The Preparation and Properties of Certain Pyridylpyrimidines and Bidiazines as Potential Chelating Agents for Iron(II)[1]

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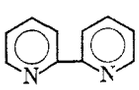
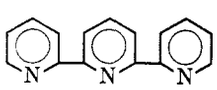
A series of pyridylpyrimidines and bidiazines related to the bidentate ligand 2,2′-bipyridine and the tridentate ligand 2,2′,2″-terpyridine were prepared and their ability to form stable chelates with iron(II) in aqueous alcoholic solution investigated. In general the ϵ_{max} values (visible) of the respective chelates were found to be less than those of the corresponding polypyridines.

The functional groupings N=CC=N (ferroin group) of the bidentate ligand 2,2′-bipyridine (I) and N=CC=NCC=N (terroin group) of the tridentate ligand 2,2′,2″-terpyridine (II) have been shown to be responsible for the characteristic stability and intense coloration of the chelate compounds formed from these ligands and several of the transition metals.[2,3]



I



II

Solutions of many of these chelate compounds absorb visible light in accordance with the Beer–Lambert law over wide ranges of concentration and thus provide a simple method for the quantitative determination of trace amounts of these metals.[4] The molar extinction coefficient (ϵ_{max}) of the chelate at the wavelength of maximum absorption (λ_{max}) may, therefore, be considered a measure of the sensitivity of the ligand for a particular metal.

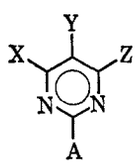
Although many compounds that incorporate a ferroin or terroin group in their structures have been described,[5] pyridylpyrimidines and bidiazines that contain these groups are relatively unknown. We have prepared a number of compounds representative of these heterocyclic systems and determined some of the properties of the chelate compounds formed from these ligands and iron(II) in aqueous alcoholic solution (Tables I and II). The methods employed to synthesize these compounds are outlined in Schemes I–IV.

As indicated, several of the requisite 2-(2-pyridyl)-pyrimidinols (III) and diols VII (Scheme I) were obtained from the condensation of picolinamidine[6] with the appropriately substituted β-keto ester or malonate ester. One of these pyrimidinols (III, R = Py) had been previously prepared by Case and Butte in low yield (8%) employing ethyl picolinoylacetate and picolinamidine prepared *in situ*.[7] We found that this yield could be substantially increased (50%) if the picolinamidine was first isolated and purified.

Bis-2-pyridylpyrimidines (VI, R′ = CH_3O, $C_5H_{10}N$) were obtained on treatment of IV (R = Py) with sodium methoxide and piperidine, respectively. In addition condensation of picolinamidine with the cyclohexanones X (R = H, Py), formylacetone dimethylacetal, and 2-pyridalacetophenone also afforded derivatives of the 2-(2-pyridyl)pyrimidine system (XI, XII, and XIII) for this study. In the case of XIII the reaction was carried out in the presence of excess pyridalacetophenone which served to oxidize the intermediate 4-phenyl-2,6-bis(2-pyridyl)-5,6-dihydropyrimidine to yield XIII. This reaction is analogous to that described for the preparation of 2,4,6-tris(phenyl)-pyrimidine from benzamidine and benzalacetophenone.[8]

TABLE I

SPECTROPHOTOMETRIC DATA FOR THE IRON(II) CHELATES OF THE BIDENTATE AND TRIDENTATE PYRIDYLPYRIMIDINE LIGANDS



Py = 2-pyridyl

Compd	A	X	Y	Z	ϵ_{max}	λ_{max}, mμ	Concn, $M_{Fe^{2+}} \times 10^5$
III	Py	Py	H	OH	10,700	568	2–10
IV	Py	Py	H	Cl	8,150	555	3–10
V	Py	Py	H	H	9,340	540	1–10
V	Py	C_6H_5	H	H	10,400	496	1–5
VI	Py	Py	H	CH_3O	9,600	560	2–10
VI	Py	Py	H	$C_5H_{10}N$	13,900	525	1–5
IX	Py	H	H	H	6,500	514	3–9
IX	Py	H	CH_3	H	6,000	485	2–10
IX	Py	H	C_6H_5	H	3,300	520	3–12
XII	Py	CH_3	H	H	6,750	520	2–10
XIII	Py	Py	H	C_6H_5	24,000	566	1–15
XV	H	Py	H	CH_3	7,250	547	2–10
XV	H	Py	H	C_6H_5	2,400	564	4–20
XV	H	Py	H	Py	6,400	568	1–6

TABLE II

SPECTROPHOTOMETRIC DATA FOR THE IRON(II) CHELATES OF THE BIDENTATE AND TRIDENTATE PYRIDYLQUINAZOLINES AND BIDIAZINE LIGANDS (PY = 2-PYRIDYL)

Compound		ϵ_{max}	λ_{max} mμ	Concn, $M_{Fe^{2+}} \times 10^5$
XI	2-(Py)-5,6,7,8-Tetrahydroquinazoline	6,150	480	2–10
XI	2,4-Bis(Py)-5,6,7,8-tetrahydroquinazoline	10,000	580	2–10
XVIII	2-(Py)-Quinazoline	11,470	442	1–8
XX	2,4-Bis(Py)quinazoline	14,700	658	1–5
XXI	3,3-Bipyridazine	6,350	517	1–8
XXII	4,4′-Bipyrimidine	440	514	...
XXV	Bipyrazine	1,533	518	10–40

(1) This work was supported by a grant from the Committee on Research and Publications of Temple University.

(2) P. Krumholz, *J. Am. Chem. Soc.*, **75**, 2163 (1953).

(3) S. Kirschner, "Advances in the Chemistry of the Coordination Compounds," Macmillan and Co., New York, N. Y., 1961, p 437.

(4) M. L. Moss and M. G. Mellon, *Ind. Eng. Chem.*, **14**, 862 (1942).

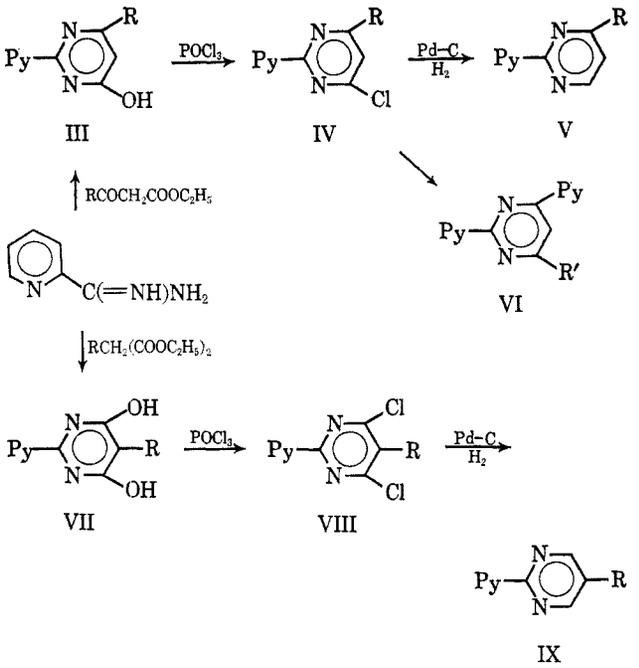
(5) F. H. Case, "A Review of Syntheses of Organic Compounds Containing the Ferroin Group," G. F. Smith Chemical Co., Columbus, Ohio, 1960.

(6) F. C. Schaffer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

(7) F. H. Case and W. Butte, *ibid.*, 4690 (1961).

(8) R. M. Dodson and J. K. Seyler, *ibid.*, **16**, 461 (1951).

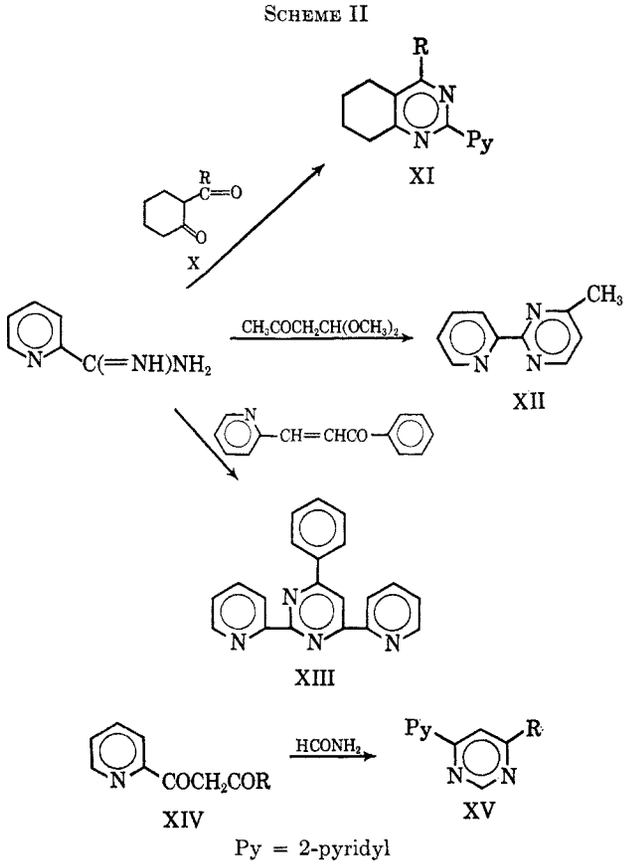
SCHEME I



Py = 2-pyridyl

Since the introduction of a 2-pyridyl substituent into the 4 position of pyrimidine will also yield a compound that contains a ferroin group in its structure, a few 4-(2-pyridyl)pyrimidines (XV, R = CH_3, C_6H_5, and Py) were also prepared for this study. The method we employed to obtain these compounds was essentially that developed by Bredereck.[9] (See Scheme II.)

SCHEME II

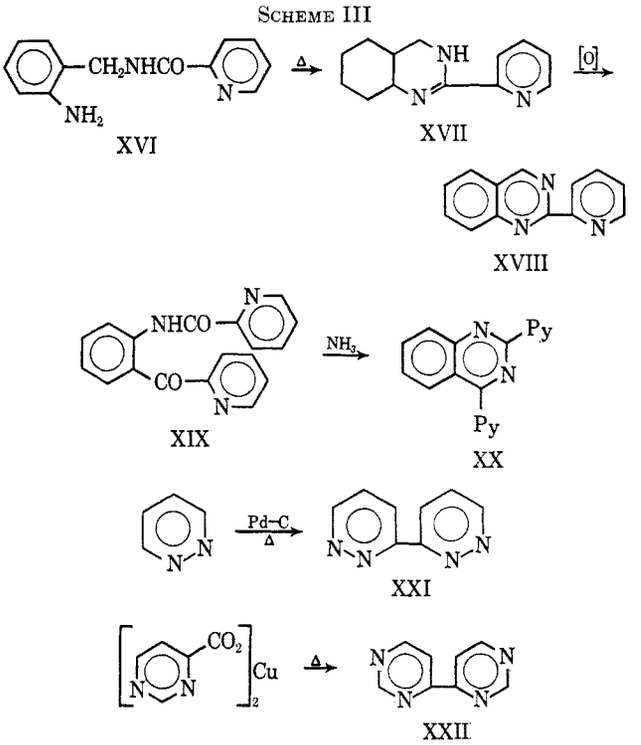


Py = 2-pyridyl

(9) H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

2-(2-Pyridyl)quinazoline (XVIII) was prepared by oxidation of the 2-(2-pyridyl)dihydropyrimidine (XVII) following the method of Elderfield.[10] 2,4-Bis(2-pyridyl)pyrimidine (XX) was readily obtained by prolonged heating of XIX in an ammonium acetate melt saturated with dry ammonia. (See Scheme III.)

SCHEME III



Py = 2-pyridyl

Of the isomeric bipyridazines only 3,3′-bipyridazine (XXI) contains a ferroin group in its structure. This compound was prepared by refluxing pyridazine in the presence of palladium on carbon following a method described by Rapoport for the preparation of biquinolines.[11] Its structure was demonstrated by a molecular weight determination as well as a positive ferroin test.

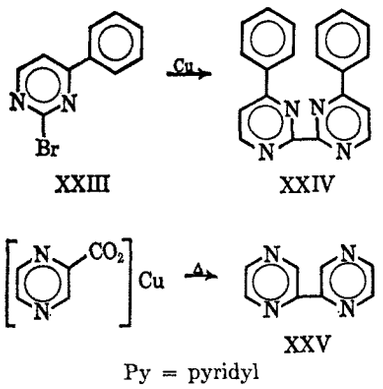
Both 2,2′-bipyrimidine described by Bly and Mellon[12] and 4,4′-bipyrimidine (XXII) contain a ferroin group. We have prepared XXII by pyrolysis of the copper(II) salt of pyrimidine-4-carboxylic acid. In addition, we have also prepared 4,4′-diphenyl-2,2′-bipyrimidine (XXIV) employing an Ullmann reaction on 2-bromo-4-phenylpyrimidine (XXIII). XXIII was obtained from the action of phosphorus oxybromide on 2-hydroxy-4-phenylpyrimidine.[13]

We had also prepared 2,2′-bipyrazine (XXV) by a pyrolysis of the copper(II) salt of pyrazine-2-carboxylic acid (Scheme IV) but unknown to us at the time a similar preparation of XXV was carried out by Lever, *et al.*, and subsequently described.[14]

Rotation of the 2-(2-pyridyl) moiety of V (R = C_5H_4N) about the carbon–carbon bond suggests that

(10) R. E. Elderfield, T. A. Williamson, W. J. Genslen, and C. B. Kremer, *J. Org. Chem.*, **12**, 405 (1947).
(11) H. Rapoport, R. Iwamoto, and J. R. Tretter, *ibid.*, **25**, 372 (1960).
(12) D. D. Bly and M. G. Mellon, *ibid.*, **27**, 2945 (1962).
(13) B. Lythgoe and L. S. Rayner, *J. Chem. Soc.*, 2323 (1951).
(14) A. B. P. Lever, J. Lewis, and R. S. Nyholm, *ibid.*, 1187 (1964).

SCHEME IV

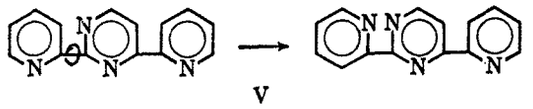


XXIII XXIV

XXV

Py = pyridyl

this compound might function as either a tridentate or a bidentate ligand toward iron(II).



V

On the basis of steric considerations, however, the ferroin group employing the 2-(2-pyridyl) substituent would be preferred to that employing the 4-(2-pyridyl) substituent in the formation of an octahedral chelate compound with iron(II).[15] A spectrophotometric titration of (V, R = C_5H_4N) with iron(II) indicated that the maximum absorption in the visible was obtained when this ligand and iron(II) were present in a ratio of 2 moles of ligand to 1 g-ion of iron(II). These data suggest that the absorbing species was the bis[2,4-bis(2-pyridyl)pyrimidine]iron(II) ion and also that V (R = C_5H_4N) behaves as a tridentate ligand toward iron(II) in solution.

Similarly a multiplicity of chelating groups are available to XX by rotation of the 2-(2-pyridyl) group. However, both of the available ferroin groups are somewhat hindered by adjacent substituents for the formation of an octahedral iron(II) chelate compound.[15] A spectrophotometric titration of XX with iron(II) suggests that this ligand also behaves as a tridentate ligand toward iron(II) employing the terroin group rather than a ferroin group in chelate formation, since the maximum absorption in the visible was obtained when the ligand and iron(II) were present in a ratio of 2 moles of the ligand to 1 g-ion of iron(II).

Compound XV (R = C_5H_4N) contains two equivalent ferroin groups in its structure. However, a spectrophotometric titration of this ligand with iron(II) indicates that the maximum absorption in the visible is reached when the ligand and the iron(II) are present in a ratio of 3 moles of (XV, R = C_5H_4N) to 1 g-ion of iron(II). These data suggest that the absorbing species is the tris[4,6-bis(2-pyridyl)pyrimidine]iron(II) ion and, therefore, only one of the ferroin groups of the ligand is employed in chelate formation. In addition, these data are in accord with those reported for related systems, such as 2,2-bipyrimidine[16] and the bis(2-pyridyl)pyrazines.[17]

The ϵ_{max} values and the respective λ_{max} values for the iron(II) chelate compounds prepared for this study are given in Tables I and II. The ϵ_{max} values for the iron(II) chelates of IX (R = H) and V (R = C_5H_4N) are both less than those of their pyridine counterparts, 2,2′-bipyridine (8600)[4] and 2,2′,2″-terpyridine (12,500).[4] Substitution of a phenyl group in the 4 position of the pyrimidine rings of these ligands (V, R = C_6H_5 and XIII) resulted in large increases in the respective ϵ_{max} values of the chelates.

These results parallel those observed when I and II are similarly substituted.[18,19] Interestingly the ϵ_{max} of the iron(II) chelate of IX (R = H) was greatly reduced by substitution of a phenyl group in the 5 position (IX, R = C_6H_5).

The ϵ_{max} values of the iron(II) chelates of XVIII and XX are also substantially increased over those of the parent compounds (IX, R = H) and (V, R = C_5H_4N). These data appear to be consistent with the increase of the ϵ_{max} value reported for the iron(II) chelate of 1-(2-pyridyl)isoquinoline (11,600)[20] over that of 2,2′-bipyridine.

Alkyl substitution of 2-(2-pyridyl)pyrimidine (V, R = CH_3, IX, R = CH_3, and XI, R = H) and 2,4-bis-(2-pyridyl)pyrimidine (XI, R = C_5H_4N) resulted in relatively minor effects on the ϵ_{max} values of the iron(II) chelates of these ligands (IX, R = H, and V, R = C_5H_4N). In the case of XV (R = CH_3), however, the ϵ_{max} of the iron(II) chelate far exceeds that of XV (R = C_6H_5) and is also greater than that of XV (R = C_5H_4N).

Substitution of the 6 position of the pyrimidine ring of V (R = C_5H_4N) by electron-donating and -withdrawing groups should affect the basicity of the pyrimidine nitrogen atom of the terroin group and consequently the stability of the iron(II) chelate in solution. Some evidence for these effects is found by comparing the ϵ_{max} values for the iron(II) chelates of III, IV (R = C_5H_4N), and VI (R′ = CH_3O and $C_5H_{10}N$).

In general we found the ϵ_{max} (visible) values for the iron(II) chelates of the bidiazines prepared for this study (XXI, XXII, XXIV, and XXV) to be far less than that of 2,2′-bipyridine. In fact the visible absorption of the iron(II) chelate of XXIV was so weak that we could obtain no meaningful value for the ϵ_{max} even in saturated solutions of XXIV. These weaker ϵ_{max} values may be in part a reflection of the weaker basicities of the respective bidiazines.

Experimental Section

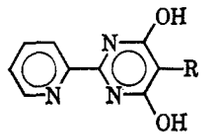
The spectrophotometric data were obtained employing the Perkin-Elmer 202 spectrophotometer. The solvent system employed for these determinations was 70% ethanol and 30% water. Except for XXI, the absorption maxima for the respective iron(II) chelates was constant over at least pH 4–7 and consequently the spectrophotometric determinations were carried out in solutions buffered to pH 5.3. In the case of XXI the maximum persisted at least over pH 5–7.2 and the determinations were carried out at pH 6.5. The respective ϵ_{max} values for the iron(II) chelates were with one exception (XXII) obtained from Beer's law plots of absorbance *vs.* concentration of iron(II) in the presence of 10% excess of ligand. These concentration ranges are given in Tables I and II. In the case of XXII the ϵ_{max} could only be obtained in the presence of a large excess of ligand. The ϵ_{max} value given in Table II was obtained employing a 50-fold excess of XXII.

4,6-Dihydroxy-2-(2-pyridyl)pyrimidines (VII, R = H, CH_3, and C_6H_5).—These compounds were obtained by condensing 0.1 *M*

(15) H. Irving and A. Hampton, *J. Chem. Soc.*, 430 (1955).
(16) D. D. Bly and M. G. Mellon, *Anal. Chem.*, **35**, 1386 (1963).
(17) H. Goodwin and F. Lions, *J. Am. Chem. Soc.*, **81**, 6415 (1959).
(18) A. A. Schilt and G. F. Smith, *Anal. Chim. Acta*, **16**, 401 (1957).
(19) D. H. Wilkins and G. F. Smith, *ibid.*, **9**, 338 (1953).
(20) R. F. Knott and J. G. Breckenridge, *Can. J. Chem.*, **32**, 512 (1954).

TABLE III

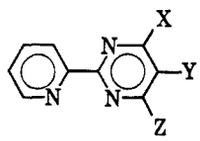
2-(2-PYRIDYL)-4,6-PYRIMIDINEDIOLS



Compd	R	Crystn solvent	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
VII	H	Ethanol	62	264–265	57.14	3.73	22.21	57.44	3.89	21.96
VII	CH_3	Ethanol	64	270–272	59.11	4.46	20.68	59.44	4.77	20.57
VII	C_6H_5	Ethanol	61	300–301	67.92	4.18	15.84	67.81	4.39	15.90

TABLE IV

4-CHLORO- AND 4,6-DICHLORO-2-(2-PYRIDYL)PYRIMIDINES

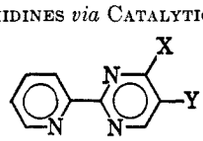


Py = 2-pyridyl

Compd	X	Y	Z	Time min	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
VIII	Cl	H	Cl	60	Cyclohexane	153–154	63	47.82	2.23	18.59	48.04	2.23	18.48
VIII	Cl	CH_3	Cl	60	Hexane	149–150	47	50.02	2.94	17.50	50.33	3.04	17.49
VIII	Cl	C_6H_5	Cl	90	Cyclohexane	156–157	42	59.62	3.00	13.91	59.66	2.92	13.68
IV	Cl	H	C_6H_5	60	Hexane	107–108	58	67.29	3.77	15.70	67.37	3.92	15.42
IV	Cl	H	Py	120	Hexane	146–147	53	62.58	3.38	20.85	62.67	3.35	20.77

TABLE V

2-(2-PYRIDYL)PYRIMIDINES *via* CATALYTIC DEHALOGENATION



Py = 2-pyridyl

Compd	X	Y	Crystn solvent	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
IX[a]	H	H	Ethanol	52[b]	189–190	46.64	2.61	21.76	46.93	2.90	21.40
IX	H	CH_3	Hexane	39	79–80	70.16	5.30	24.55	70.05	5.41	24.74
IX	H	C_6H_5	Benzene	37	159–160	77.23	4.75	18.01	77.13	4.69	18.02
V	C_6H_5	H	Ether	40	76–77	77.23	4.75	18.01	77.34	4.82	18.08
V	Py	H	Ethanol	44	103–104	71.78	4.30	23.92	71.98	4.54	23.81

[a] Picrate salt except where noted. [b] Free base.

diethyl malonate, diethyl methylmalonate, and diethyl phenylmalonate, respectively, with 0.1 *M* picolinamidine in 400 ml of absolute ethanol containing 0.26 g-atom of sodium. In each case the mixture was refluxed for 3 hr, cooled, and the alcohol was distilled *in vacuo* until the reaction volume was approximately 100 ml. The mixtures were made slightly acidic with hydrochloric acid and diluted with 100 ml of water to precipitate the crude products. The respective crystallizing solvents, melting points, etc., are given in Table III.

4-Chloro- and 4,6-Dichloro-2-(2-pyridyl)pyrimidines (IV and VIII).—These compounds were obtained by heating one part by weight of the corresponding pyrimidinols or pyrimidinediols (VII, R = H, CH_3, and C_6H_5), 4-hydroxy-6-phenyl-2-(2-pyridyl)pyrimidine,[21] and III (R = C_5H_4N) in ten parts by weight of refluxing phosphorus oxychloride. On cooling the excess phosphorus oxychloride was distilled *in vacuo* and the residues were made alkaline with 10% sodium hydroxide and extracted with ether. The ethereal extracts were dried over magnesium sulfate, filtered, and the ether was removed *in vacuo* to yield the crude products. The respective reaction times, crystallizing solvents, and analytical data are given in Table IV.

2-(2-Pyridyl)pyrimidines (IX, R = H, CH_3, and C_6H_5; V, R = C_6H_5 and C_5H_4N).—These compounds were obtained by the catalytic dehalogenation of the respective chloro- and dichloropyrimidines (IV, R = H, CH_3, and C_6H_5, and VIII, R = C_6H_5 and C_5H_4N) over palladium on carbon (5%) in ethanolic solution containing sufficient sodium acetate to neutralize the liberated hydrogen chloride. The initial hydrogen pressures were 30 psi. The mixtures were filtered, the alcohol was distilled *in vacuo*, and the residues were extracted with ether. The ethereal extracts were dried over magnesium sulfate, filtered, and the ether was removed *in vacuo* to yield the crude products. Compound IX (R = H) was obtained as a hygroscopic oil which was distilled at 130–131° (0.75 mm) and a sample was converted to a picrate salt in alcohol for characterization. The yields, crystallizing solvents, etc., are given in Table V.

4-Hydroxy-2,6-bis(2-pyridyl)pyrimidine (III).—A mixture of 19.3 g of ethyl picolinoyl acetate, 4 g of sodium hydroxide, 15.7 g of picolinamidine hydrochloride, 10 ml of water, and 200 ml of ethanol was stirred for 3 days at 25°. The reaction mixture was concentrated to 100 ml and then diluted with 100 ml of water. The precipitate was crystallized from alcohol to give 12.5 g (50%) of product, mp 219–220°.

Anal. Calcd for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 67.22; H, 4.19; N, 22.70.

4-Methyl-2-(2-pyridyl)pyrimidine (XII).—A solution of 0.1 *M* picolinamidine, 0.1 *M* formylacetone dimethyl acetal, and 2.5 g of sodium in 350 ml of absolute ethanol was refluxed for 3 hr. After cooling the solution was acidified with acetic acid and concentrated *in vacuo* to an oily residue. The residue was

(21) A. Pinner, *Ber.*, **22**, 1612 (1889).

dissolved in 30 ml of water and continuously extracted with chloroform for 30 hr. The chloroform extract was dried over magnesium sulfate, filtered, and the chloroform was removed *in vacuo*. The crude product was crystallized from ether to give 10.3 g (60%) of pure XII, mp 69–70°.

Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 69.97; H, 5.38; N, 24.71.

4-Phenyl-2,6-bis(2-pyridyl)pyrimidine (XIII).—A solution of 0.025 *M* picolinamidine hydrochloride, 0.05 *M* pyridalacetophenone,[22] and 0.05 *M* potassium hydroxide in 100 ml of ethanol was refluxed for 3 hr. After cooling the solution was concentrated to approximately 40 ml and diluted with 100 ml of water. The precipitate was crystallized from alcohol to give 5.4 g (70%) of product, mp 207–208°.

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.59; H, 4.67; N, 18.01.

2-(2-Pyridyl)-5,6,7,8-tetrahydroquinazoline (XI, R = H).—To 30 ml of absolute ethanol were added 3.2 g of 2-formylcyclohexanone,[23] 3.9 g of picolinamidine hydrochloride, and 2 g of piperidine. The mixture was refluxed for 2 hr and cooled. The ethanol was removed *in vacuo* and the residual gum was washed with water and extracted with ether. The ethereal extracts were dried over magnesium sulfate, filtered, and the ether was removed *in vacuo*. The residue was crystallized from cyclohexanone to yield 1.2 g (24%) of product, mp 82–83°.

Anal. Calcd for $C_{13}H_{13}N_3$: C, 73.91; H, 6.20; N, 19.89. Found: C, 73.81; H, 6.27; N, 19.66.

1,3-Bis(2-pyridyl)-1,3-propanedione (XIV, R = C_5H_4N).—To a mixture of 14.4 g of sodium methoxide and 250 ml of anhydrous ether were added in succession 34.3 g of methyl picolinate and 68.5 g of 2-acetylpyridine each dissolved in 125 ml of anhydrous ether. The mixture was stirred and refluxed for 2 hr. After cooling, 15 g of glacial acetic acid was added and the mixture was filtered. The solvents were removed *in vacuo* and the residue was crystallized from ether to give 35.6 g (63%) of product, mp 105–106°.

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.87; H, 4.54; N, 12.50.

4-Phenyl-6-(2-pyridyl)pyrimidine (XV, R = C_6H_5).—A mixture of 4 g of 1-phenyl-3-(2-pyridyl)-1,3-propanedione[24] and 50 g of formamide was gently refluxed for 6 hr. The mixture was concentrated to one-half of the original volume *in vacuo* and diluted with 100 ml of water. The oily precipitate was washed several times with water and extracted with ether. The ethereal extract was dried over magnesium sulfate, filtered, and the ether was removed *in vacuo*. The residue was sublimed at 90° (10 μ) and the crude sublimate was crystallized from ether to yield 1.1 g (28%) of product, mp 102–103°.

Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.16; H, 4.72; N, 17.80.

4,6-Bis(2-pyridyl)pyrimidine (XV, R = C_5H_4N).—The preparation of this compound was carried out exactly as described for XV (R = C_6H_5) employing 4.1 g of 1,3-bis(2-pyridyl)-1,3-propanedione in place of 1-phenyl-3-(2-pyridyl)-1,3-propanedione. The crude material was sublimed at 90° (10 μ) and crystallized from ether to give 1.2 g (30%) of product, mp 113–114°.

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.71; H, 4.34; N, 23.82.

4-Methyl-6-(2-pyridyl)pyrimidine (XV, R = CH_3).—A solution of 6.8 g of 1-(2-pyridyl)-1,3-butanedione in 75 ml of formamide was gently refluxed for 6 hr. The reaction mixture was concentrated *in vacuo* to an oily residue. The residue was treated with 20 ml of water and continuously extracted with chloroform for 3 days. The chloroform extracts were dried over magnesium sulfate, filtered, and the chloroform was distilled *in vacuo*. The residue was crystallized from petroleum ether (bp 30–60°) to give 2.1 g of product (25%), mp 39–40°.

Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.55. Found: C, 70.03; H, 5.26; N, 24.29.

2-Picolinoylcyclohexanone (X, R = C_5H_4N).—A solution of 13.7 g of methyl picolinate in 25 ml of benzene was added with stirring to a suspension of 2.4 g of sodium hydride in benzene followed by a solution of 4.8 g of cyclohexanone in 25 ml of benzene. The mixture was stirred at reflux for 6 hr. On cooling, 10 ml of methanol followed by 10 ml of water were added dropwise. Acetic acid (3 g) in 10 ml of water was added and the organic layer was separated, washed with water, and dried over magnesium sulfate. The solution was filtered and the benzene was removed *in vacuo*. The residue was distilled at 135–137° (1 mm). The distillate crystallized on standing to give 2.8 g (28%) of product, mp 70–73°.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45. Found: C, 71.24; H, 6.80.

2,4-Bis(2-pyridyl)-5,6,7,8-tetrahydroquinazoline (XI, R = C_5H_4N).—A mixture of 2 g of 2-picolinoylcyclohexanone, 1.6 g of picolinamidine hydrochloride, 0.8 g of piperidine, and 25 ml of absolute ethanol was refluxed for 3 hr. Water (25 ml) was then added and the oily precipitate was extracted with ether. The ethereal extracts were dried over magnesium sulfate, filtered, and the ether was distilled *in vacuo*. The residue was crystallized from cyclohexanone to give 1 g (36%) of product, mp 136–137°.

Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.67; H, 5.80; N, 19.19.

4-Methoxy-2,6-bis(2-pyridyl)pyrimidine (VI, R′ = CH_3O).—A solution of 1.3 g of 4-chloro-2,6-bis(2-pyridyl)pyrimidine, 1 g of sodium methoxide, and 20 ml of methanol was refluxed for 2 hr and then diluted with 20 ml of water. The precipitate was crystallized from ether to give 0.97 g (74%) of product, mp 139–140°.

Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.30; H, 4.62. N, 21.23.

4-(1-Piperidyl)-2,6-bis(2-pyridyl)pyrimidine (V, R′ = C_5H_4N).—A solution of 1.3 g of 4-chloro-2,6-bis(2-pyridyl)pyrimidine, 5 ml of piperidine, and 20 ml of methanol was refluxed for 2 hr. The solvents were removed *in vacuo* and the residue was extracted with cyclohexane. The extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was crystallized from cyclohexane to give 0.6 g (38%) of product, mp 179–180°.

Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07. Found: C, 72.15; H, 6.10; N, 21.81.

2,4-Bis(2-pyridyl)quinazoline (XX).—A solution of 2 g of 2-aminophenyl-2-pyridylketone[25] in 50 ml of dry dioxane was added at 10° to a 20% excess of the mixed anhydride obtained from picolinic acid and ethylchloroformate by the method of Rinderknecht.[26] The mixture was stirred for 2 hr while the temperature was allowed to rise to 25°. The volatile material was removed *in vacuo* and the residue was washed with water and dried. The crude N-(2-picolinoylphenyl)picolinamide (XIX) was mixed with 15 g of ammonium acetate and heated for 6 hr at 165° while a stream of dry ammonia gas was passed through the melt. The mixture was cooled, washed with water, and extracted with cyclohexane. The cyclohexane extracts were dried over magnesium sulfate, filtered, and concentrated. The precipitate was again crystallized from cyclohexane to give 1.5 g (54%) of product, mp 139–140°.

Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.34; H, 4.39; N, 19.72.

N-(2-Aminobenzyl)picolinamide (XVI).—A solution of 15.2 g of 2-nitrobenzylamine[27] in 200 ml of dry dioxane was added at 10° to a solution of the mixed anhydride (20% excess) of picolinic acid and ethylchloroformate prepared by the method of Rinderknecht.[26] The mixture was stirred for 2 hr while the temperature was allowed to rise to 27°. It was then filtered and the filtrate was evaporated to dryness *in vacuo* to give 12.9 g of crude N-(2-nitrobenzyl)picolinamide. A small sample, crystallized from ether (mp 97–98°), was analyzed.

Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.34. Found: C, 61.00; H, 4.51; N, 15.99.

The N-(2-nitrobenzyl)picolinamide (12 g) was dissolved in 100 ml of ethanol and reduced over Raney nickel at 40 psi (27°). The mixture, after filtration and concentration, precipitated 4.5 g (40%) of XII, mp 115–116°.

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77. Found: C, 68.51; H, 6.11.

2-(2-Pyridyl)quinazoline (XVIII).—N-(2-Aminobenzyl)picolinamide (10 g) was heated for 6 hr at 250–280°. After cooling the residue was extracted with boiling hexane. The extracts were filtered and the hexane was distilled *in vacuo* to give crude 2-(2-pyridyl)-3,4-dihydroquinazoline (XVII) which was oxidized by the method of Elderfield[10] to give 0.62 g (6%) of product crystallizing from hexane, mp 86–87°.

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Anal. Calcd for $C_{13}H_9N_3$: C, 75.34; H, 4.38. Found: C, 75.52; H, 4.43.

2,2'-Bipyrazine (XXV).—Pyrazine carboxylic acid (12.4 g) was dissolved in a slight excess of aqueous ammonia and the solution was evaporated to dryness. The residue was added to a saturated solution of cupric acetate and allowed to stand overnight. The crude precipitated copper(II) salt of the pyrazine carboxylic acid was filtered and dried. Pyrolysis of the salt was carried out at atmospheric pressure in a short-path still and yielded 0.55 g (7%) of product crystallizing from hexane, mp 183–184°.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82. Found: C, 61.08; H, 3.80.

4,4'-Bipyrimidine (XXII).—The preparation of XXII was carried out in exactly the same manner as that employed for XXV. From 12.4 g of pyrimidine-4-carboxylic acid was obtained 0.39 g (5%) of product, mp 203–204°.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82. Found: C, 60.86; H, 3.99.

3,3'-Bipyridazine (XXI).—A mixture of 8 g of pyridazine and 0.8 g of 5% palladium on carbon was stirred and refluxed for 24 hr. The mixture was cooled, diluted with 25 ml of chloroform, and filtered. The spent catalyst was twice extracted with 25 ml of chloroform. The filtrate and chloroform extracts were combined and the volatile material was removed *in vacuo*. The residue of crude XXI was sublimed at 130° (50 μ) and crystallized from ether to give 0.79 g (10%) of product, mp 224–226°. The molecular weight was found to be 155 (osmometer); calculated molecular weight was 158.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.43. Found: C, 61.08; H, 3.94; N, 35.09.

2-Bromo-4-phenylpyrimidine (XXIII).—A mixture of 8.6 g of 2-hydroxy-4-phenylpyrimidine and 40 g of phosphorus oxybromide was heated at 150° for 4 hr. The mixture was cooled and treated with 300 g of ice. The aqueous solution was made alkaline with sodium hydroxide solution (10°) and extracted with ether. The ethereal extracts were dried over magnesium sulfate, filtered and the ether was removed *in vacuo*. The residue was crystallized from benzene to give 5.8 g (58%) of product, mp 84–85°.

Anal. Calcd for $C_{10}H_7BrN_2$: C, 51.06; H, 3.11. Found: C, 51.31; H, 3.20.

4,4'-Diphenyl-2,2'-bipyrimidine (XXIV).—A mixture of 4.7 g of 2-bromo-4-phenylpyrimidine, 5 g of activated copper powder, and 75 ml of dimethylformamide was stirred and heated at reflux for 6 hr. The dimethylformamide was removed *in vacuo* and the residue was washed several times with 50 ml of aqueous ammonia containing 5% of potassium cyanide. The dry solid was extracted with chloroform. The extracts were dried over magnesium sulfate, filtered, and the chloroform was removed *in vacuo*. The residue was crystallized from ether to give 0.62 g (20%) of product, mp 155–156°.

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55. Found: C, 77.60; H, 4.73.

Registry No.—III, 10239-68-6; IV (Z = C_6H_5), 10198-67-1; IV (Z = Py), 10198-68-2; V (X = C_6H_5), 10198-69-3; V (X = C_6H_5) picrate, 10198-70-6; V (X = Py), 10198-71-7; V (X = Py) picrate, 10198-72-8; VI (R′ = CH_3O), 10198-73-9; VII (R = H), 10198-74-0; VII (R = CH_3), 10198-75-1; VII (R = C_6H_5), 10198-76-2; VIII (Y = H), 10235-65-1; VIII (Y = CH_3), 10198-77-3; VIII (Y = C_6H_5), 10198-78-4; IX (Y = CH_3), 10198-79-5; IX (Y = CH_3) picrate, 10198-80-8; IX (Y = C_6H_5), 10198-81-9; IX (Y = C_6H_5) picrate, 10198-82-0; IX (Y = H), 10198-83-1; X (R = C_5H_4N), 10198-84-2; XI (R = H), 10198-85-3; XI (R = C_5H_4N), 10198-86-4; XII, 10198-87-5; XIII, 10198-88-6; XIV (R = C_5H_4N), 10198-89-7; XV (R = C_6H_5), 10198-90-0; XV (R = C_5H_4N), 10198-91-1; XV (R = CH_3), 10198-92-2; XVI, 10198-93-3; XVIII, 10198-94-4; XX, 10198-95-5; XXI, 10198-96-6; XXII, 2426-94-0; XXIII, 10198-98-8; XXIV, 10198-99-9; XXV, 10199-00-5; 4-(1-piperidyl)-2,6-bis(2-pyridyl)pyrimidine, 10199-01-6.

Synthesis and Transformations of a Heptacyclic Triazoline Derived from Pseudodiosgenin

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Displacement of the *p*-toluenesulfonate function of pseudodiosgenin 27-*p*-toluenesulfonate with potassium azide in dimethylformamide was followed by a 1,3-dipolar cycloaddition to the enol ether olefinic bond of ring E to furnish a triazoline derivative. Protonation of the triazoline in methanol solution led to abrupt evolution of nitrogen with genesis of a secondary amino methyl ketal. Transformation products of the methyl ketal include the hemiketal, the ethyl ketal, an enol ether tertiary amide originating from hemiketal dehydration, and a 16β-hydroxy acetylamino ketone resulting from opening of the ketal ring system.

The versatile pseudodiosgenin 27-*p*-toluenesulfonate (**1**),[1] prepared in 80% yield by selective hydrolysis of the 3β-homoallylic ester function of pseudodiosgenin 3β,27-di-*p*-toluenesulfonate, has proved useful as an intermediate in the synthesis of solasodine,[2] N-methylsolasodine,[3] a diosgenin ring-F thia counterpart,[1] and the novel hexacyclic hemiketal **6** arising from participation of the ring-E enol ether olefinic bond in a solvolytic ring closure.[4] In these, and in related transformations, *p*-toluenesulfonate displacement has been shown to proceed normally, without side-chain rearrangement through a 1,2-hydrogen migration.

When **1** was allowed to react with potassium azide in dimethylformamide at 100° during 50 hr, rods melting at 224–230° with brisk ebullition were produced in 85% yield. The high melting point, accompanied by escape of nitrogen, together with absence of the enol ether absorption band from the infrared spectrum, inferred that tosylate displacement by azide ion had been followed by a 1,3-dipolar cycloaddition[5] to the dihydrofuranoid olefinic bond of ring E, affording the heptacyclic triazoline (**2**).[6]

Acidification of a methanolic suspension of **2** with hydrochloric acid led to prompt dissolution with evolvement of nitrogen and thereafter to rapid crystal-

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(2) F. C. Uhle, *J. Am. Chem. Soc.*, **83**, 1460 (1961).
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(5) For discussion of the concept of 1,3-dipolar cycloaddition, with a comprehensive review of examples, see R. Huisgen, *Angew. Chem.*, **75**, 604, 742 (1963); *Angew. Chem. Intern. Ed. Engl.*, **2**, 565, 633 (1963).

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