# Compounds in the Pyrrolo[3,4-*d*]pyrimidine Series. Syntheses Based on 2,3-Dioxopyrrolidines[1]

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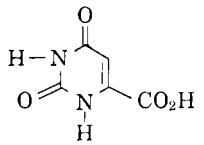
Three procedures have been developed for the synthesis of the pyrrolo[3,4-*d*]pyrimidine ring system: (1) condensation of a 4-carbethoxy-3-amino-2-oxo-3-pyrroline (III) with guanidine, (2) condensation of a 4-carbethoxy-2,3-dioxopyrrolidine (enol form, I) with urea or guanidine, or (3) condensation of a 4-benzylidene-2,3-dioxopyrrolidine (VIII) with guanidine.

The efficacy of analogs of the naturally occurring purines and pyrimidines as antimetabolites, and in particular the useful antitumor activity of such compounds as 6-mercaptopurine and 5-fluorouracil, has prompted the synthesis of a large number of these analogs. The present investigation is concerned with the pyrrolo[3,4-*d*]pyrimidine series, which appears to have received no attention previously.[2] Such compounds can be regarded as purine analogues as well as pyrimidine derivatives of a new type. Moreover, in the members of the series which will be described here (see formulas IV, VII, and X) the pyrrolidone carbonyl group is attached to the 4-position of the pyrimidine ring, the position occupied by the carboxyl group in orotic acid (A), which is a precursor in the biosynthesis of pyrimidines and pyrimidine nucleotides both in animals and in microörganisms.[3] Examination of the new synthetic compounds for possible antimetabolite activity therefore should be of considerable interest.



A

Chart I illustrates the reactions investigated. In the discussion of individual compounds, the letter h following the numeral which designates the formulas in Chart I will indicate that R is hydrogen, b that R is benzyl, and c that R is cyclohexyl. In order to keep the nomenclature as simple as possible, the common practice of naming pyrimidines as derivatives of the fully aromatic form of the pyrimidine system has been followed. The formulas in Chart I correspond to these names, with oxygens shown as incorporated in hydroxyl groups, although the infrared data indicate the presence of carbonyl groups in the pyrimidine portions of structures IV and VII.

2,3-Dioxopyrrolidines with functional substituents in the 4-position appeared to be suitable starting materials for the preparation of compounds in the pyrrolo[3,4-*d*]pyrimidine series. However, the 4-carbethoxy-2,3-dioxopyrrolidines, which, as β-keto esters, might perhaps have been expected to yield the pyrimidine ring readily by reaction with guanidine or urea,[4] afforded the desired products only after the usual procedures for related pyrimidine syntheses were considerably modified. It seems evident that the difficulty resided in the fact that the 4-carbethoxy-2,3-dioxopyrrolidines actually exist almost entirely in the form of enols (I), which are exceptionally acidic ($pK_a$ = *ca.* 4.25),[5] and evidently yield enolate anions which are stabilized by resonance against nucleophilic attack at either the ester or ketonic function. Thus treatment of Ib with guanidine yielded the guanidinium salt IIb, which did not readily undergo the elimination of water and ethanol which would have produced the pyrrolopyrimidine IVb; initial attempts to obtain IVb from IIb by refluxing with excess guanidine in ethanol led to partial decomposition to blue-colored by-products, and recovery of most of the salt (IIb) unchanged.

To obtain compounds with the increased reactivity toward guanidine, it proved expedient to convert the compounds of type I into 2-amino derivatives (III), which do not form enolate anions. The 3-amino derivatives were easily obtained in satisfactory yield (*ca.* 85%) by treatment of compounds of type I with ammonium formate. Unfortunately, no guanidino derivatives analogous to III were obtained when guanidine salts (carbonate, acetate or hydrochloride) were used in place of ammonium formate; the esters I were recovered unchanged from such experiments.

The 3-amino derivatives (IIIh and IIIb) reacted satisfactorily with excess guanidine in refluxing absolute ethanol in the presence of one mole of sodium ethoxide to yield 2-amino-4-hydroxyl-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)-ones (IVh and IVb). In the absence of sodium ethoxide, yields of the benzyl derivative IVb were somewhat reduced and there were indications of the presence of lower-melting products. The best of the procedures thus far investigated afforded *ca.* 85% yields of IVb and *ca.* 58% yields of IVh. Yields were unreliable unless the ethanol used was thoroughly dried and purified by distillation from magnesium ethoxide. A recent experiment has shown, moreover, that by using highly purified ethanol and a large excess of

(1) This investigation was supported by a research grant (RG-4371) from the National Institutes of Health, U. S. Public Health Service.

(2) On the other hand, a considerable amount of work on compounds in the pyrrolo[2,3-*d*]pyrimidine series has appeared recently. See (a) R. A. West, K. Ledig, and G. H. Hitchings, British Patent 812,366 (April 22, (1959); *Chem. Abstr.*, **54**, 592 (1960); (b) R. A. West and L. Beauchamp, *J. Org. Chem.*, **26**, 3809 (1961); (c) R. A. West, *ibid.*, **26**, 4959 (1961); (d) J. Davoll, *J. Chem. Soc.*, 131 (1960).

(3) See, for example, (a) F. W. Chattaway, *Nature*, **153**, 250 (1944); (b) H. J. Rogers, *ibid.*, **153**, 251 (1944); (c) H. S. Loring and J. G. Pierce, *J. Biol. Chem.*, **153**, 61 (1944); (d) H. K. Mitchell, M. B. Houlahan, and J. F. Nyc, *ibid.*, **172**, 525 (1948); (e) S. Bergstrom, *et al.*, *ibid.*, **177**, 495 (1949); (f) H. Arvidson, *et al.*, *ibid.*, **179**, 167 (1949); (g) L. L. Weed, M. Edmunds, and D. W. Wilson, *Proc. Soc. Exptl. Biol. Med.*, **75**, 192 (1950); (h) L. D. Wright, *et al.*, *J. Am. Chem. Soc.*, **73**, 1898 (1951); (i) R. B. Hurlbert and V. R. Potter, *J. Biol. Chem.*, **195**, 257 (1952); (j) I. Lieberman and A. Kornberg, *ibid.*, **207**, 911 (1954).

(4) *Cf.*, for example, the review of synthetic methods for pyrimidines by G. W. Kenner and A. Todd in R. C. Elderfield's "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 234.

(5) (a) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).

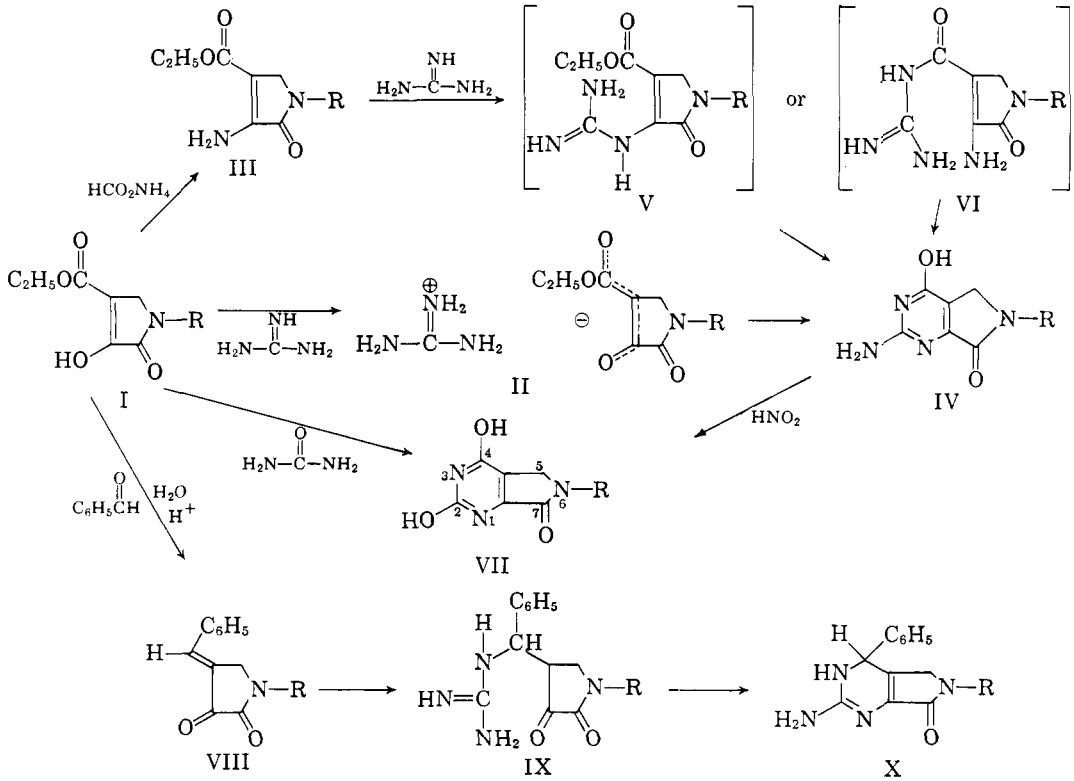


CHART I

guanidine, a partial conversion of the ester Ib to the pyrrolopyrimidine IVb can be achieved; decomposition of the guanidine salt IIb evidently is retarded under these conditions, and the pyrimidine ring closure takes place slowly. There are several mechanisms by which compounds of type IV could be formed by base-promoted reactions of compounds of type III with guanidine. Presumably, intermediates of the types V and/or VI are involved, but it has not been determined whether the ammonia which is eliminated arises from the amino group of III or from the guanidine.[6]

After a number of unsuccessful attempts had been made to condense urea with Ib with the aid of bases or acids in ethanol or dioxane, the desired reaction was obtained by heating Ib in fused urea under reduced pressure at 180°.[7] The conversion of Ib to the dihydroxypyrrolopyrimidine VIIb was rather low (14%), but much of the starting material (*ca.* 69%) was recovered in the form of the 3-amino derivative IIIb, which could be used in the preparation of the amino hydroxy pyrrolopyrimidine IVb.

The dihydroxy derivative VIIb could also be obtained through the nitrous acid deamination of compound IVb. This conversion, achieved in 42% yield without any extended study of reaction conditions, provided confirmation of the assumed close structural relationship between compounds VIIb and IVb. Compound VIIh, the dihydroxy derivative having an unsubstituted pyrrolidine nitrogen, was not obtained by means of the reaction of urea with the unsubstituted 4-carbethoxy-2,3-dioxopyrrolidine Ih; even fusion of these reactants failed to yield any of the desired pyrrolopyrimidine. However, compound VIIh was obtained in 47% yield by nitrous acid deamination of compound IVh.

The pyrrolo[3,4-*d*]pyrimidines of the types IV and VII displayed the expected properties. They melted with decomposition or decomposed without melting only at high temperatures, and, while insoluble in water, dissolved in aqueous sodium hydroxide solutions. The 2-amino compound IVb, although insoluble in aqueous ethanol alone, dissolved in aqueous ethanol to which some hydrochloric acid had been added; the expected basicity of the 2-aminopyrimidine structure was evident. Compound IVh dissolved easily in hot water when acid was added. The ultraviolet spectra (Table I), most of which were measured in 0.1 *N* sodium hydroxide solution because of the low solubility of the compounds in other solvents, were rather similar to those of related pyrimidines such as orotic acid,[8] but in alkaline solution the absorption bands for the pyrrolopyrimidines occurred at somewhat longer wave lengths, apparently as a result of the presence of the pyrrolidone carbonyl group, which in these structures would be held in the plane of the pyrimidine ring. The infrared spectra (see Experimental), as expected, showed absorption in the 3-$\mu$ region (OH, NH, $NH_2$, and/or =NH groups) and the 6-$\mu$ region (lactam carbonyl, imino, and/or olefinic groups). The large number of absorption bands in the 6.0-$\mu$ region of the Nujol mull spectra of several of these compounds probably reflects splitting of carbonyl absorptions by hydrogen bonding.

As expected, the nuclear magnetic resonance (n.m.r.) spectra of IVb and VIIb, which were measured at 60

(6) If it is the amino nitrogen of the compounds III which is retained in the final products, this pyrimidine ring closure could be regarded as somewhat analogous to the synthetic method recently introduced by Taylor, in which formamidine acetate reacts with o-aminonitriles to form fused-ring structures incorporating the pyrimidine system. See E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).

(7) Heating of suitable intermediates in fused urea occasionally has been employed in the past to form 2,4-dihydroxypyrimidine derivatives. See, for example, E. Fischer and G. Roeder, *Ber.*, **34**, 3751 (1901).

(8) *Cf.*, The table of ultraviolet data provided by A. Bendich and E. Chargaff and J. N. Davidson's "The Nucleic Acids," Vol. I, Academic Press, Inc., New York, N. Y., 1955, p. 108.

TABLE I

ULTRAVIOLET DATA. PYRROLO[3,4-*d*]PYRIMIDINES

| Compound | Solvent | —Maxima— $\lambda_{m\mu}$ | log $\epsilon$ | —Minima— $\lambda_{m\mu}$ | log $\epsilon$ | "End" absorption[a] at 220 m$\mu$, log $\epsilon$ |
|---|---|---|---|---|---|---|
| IVb | NaOH, 0.1 *N* | 223 | 4.26 | 277 | 3.30 | .. |
| | | 306 | 3.67 | | | |
| IVh | NaOH, 0.1 *N* | 220 | 4.17 | 265 | 3.08 | .. |
| | | 304 | 3.70 | | | |
| VIIb | NaOH, 0.1 *N* | 314 | 3.79 | 278 | 3.33 | 4.23 |
| | Ethanol, 95% | 264 | 4.04 | 228 | 3.75 | 3.92 |
| VIIh | NaOH, 0.1 *N* | 312 | 3.82 | 266 | 3.05 | 4.16 |
| Orotic acid | NaOH, 0.1 *N* | 286 | 3.74 | 248 | 3.34 | 3.92 |
| Xb | HCl, 0.1 *N* | *ca.* 275[b] | 3.34 | .. | .. | 4.26 |
| | | *ca.* 255[b] | 3.52 | | | |
| | | *ca.* 245[b] | 3.68 | | | |
| Xc | HCl, 0.1 *N* | *ca.* 275[b] | 3.36 | .. | .. | 4.26 |
| | | *ca.* 255[b] | 3.62 | | | |
| | | *ca.* 245[b] | 3.74 | | | |

[a] Log $\epsilon$ values at 220 m$\mu$ are listed for those compounds showing strong and evidently rising absorption at that point. Some pyrimidines (see ref. 8) show an additional maximum not far below this lower limit of the wave-length range measured in the present work. [b] Inflection.

Mc. in trifluoroacetic acid solution, showed two unsplit lines of equal intensity which could be assigned to the two equivalent hydrogens of the methylene portion of the benzyl group and the two equivalent hydrogens of the methylene group at position 5 of the ring system. Compounds IVh and VIIh showed an unsplit line due to the methylene protons of position 5. A detailed discussion of the n.m.r. results will be provided elsewhere.[9]

Suitable starting materials were also at hand for the preparation of pyrrolo[3,4-*d*]pyrimidine derivatives containing a dihydropyrimidine ring. The 4-benzylidene-2,3-dioxopyrrolidines VIII,[10] which have a bright yellow color, were decolorized rapidly when treated with guanidine in ethanol solution, evidently due to formation of colorless, ethanol-soluble guanidine adducts for which the structure IX is suggested. In experiments with VIIIb a precipitate was deposited over a period of three days when the solutions were stirred at room temperature following this loss of color. As discussed below, this product showed the composition and properties expected for 2-amino-6-benzyl-4-phenyl - 3,4 - dihydro - 5*H* - pyrrolo[3,4 - *d*]pyrimidin-7(6*H*)-one (Xb). A similar result was obtained starting with compound VIIIc, but the product Xc did not precipitate, and was isolated by removal of the solvent. The apparent second (ring-closure) phase of these reactions could be brought about in a one-hour period by heating the solutions at temperatures in the range 60 to 80°.[11]

Compounds Xb and Xc were high-melting and insoluble in water, but quite soluble in aqueous alcoholic hydrochloric acid. The acid solutions of these compounds showed a strong blue-green fluorescence when exposed to ultraviolet light. In 0.1 *N* hydrochloric acid the compounds gave ultraviolet absorption curves (see Table I) which increased rapidly in intensity as the lower end (220 m$\mu$) of the measured wave-length range was approached, and showed several inflections, but no maxima.[12] The n.m.r. spectra of Xb and Xc, obtained in trifluoroacetic acid solution, showed the expected one-proton singlet due to the hydrogen at position 4, and an AB pattern[13] assigned to the methylene group at position 5 which indicates two spin-coupled protons separated in the spectrum by a very small chemical shift. In the spectrum of Xb, the N-benzyl methylene protons give rise to an additional similar AB pattern of equal intensity. The methylene groups in these compounds contain nonequivalent protons because of the unsymmetrical (phenyl) substitution at position 4.[14] The n.m.r. data are consistent only with a structure in which the two carbons of the ring junction are joined by a double bond; compounds Xb and Xc may be regarded as derivatives of 1,4 or 3,4-dihydropyrimidine (depending upon the tautomeric form of the guanidino portion of the ring) but not as 4,5 or 5,6-dihydropyrimidines.

Work is in progress on preparation of additional members of the pyrrolo[3,4-*d*]pyrimidine series.

## Experimental[15,16]

**3-Amino-1-benzyl-4-carbethoxy-2-oxo-3-pyrroline (IIIb).**—1-Benzyl-4-carbethoxy-2,3-dioxopyrrolidine (Ib)[5] (41.6 g.; 0.16 mole) and 20.0 g. (0.32 mole) of ammonium formate in 200 ml. of absolute ethanol were refluxed for 24 hr. The solution was then concentrated to dryness under reduced pressure over a steam cone, and the solid residue was washed with 100 ml. of water, filtered and dried. The crude product was dissolved in 300 ml. of boiling 95% ethanol, and the hot solution was treated with Norit, concentrated to 200 ml., and cooled. The product (31.0 g.) separated as white needles, m.p. 114–115°. An additional 7.8 g. of product, m.p. 112–114° was obtained from the mother liquor; the total yield was 38.8 g. (93%). The m.p. remained at 114–115° following two further recrystallizations from ethanol.

*Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.62; H, 5.97; N, 10.68.

Infrared spectrum (Nujol mull): 2.84m, 2.97i, 3.06sm, 3.14m, 3.39i, 3.46i, 5.91i, 6.07i, 6.12i, 6.35i, 6.68m, 6.82i, 6.89i, 6.97i, 7.07m, 7.22w, 7.28w, 7.35m, 7.43m, 7.54w, 7.73bi, 7.85bi, 8.05i, 8.27m, 8.57w, 8.65w, 8.95i, 9.09i, 9.26m, 9.79m, 10.04w, 10.32w, 11.22w, 11.66w, 12.18w, 12.72w, 12.98m, 13.08i, 13.64m, 14.24i.

Acid hydrolysis of the product IIIb reconverted it to the starting material (Ib).

**3-Amino-4-carbethoxy-2-oxo-3-pyrroline (IIIh).**—4-Carbethoxy-2,3-dioxopyrrolidine (Ih)[5b] (10.0 g.; 0.058 mole) and 7.3 g. (0.106 mole) of ammonium formate in 500 ml. of absolute ethanol were refluxed for 48 hr. The crude product, isolated in the same way as the 1-benzyl derivative (IIIb) described above, consisted of 8.7 g. of pink crystals, m.p. 212–215°. Recrystallization from 250

(9) The authors are indebted to Mr. George E. Milliman and Dr. R. J. Kurland for the n.m.r. measurements.

(10) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962).

(11) The formation of 2-amino-5,6-dihydropyrimidines by condensation of guanidine with $\alpha,\beta$-unsaturated ketones has been described by W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).

(12) 5,6-Dihydropyrimidines also lack ultraviolet maxima above 220 m$\mu$ when measured in acid solutions. See K.-Y. Zee-Cheng, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 1877 (1961).

(13) See (a) H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957); (b) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 119–123; (c) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 89–90.

(14) See ref. 13c, p. 101–103.

(15) Melting points are uncorrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England; A. Bernhardt, Max Planck Institute for Coal Research, Mülheim (Ruhr), Germany; and Galbraith Laboratories, Inc., Knoxville, Tenn.

(16) Infrared spectra were determined with a Perkin–Elmer Infracord spectrophotometer. Figures quoted are wave lengths in microns. Letters following the figures describe bands as follows: i = intense—>60% absorption; m = medium—30–60% absorption; w = weak—<30% absorption; b = broad band; s = shoulder. Ultraviolet spectra were measured with a Cary recording spectrophotometer.

ml. of 95% ethanol with decolorization by Norit yielded 8.3 g. (84%) of white plates, m.p. 214–215°, which were not changed in m.p. by further recrystallizations.

*Anal.* Calcd. for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.68; H, 5.90; N, 16.14.

Infrared spectrum (Nujol mull): 2.89i, 2.98i, 3.10i, 3.21m, 3.42i, 3.49i, 5.80i, 5.84i, 5.89i, 5.95i, 6.08i, 6.13i, 6.25i, 6.30bi, 6.44sm, 6.67w, 6.79sm, 6.83i, 6.92i, 7.22i, 7.35i, 7.88bi, 8.08i, 8.62m, 8.95i, 9.10bi, 9.55m, 9.80m, 10.10w, 10.89bw, 11.55w, 12.62m, 12.81m, 13.02bi, 13.53bm.

**2-Amino-6-benzyl-4-hydroxy-5*H*-pyrrolo[3,4-*d*]pyrimidin-7-(6*H*)-one (IVb).**—A solution of guanidine and sodium ethoxide in absolute ethanol was prepared from 2.7 g. (0.12 g.-atom) of sodium dissolved in 100 ml. of absolute ethanol (freshly dried over magnesium ethoxide[17]), and 9.6 g. (0.10 mole) of guanidine hydrochloride, also dissolved in 100 ml. of specially dried absolute ethanol. Compound IIIb (5.2 g.; 0.02 mole) was added and the mixture was refluxed with stirring for 73 hr. in an apparatus protected from moisture. Removal of nearly all of the ethanol under reduced pressure over a steam cone left a residue containing the sodium derivative of IVb, which was dissolved in 100 ml. of water. Addition of glacial acetic acid until a pH of 6 was reached caused precipitation of 4.4 g. (86%) of a white product, m.p. > 340°.[18] After it was washed with 50 ml. of ethanol and dried, the product was recrystallized from 500 ml. of dimethylformamide to yield 2.5 g. of white plates, m.p. *ca.*, 360° dec. The analytical sample was recrystallized again from the same solvent.

*Anal.* Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.81; H, 4.83: N, 21.82.

Infrared spectrum (Nujol mull): 3.03m, 3.14m, 3.39i, 3.46m, 5.95i, 5.99i, 6.19m, 6.24sm, 6.62w, 6.73w, 6.84m, 6.91m, 7.04w, 7.25bm, 7.59w, 7.74m, 7.91w, 8.28w, 8.33sw, 8.72w, 9.03w, 9.30w, 9.40w, 9.69w, 11.91w, 12.13w, 12.29bm, 12.68w, 13.13m, 13.88w, 14.27m, 14.93m.

**2-Amino-4-hydroxy-5*H*-pyrrolo[3,4-*d*]pyrimidine-7(6*H*)-one (IVh).**—The procedure for conducting the reaction was the same as that described above for preparation of IVb; 7.6 g. (0.33 g.-atom) of sodium, 28.7 g. (0.3 mole) of guanidine hydrochloride, 5.0 g. (0.029 mole) of compound IIIh, and a total of 600 ml. of specially dried absolute ethanol were used. The sodium derivative of the crude product, isolated as described above for IVb, was dissolved in 100 ml. of water and decolorized by treatment of the solution with Norit at the boiling point. The filtered solution was cooled to room temperature and adjusted to pH 6 by addition of glacial acetic acid. The product, which was precipitated as a pale yellow solid, weighed 2.8 g. (58%) after being washed on the filter with water and dried. It did not melt below 360°. It was suspended in boiling water and dissolved by portionwise addition of 20% hydrochloric acid until a clear solution was obtained. After decolorization with Norit and cooling of the filtered solution, the product separated as yellow needles. The analytical sample, which was further treated by a period of heating in suspension in boiling distilled water, was a white, microcrystalline material.

*Anal.* Calcd. for $C_6H_6O_2N_4$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.50; H, 3.74; N, 33.41.

Infrared spectrum (Nujol mull): 3.01i, 3.14i, 3.40i, 3.47m, 5.83i, 5.90i, 6.01i, 6.17sm, 6.23m, 6.60w, 6.85m, 6.95sw, 7.24-bm, 7.42sw, 7.60w, 7.79m, 8.20bw, 8.65bw, 9.00w, 9.44w, 10.29-w, 12.03m, 12.32bm, 13.20m, 13.57bw, 14.53bm.

**6-Benzyl-2,4-dihydroxy-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)-one (VIIb).** **(A) From Compound Ib.**—A 15.6-g. quantity (0.06 mole) of compound Ib was mixed thoroughly with 72 g. (1.2 moles) of urea and heated at 180° for 15 min. in an oil bath. During this period the flask containing the melt was evacuated with an aspirator. The mixture was allowed to cool and then was treated with 300 ml. of boiling water. The water-insoluble fraction was collected by filtration, then extracted with 200 ml. of 95% ethanol at the boiling point. The remaining insoluble residue (2.2 g.; 14% yield) was a white solid, m.p. *ca.* 315–320° dec. It was recrystallized from 50 ml. of dimethylformamide to yield 2 g. of compound VIIb, m.p. *ca.* 315–318° dec.

*Anal.* Calcd. for $C_{13}H_{11}O_3N_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.96; H, 4.29; N, 16.54.

Infrared spectrum (Nujol mull): 3.24m, 3.38i, 3.45i, 5.74i, 5.94si, 6.02i, 6.33m, 6.42m, 6.75w, 6.86m, 6.89sm, 6.97m, 7.09m, 7.30w, 7.36w, 7.59bw, 7.76w, 7.93m, 8.33m, 8.49w, 8.64w, 8.68w, 9.20bw, 9.35w, 9.76w, 9.93w, 11.82bw, 12.15bm, 13.03m, 13.53m, 13.75w, 14.15m, 14.64w.

The ethanol extract of the water-insoluble fraction yielded 8.2 g. (69%) of compond IIIb as white needles, m.p. 110–113°, when concentrated to 50 ml. and cooled to induce crystallization.

**(B) From Compound IVb.**—Compound IVb (2.56 g.; 0.01 mole) was dissolved in 150 ml. of boiling water to which sufficient concentrated hydrochloric acid had been added (*ca.* 50 ml.) to give a clear solution. An additional 10 ml. of concentrated hydrochloric acid was added and the mixture was stirred and maintained at 90° while a solution of 2.07 g. (0.03 mole) of sodium nitrite in 20 ml. of water was added dropwise. The temperature was kept at 90° for an additional 15 min. after the nitrite addition was complete, then the mixture was filtered while still hot to collect the precipitated product, which was washed on the filter and dried.[19] The yield was 1.08 g. (42%) of a white solid, m.p. *ca.* 315–317° dec., which was identical to the product obtained by the urea condensation described under A above.

**2,4-Dihydroxy-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)-one (VIIh).**—Compound IVh (1.0 g.; 0.006 mole) was suspended in a solution prepared from 10 ml. of concentrated sulfuric acid and 20 ml. of water. To the stirred suspension, cooled to 0–5°, 0.41 g. (0.006 mole) of sodium nitrite dissolved in 10 ml. of water was added dropwise. After the addition was complete the reaction was allowed to proceed at room temperature for 27 hr.[20] The product was removed by filtration, washed on the filter with water, and dried to yield 0.47 g. (47%) of a pale yellow solid, m.p. >360°. It was purified for analysis first by washing in 10 ml. of boiling 20% hydrochloric acid followed by 10 ml. of boiling water. The washed product was then dissolved in 50 ml. of boiling concentrated ammonium hydroxide, and decolorized with Norit. When the filtered, cooled solution was acidified to pH 6 with glacial acetic acid, a white microcrystalline solid precipitated and was collected by filtration, washed on the filter with water, and dried. The recovery was 0.2 g. of material which did not melt below 360°.

*Anal.* Calcd. for $C_6H_5O_3N_3$: C, 43.13; H, 3.02; N, 25.15. Found: C, 42.93; H, 2.88; N, 25.07.

Infrared spectrum (Nujol mull): 2.99m, 3.13m, 3.25m, 3.38i, 3.45i, 5.78si, 5.83i, 5.89si, 5.94si, 6.01i, 6.45m, 6.86m, 6.93m, 7.00m, 7.10m, 7.20bm, 7.60m, 8.04m, 8.24m, 8.65w, 9.01bw, 9.62m, 10.37bw, 11.45bm, 12.02bm, 12.70bm, 13.05m, 13.56bm, 13.82bm.

**2-Amino-6-benzyl-4-phenyl-3,4-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)-one (Xb).**—An ethanolic sodium ethoxide solution prepared from 1.15 g. (0.05-g. atom) of sodium and 50 ml. of absolute ethanol was added with stirring to a solution of 5.0 g. (0.05 mole) of guanidine hydrochloride in 50 ml. of absolute ethanol. The precipitated sodium chloride was removed by filtration, and the filtered guanidine solution was added over a period of *ca.* 15 min. to a stirred suspension of 2.75 g. (0.01 mole) of compound VIIIb in 250 ml. of absolute ethanol. After compound VIIIb had dissolved, the solution was heated to 60° and held at this temperature for 1 hr. while stirring was continued. Precipitation of the product started after *ca.* 15 min. After the reaction mixture had cooled to room temperature, 2.80 g. (88%) of a pale yellow precipitate was removed by filtration. The product melted at 272–273° dec. No satisfactory method of crystallization was found for this compound.

Infrared spectrum (Nujol mull): 2.88i, 2.93sm, 3.05i, 3.38i, 3.45i, 5.97i, 6.05i, 6.11i, 6.31sm, 6.38m, 6.53i, 6.62i, 6.82i, 7.13i, 7.56m, 7.76i, 8.09w, 8.52sm, 8.60m, 8.66bm, 8.99w, 9.14m, 9.31m, 9.74w, 9.99bw, 10.26w, 10.52w, 10.85w, 11.91w, 12.10w, 12.20w, 12.45w, 12.82w, 13.33m, 13.58i, 14.26i.

The hydrochloride was prepared in order to permit recrystallization of a sample for analysis. One gram of Xb was suspended in 100 ml. of absolute ethanol and dry hydrogen chloride was passed into the suspension with stirring. The free base dissolved and the hydrochloride precipitated after a few minutes. After 15 min., introduction of the gas was stopped and the reaction mixture was concentrated to dryness under reduced pressure over a steam cone. The residue was recrystallized twice from

(17) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931); H. Lund, *ibid.*, **37**, 936 (1934); *J. Am. Chem. Soc.*, **74**, 3188 (1952).

(18) A reaction between the enol Ib and guanidine carried out in the same fashion, but without sodium ethoxide (omitted to avoid sodium enolate formation), led to a 24% yield of crude IVb and recovery of *ca.* 60% of Ib.

(19) Procedure based on the deamination method of H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 3046 (1959).

(20) Procedure based on the deamination method of L. O. Ross, L. Goodman, and B. R. Baker, *ibid.*, **81**, 3108 (1959).

95% ethanol to yield 0.6 g. of the hydrochloride of Xb, m.p. 273–274° dec.

*Anal.* Calcd. for $C_{19}H_{19}ON_4Cl$: C, 64.31; H, 5.40; N, 15.79. Found: C, 64.61; H, 5.44; N, 15.93.

Infrared spectrum of the hydrochloride of Xb (Nujol mull): 2.91m, 3.02m, 3.40i, 3.47i, 5.87i, 5.97i, 6.29m, 6.39i, 6.71m, 6.90i, 6.99sm, 7.18m, 7.30w, 7.36m, 7.59m, 7.90w, 8.06w, 8.44m, 8.61w, 8.91bw, 9.34w, 9.76w, 10.05w, 10.31w, 10.49w, 12.03w, 12.65bw, 12.99m, 13.90m, 14.09m, 14.40bm.

**2-Amino-6-cyclohexyl-4-phenyl-3,4-dihydro-5*H*-pyrrolo[3,4-*d*]-pyrimidin-7(6*H*)-one (Xc).**—A solution of guanidine in absolute ethanol was prepared from 2.0 g. (0.02 mole) of guanidine hydrochloride, 0.46 g. (0.02 g.-atom) of sodium and a total of 50 ml. of absolute ethanol, by the same procedure used in the preparation of Xb, described previously. Reaction of the guanidine solution with 2.7 g. (0.01 mole) of compound VIIIc in 200 ml. of ethanol was carried out at the reflux temperature, but otherwise the procedure was as described above. When the reaction mixture was then concentrated nearly to dryness under reduced pressure over a steam cone, a yellow gum separated and was washed with 200 ml. of water. The resulting cream-colored solid was collected by filtration and dried in a desiccator. The yield was 3.0 g. (95%); m.p. 244–247° dec. The compound was obtained as a white microcrystalline solid, m.p. 247–249° dec., after it had been washed with dimethylformamide, then with acetone. After recrystallization from a small volume of methanol the m.p. was 254–256° dec.

*Anal.* Calcd. for $C_{18}H_{22}ON_4$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.14; H, 6.85; N, 18.16.

Infrared spectrum (Nujol mull): 2.86m, 2.95i, 3.06m, 3.38i, 3.45i, 6.02i, 6.07i, 6.24i, 6.34i, 6.61i, 6.71sm, 6.82sm, 6.92i, 7.04m, 7.19i, 7.28sm, 7.46bm, 7.80i, 7.90m, 8.13m, 8.26w, 8.45m, 8.54m, 8.73bm, 9.18m, 9.73w, 10.16w. 11.19w, 11.36w, 11.98w, 12.28w, 12.52w, 12.72m, 12.89w, 13.32m, 14.20i.

The substance yielded a hydrochloride in the form of white crystals, m.p. 298–299° dec. when recrystallized from 10% hydrochloric acid containing some ethanol.

*Anal.* Calcd. for $C_{18}H_{23}ON_4Cl$: C, 62.33; H, 6.68; N, 16.15. Found: C, 62.65; H, 6.75; N, 15.84, 15.70.

Infrared spectrum (Nujol mull): 3.03bm, 3.19m, 3.38i, 3.45i, 5.83m, 6.00i, 6.19m, 6.34i, 6.71w, 6.89i, 7.09m, 7.13sm, 7.30w, 7.46w, 7.88m, 8.00w, 8.01m, 8.33m, 8.39sw, 8.50w, 8.75bw, 9.03bw, 10.14w, 11.20w, 12.13bw, 12.54w, 12.89bm, 14.23bm, 14.35m.

It was advantageous to obtain the purified free base Xc from the purified hydrochloride rather than by the direct methanol recrystallization. The hydrochloride was dissolved in boiling water and the free base was precipitated by addition of a few drops of concentrated ammonium hydroxide, then collected and washed on the filter with water and acetone to give material melting at 254–256° dec.

# Investigations in Heterocycles. XII. The Synthesis of Pyrazolo[1,5-*c*]quinazolines[1]

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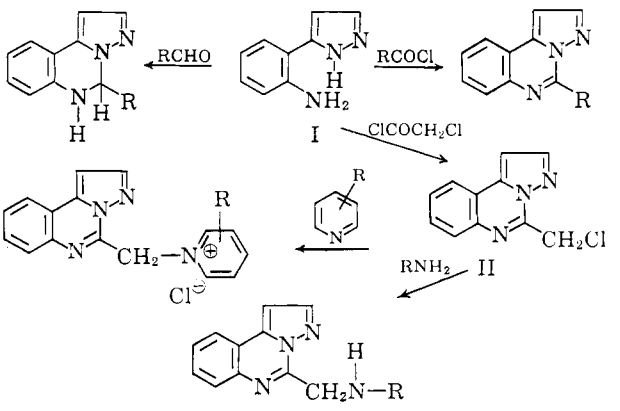
The facile rearrangement of 4-hydroxyquinoline and its derivatives in the presence of excess hydrazine hydrate gives rise to 5(*o*-aminophenyl)pyrazoles. These compounds in turn serve as intermediates in the synthesis of some new heterocycles, pyrazolo[1,5-*c*]quinazolines. The chemical and spectral properties of these substances are discussed.

In a recent review[2] we discussed the application of the intramolecular Mannich reaction and the organic acid ring closure condensations in the synthesis of several new heterocyclic systems; *e.g.*, dihydrobenzothiadiazine 1,1-dioxide, tetrahydro-1,3-benzodiazepines, and indolo[2,3-*a*]quinolizines. The principle therein expounded, *i.e.*, insertion of a one carbon fragment between two hetero atoms to form a ring, has now been extended to include the preparation of other heterocycles. Thus, the synthesis and the chemical and physical properties of pyrazolo[1,5-*c*]quinazolines will be the subject of this report.

The preparation of this new heterocycle has been facilitated by the ready availability of 5(*o*-aminophenyl)-pyrazole (I). This substance was reported recently by Alberti[3] to be obtainable *via* a one-step synthesis. Compound I is similar from a reactivity standpoint to *o*-aminobenzamide. This was indeed manifested by its condensation with aldehydes or acid chlorides, and acid anhydrides. Some of these reactions leading to the synthesis of various pyrazolo[1,5-*c*]quinazolines are outlined in Scheme I and the compounds prepared in this series are listed in Table I.

Condensation of I with excess formic acid under reflux gave a 78% yield of the parent heterocycle (compound 1, Table I). However, when I was allowed to react with excess acetic anhydride under reflux, the sole

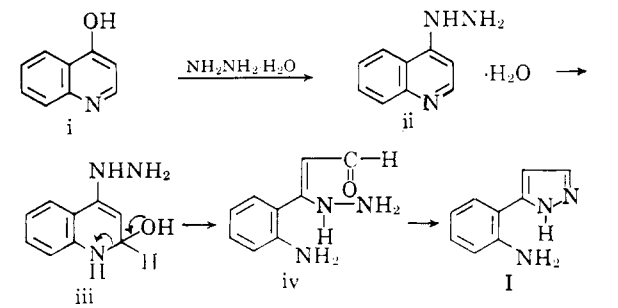



SCHEME I

(1) This subject was discussed in part by G. deStevens in a Symposium lecture on The Chemistry of Nitrogen Heterocycles sponsored by the Medicinal Chemistry Division, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) G. deStevens, *Record Chem. Progr.*, **23**, No. 2, 195 (1962).

(3) G. Alberti, *Gazz. chim. ital.*, **87**, 772 (1957). Although this author did not express a mechanistic rationale for this transformation, it seems more than likely that a pseudo base is generated leading to an $\alpha,\beta$-unsaturated




aldehyde which undergoes intramolecular dehydrative condensation with the hydrazino portion of the molecule to form I.