturated sodium bicarbonate solution and then with 0.5 *M* hydrochloric acid until the washings remained acidic. On chilling the chloroform solution, 0.50 g. of product, m.p. 97–104°, crystallized and was collected. The mother liquors were evaporated *in vacuo* and the residue was recrystallized from 3 ml. of chloroform yielding 0.15 g. more of crude XXII and giving a total crude yield of 87%. Several recrystallizations of the crude product from methanol-water gave the analytical sample, which showed a double melting point of 88–96° and 164–166° and had $\lambda_{max(\mu)}^{KBr}$ 3.05 (NH), 5.98 (amide C=O), 6.25 and 6.67 (aryl), 6.50 (NH and pyrimidine ring), 12.00 (*p*-disubstituted phenyl); $\lambda_{max(m\mu)}^{95\%\ EtOH}$ 252 (ϵ 23,800). On paper chromatography in solvent G, the product showed a single spot at R_{Ad} 1.23.

Anal. Calcd. for $C_{15}H_{12}Cl_3N_3O$: C, 50.6; H, 3.39; Cl, 29.8. Found: C, 50.6; H, 3.62; Cl, 29.4.

2,4-Diamino 5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXV). To 15 ml. of absolute ethyl alcohol previously saturated with ammonia at 0° was added 1.0 g. (4.2 mmoles) of dichloro amide (XX) and the mixture was heated at 150° for 15 hr. in a stainless steel bomb. The cooled solution was transferred and evaporated *in vacuo*. Water (10 ml.) was added to the residue and the *p*H was adjusted to 1 with concentrated hydrochloric acid. The solution was filtered, the filtrate was brought to *p*H 9–10 with 10% sodium hydroxide and chilled, giving 0.55 g. (66%) of product, m.p. >300°. This was recrystallized from *N,N*-dimethylformamide-water (1:1) to give the analytical sample, m.p. >300°; $\lambda_{max(\mu)}^{KBr}$ 2.95 (NH), 6.00 (amide C=O), 6.20–6.35 (NH_2, NH and pyrimidine ring); $\lambda_{max(m\mu)}^{pH\ 1}$ 272 (ϵ 7230), $\lambda_{max(m\mu)}^{pH\ 7}$ (ϵ 6280). On paper chromatography in solvent C, the product showed a single spot with R_{Ad} 1.20.

Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.2; H, 6.32; N, 33.8. Found: C, 51.7; H, 6.15; N, 32.8.

2,4-DiaminoN,N-diethyl-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXVI). A mixture of 1.0 g. (3.4 mmoles) of dichloro amide (XXI) in 10 ml. of absolute ethanolic ammonia (saturated at 0°) was heated at 150° for 10 hr. in a stainless steel bomb. The cooled solution was transferred, evaporated *in vacuo*, and the residue was dissolved in 5 ml. of water. The solution was filtered and the filtrate adjusted to *p*H 10 with saturated sodium carbonate solution. The precipitate, 0.59 g. (68%), was collected and was recrystallized from water to give the analytical sample, which showed a crystal transition at 70–75° and a double melting point of 115–118° and 231–234°; $\lambda_{max(\mu)}^{KBr}$ 3.00 (NH), 6.10 (amide C=O and pyrimidine ring), 6.90 (pyrimidine ring); $\lambda_{max(m\mu)}^{95\%\ EtOH}$ 285 (ϵ 7250). On paper chromatography in solvent C it showed a single spot with R_{Ad} 1.14.

Anal. Calcd. for $C_{13}H_{21}N_5O$: C, 59.3; H, 8.04; N, 26.6. Found: C, 59.1; H, 8.09; N, 26.3.

2,4-Diamino-4'-chloro-5,6,7,8-tetrahydro-6-quinazolinecarboxanilide (XXVII). The dichloro anilide (XXII), 1.0 g. (2.9 mmoles) was ammonolyzed by the procedure used for the preparation of XXVI except that the time of heating was 15 hr. The solution was evaporated *in vacuo* and the residue was dissolved in 10 ml. of water. The solution was brought to *p*H 10–11 with 10% aqueous sodium hydroxide and warmed on the steam bath for 10 minutes. After it had stood 3 hr. at room temperature, the mixture was filtered and the precipitate washed with water to give 0.48 g. (55%) of product, which was recrystallized from 4 ml. of *N,N*-dimethylformamide–water (4:1) to give 0.44 g. (50%) of product, m.p. 285–286°; $\lambda_{max(\mu)}^{KBr}$ 2.95–3.00 (NH), 5.92 (amide C=O), 6.05 (NH_2), 6.30 and 6.70 (aryl), 6.50 (NH and pyrimidine ring), 6.95 (pyrimidine ring), 12.15 (*p*-disub-

(20) In a later preparation, the precipitate was triturated with 1 *M* hydrochloric acid to remove traces of ring aminated material and gave 40 g. (90%) of product, m.p. 225–227°.

(21) Adenine does not move in solvent F and so no R_{Ad} value is possible.

stituted phenyl). On paper chromatography in solvent C, the product showed a single spot with R_{Ad} 1.27.

Anal. Calcd. for $C_{15}H_{16}ClN_5O$: C, 56.7; H, 5.08; Cl, 11.2. Found: C, 56.6; H, 5.29; Cl, 11.2.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinemethanol (XIX). A mixture of 10.0 g. (40.5 mmoles) of dichloro acid (XVI) and 50 ml. of phosphoryl chloride was heated under reflux for 2 hr., evaporated *in vacuo*, and the residue dissolved in 50 ml. of dry diglyme.[5] The solution was added dropwise during 25 minutes to a suspension of 3.0 g. (78 mmoles) of sodium borohydride in 50 ml. of dry diglyme, cooled to −40° in a Dry Ice, carbon tetrachloride–chloroform (95:5) bath. The temperature was maintained at −20 to −15° during the addition, then was stirred 5 minutes longer at that temperature and poured into a mixture of 300 ml. of saturated sodium bicarbonate solution and 200 g. of ice. The resulting solution was extracted with 250 ml. of chloroform, the chloroform was washed with 250 ml. of water and was dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* left 6.4 g. of oil which was taken up in 100 ml. of chloroform and the solution washed with 20 ml. of saturated sodium bicarbonate solution and 100 ml. of water, then dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* left 4.9 g. (52%) of a viscous oil which crystallized on standing but which resisted further purification efforts. It had $\lambda_{max(\mu)}^{film}$ 2.92 (OH), 6.50 (pyrimidine ring), 9.30 (alcohol C—O), and $\lambda_{max(m\mu)}^{95\%\ EtOH}$ 218 (ε 7200), 267 (ε 4700).

Anal. Calcd. for $C_9H_{10}Cl_2N_2O$: C, 46.6; H, 4.33; Cl, 30.5. Found: C, 46.8; H, 4.82; Cl, 28.2, 28.3.

Compound XIX was unstable and lost hydrogen chloride slowly on standing at room temperature.

2,4-Bis(benzylamino)]-5,6,7,8-tetrahydro-6-quinazolinemethanol (XXVIII). To a solution of 3.28 g. (14.1 mmoles) of dichloro alcohol (XIX) in 18 ml. of absolute ethyl alcohol was added 10 ml. (90 mmoles) of benzylamine and the mixture was heated at 150° for 15 hr. in a stainless steel bomb. The cooled solution was transferred, evaporated *in vacuo*, and to the residue was added 25 ml. of water. The aqueous mixture was extracted with 25 ml. of chloroform, the chloroform solution was dried over magnesium sulfate and evaporated *in vacuo*. The residue was carefully triturated with 25 ml. of hexane and the undissolved solid was recrystallized from 18 ml. of benzene-hexane (5:1), yielding 4.17 g. (79%) of product, m.p. 130–131°; $\lambda_{max(\mu)}^{KBr}$ 2.90 (OH), 3.05 (NH), 6.30 (aryl and pyrimidine ring), 6.60 (aryl, pyrimidine ring, and NH), 9.35 (alcohol C—O), 13.60 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{23}H_{26}N_4O$: C, 73.8; H, 7.00; N, 15.0. Found: C, 73.8; H, 7.28; N, 14.7, 14.9.

2,4-Bis(benzylamino)-6-(chloromethyl)-5,6,7,8-tetrahydroquinazoline (XXX). To 3.0 ml. of thionyl chloride was added 0.30 g. (0.80 mmole) of bis-(benzylamino) alcohol (XXVIII) and the mixture was heated under reflux for 2 hr., evaporated *in vacuo* to about 1 ml., and poured over 10 g. of ice. The mixture was extracted with 10 ml. of chloroform, the chloroform solution was washed with 5 ml. of saturated sodium bicarbonate solution and 5 ml. of water, and dried over magnesium sulfate. The solution was evaporated *in vacuo* to give 0.25 g. (80%) of product, m.p. 138–140°, which was recrystallized from 2 ml. of benzene to give 0.15 g. (48%) of the analytical sample, m.p. 141–142°; $\lambda_{max(\mu)}^{KBr}$ 2.95 and 3.10 (NH), 6.27 (aryl and pyrimidine ring), 6.45–6.60 (aryl, pyrimidine ring, and NH), 13.55–13.70 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{23}H_{25}ClN_4$: C, 70.4; H, 6.42; Cl, 9.04. Found: C, 70.9; H, 6.35; Cl, 9.38.

2,4-Bis(benzylamino)-6-(bromomethyl)-5,6,7,8-tetrahydroquinazoline (XXXI). A mixture of 1.0 g. (2.7 mmoles) of bis-(benzylamino) alcohol (XXVIII) and 5 ml. of phosphorus tribromide was heated with stirring for 2.5 hr. at 90–100°. The solution was cooled and poured into 50 g. of ice and the resulting solution stirred for 15 minutes. The solution was extracted with 25 ml. of chloroform, which was washed with 15 ml. of saturated sodium bicarbonate solution and then 20 ml. of water, and dried over magnesium sulfate. The chloroform solution was evaporated *in vacuo* to give 0.80 g. of white solid, which was recrystallized from 6 ml. of benzene-hexane (9:1) to give 0.68 g. (58%) of product, m.p. 140–143°. A further recrystallization gave the analytical sample, m.p. 140–143°; $\lambda_{max(\mu)}^{KBr}$ 2.90, 3.10 and 6.50 (NH), 6.25–6.30 and 6.60 (aryl and pyrimidine ring), 13.50 and 14.50 (monosubstituted phenyl); there was no alcohol C—O band near 9.30.

Anal. Calcd. for $C_{23}H_{25}BrN_4$: C, 63.3; H, 5.77; N, 12.8. Found: C, 63.2; H, 5.66; N, 13.1.

2,4-Dichloro-5,6,7,8-tetrahydro-6-quinazolinecarbonitrile (XXXII). A mixture of 2.4 g. (10.0 mmoles) of dichloro amide (XXIX) and 12 ml. of phosphoryl chloride was heated under reflux for 2 hr. The solution was evaporated *in vacuo* and 15 ml. of cold water was added to the residue. The aqueous solution was extracted with 20 ml. of chloroform and the extract was washed with 15 ml. of saturated sodium bicarbonate solution, then 15 ml. of water, and dried over magnesium sulfate. The chloroform solution was evaporated *in vacuo* leaving 2.18 g. of residue, which was recrystallized from 12 ml. of benzene-hexane (1:1) to yield 1.77 g. (80%) of product, m.p. 108–109°; $\lambda_{max(\mu)}^{KBr}$ 4.50 (C≡N), 6.45 and 6.55 (pyrimidine ring).

Anal. Calcd. for $C_9H_7Cl_2N_3$: C, 47.4; H, 3.09; Cl, 31.1. Found: C, 47.4; H, 3.28; Cl, 31.4.

2,4-Bis(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinecarbonitrile (XXXIII). To 5 ml. of a 35% solution of benzylamine in absolute ethyl alcohol was added 0.50 g. (2.2 mmoles) of dichloro nitrile (XXXII) and the mixture was heated at 150° for 9 hr. in a stainless steel bomb. The cooled solution was transferred and evaporated *in vacuo* and the residue was thoroughly triturated with 20 ml. of water, then with 20 ml. of hexane. The undissolved solid was recrystallized twice from toluene–ethyl alcohol (5:1) to give 0.30 g. (37%) of product, m.p. 212–214°; $\lambda_{max(\mu)}^{KBr}$ 3.00 and 3.10 (NH), 4.50 (C≡N), 6.25–6.30 (aryl and pyrimidine ring), 6.50 (NH and pyrimidine ring), 13.65 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{23}H_{23}N_5$: C, 74.8; H, 6.28; N, 19.0. Found: C, 75.0; H, 6.29; N, 18.9.

2,4-Diamino-5,6,7,8-tetrahydro-7-quinazolinecarbonitrile (XXXIV). A mixture of 0.70 g. (3.1 mmoles) of dichloronitrile (XXXII) and 7 ml. of absolute ethanolic ammonia solution (saturated at 0°) was heated for 15 hr. at 150° in a stainless steel bomb. The cooled solution was transferred, evaporated *in vacuo*, and the residue stirred in 10 ml. of 0.1 *M* hydrochloric acid for 1 hr., most of the material remaining undissolved. The mixture was filtered and the filtrate adjusted to *p*H 10 with 10% aqueous sodium hydroxide, giving 0.10 g. of white solid. The acid-insoluble material was stirred with aqueous sodium hydroxide (*p*H 11), the mixture filtered, and the solid washed thoroughly with water, yielding 0.35 g. of solid. The total of the crude solids (0.45 g.) was extracted with 2 ml. of hot N,N-dimethylformamide and the undissolved solid collected to give 0.28 g. (48%) of product, m.p. >290°; $\lambda_{max(\mu)}^{KBr}$ 2.95 and 3.20 (NH), 4.50 (C≡N), 6.02 and 6.18 (NH_2), 6.35 and 6.90 (pyrimidine ring). On paper chromatography in solvent C, the product moved as a single spot with R_{Ad} 0.90.

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.1; H, 5.86; N, 37.0. Found: C, 57.2; H, 6.00; N, 37.4, 37.7.

2,4-Bis-(benzylamino)-5,6,7,8-tetrahydro-6-quinazolinecarboxylic acid (XXXV). (A) A mixture of 0.50 g. (1.4 mmoles) of bis-(benzylamino) nitrile (XXXIII) and 4 ml. of 25% aqueous sulfuric acid was refluxed for 15 hr. The mixture was made basic with 10% aqueous sodium hydroxide until complete solution resulted (*p*H ~12) and the product was reprecipitated with 0.5 *M* sulfuric acid by adjusting the *p*H to 4–5. The solid, 0.47 g. (90%) was recrystallized several times from *N,N*-dimethylformamide–water; the various recrystallization products showed widely variable melting points, 152–156°, 214–219° and 168–195°. The sample for

analysis had m.p. 168–195° and $\lambda_{max(\mu)}^{Nujol}$ 3.05 and 6.40 (NH), 3.6–3.9 (broad carboxyl OH), 5.95 (carboxyl C=O),[22] 6.05 (pyrimidine ring), 13.30 and 14.35 (monosubstituted phenyl). On paper chromatography in solvent C, the product moved as a single spot with R_{Ad} 1.50.

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.1; H, 6.23; N, 14.4. Found: C, 70.2; H, 6.29; N, 14.1.

(B) A better method of preparation of XXXV was available by the reaction of 0.50 g. (2.0 mmoles) of dichloro acid (XVI) with 2 ml. of benzylamine, the mixture heated for 17 hr. on the steam bath. Water (10 ml.) was added to the residue along with enough 10% aqueous sodium hydroxide to dissolve all the solid. The basic solution was extracted with two 10-ml. portions of ethyl ether and was neutralized with glacial acetic acid. The precipitate, 780 mg. (100%), was washed and dried and shown to be identical with the acid from the nitrile hydrolysis by identical infrared spectra[23] and paper chromatographic behavior.

When the mixture of dichloro acid (XVI) and benzylamine was refluxed for 3 hr., a solid product was obtained whose infrared spectrum suggested that it was the bis-(benzylamino) benzylamide (XXXVI). After recrystallization from ethyl alcohol the compound melted at 169–170°; $\lambda_{max(\mu)}^{KBr}$ 2.95–3.05 (NH), 6.05 (amide C=O), 6.32 (aryl and pyrimidine ring), 6.56–6.68 (aryl, pyrimidine ring and NH), 13.68 and 14.33 (monosubstituted phenyl). There was no broad carboxyl OH absorption in the 3.5 to 4.0 μ region and the intensity of the 13.7 and 14.3 μ bands was greater than in the acid (XXXV) spectrum. The material was not otherwise characterized.

2,4-Bis-(benzylamino)-N,N-diethyl-5,6,7,8-tetrahydro-6-quinazolinecarboxamide (XXXVII). A mixture of 3.0 g. (7.8 mmoles) of bis(benzylamino) acid (XXXV) and 7 ml. of thionyl chloride was heated under reflux for 45 minutes. The mixture was evaporated *in vacuo* and two 5-ml. portions of benzene were separately evaporated *in vacuo* from the residue. The final residue was dissolved in 20 ml. of methylene chloride and added dropwise to a stirred solution of 9 ml. of diethylamine in 10 ml. of methylene chloride. After the mixture had stood overnight, it was evaporated *in vacuo* and 25 ml. of water was added to the residue. The aqueous mixture was extracted with 25 ml. of methylene chloride, the organic solution was washed with 20 ml. of 0.1 *M* aqueous sodium hydroxide and two 20-ml. portions of water and was dried over magnesium sulfate. Evaporation of the methylene chloride solution left 3.1 g. of residue, which was recrystallized from 10 ml. of benzene to give 1.7 g. (50%) of product, m.p. 82–90°. A small amount of material was recrystallized from benzene-hexane (9:1) to give a solid, m.p. 82–85°; $\lambda_{max(\mu)}^{KBr}$ 3.00 and 6.52 (NH), 6.14 (amide C=O), 6.30 (aryl and pyrimidine ring), 6.89 (pyrimidine ring), 13.60 and 14.30 (monosubstituted phenyl). This material was not analytically pure.

Anal. Calcd. for $C_{27}H_{33}N_5O$: C, 73.1; H, 7.50; N, 15.8. Found: C, 74.1; H, 7.53; N, 15.3.

Attempts to cleave the benzyl groups of XXXVII by hydrogenolysis to give the diamino amide (XXV) were unsuccessful. The use of platinum oxide as catalyst gave an excessive uptake of hydrogen but infrared examination of the product showed no loss of benzyl groups. The use of 5% palladium-on-charcoal led to no uptake of hydrogen.

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MENLO PARK, CALIF.

(22) When the spectrum was run in KBr, the acid carbonyl occurred at 6.05 μ.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXVI. Synthesis of Nucleosides Derived from D-Fructose

ELMER J. REIST, PHILLIP A. HART, AND B. R. BAKER

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The reaction of chloromercuri derivatives of purines with the appropriately blocked derivatives of D-fructose has been utilized to synthesize 9-α-D-fructofuranosyladenine (II) and 9-β-D-fructopyranosyladenine (III). The stereochemistry of these ketose nucleoside condensations is discussed.

As part of an intensive program on the synthesis of C′-methyl- and C′-hydroxymethylpentofuranosyl nucleosides, the syntheses of a number of C_5′-methylpentofuranosyl nucleosides have been reported from this Laboratory.[2–6] A logical continuation of this work involves the syntheses of C_1′-methyl- and C_1′-hydroxymethyl nucleosides (I, R + H or OH). As the majority of the naturally occurring nucleosides contain the β-D-ribofuranose configuration,[7] it was most desirable to prepare the C_1′-substituted nucleosides in which the sugar

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