column eluting with chloroform to give recovered **2** (0.32 g, 32% recovery) and 4-azabishomoadamantan-5-one (**3**) (0.58 g, 58%) as colorless crystals from acetone: mp 184–185°; ir (KBr) 3440, 3240, 3140, 3000, and 1635 cm^{-1}; nmr ($CDCl_3$) τ 2.95 (br s, 1, NH), 3.52 (q, 1, J = 7.5 Hz, C_3 methine, t in $CDCl_3$–D_2O), 7.34 (d, 2, J = 3.7 Hz, C_6 methylene), and 7.48–8.85 (m, 13, other ring protons); mass spectrum m/e (rel intensity) 179 (M^+, 100), 164 (20), and 151 (50).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.36; H, 9.47; N, 7.89.

B. With Sulfuric Acid.—A solution of **2** (0.20 g, 1.3 mmol) in 85% (v/v) sulfuric acid (6.5 ml) was heated at 110° for 12 min. The cooled solution was poured onto ice–water (20 ml), neutralized with solid sodium bicarbonate, and extracted with chloroform (five 20-ml portions). The washed and dried (Na_2SO_4) extract was evaporated to give a solid residue which was purified on a silica gel column, eluting with chloroform to afford a 1:4 mixture of the lactams **3** and **4** (0.12 g, 60%).

Tetrazolo[4,5-*d*]-4-azabishomoadamantane (5).—To a solution of phosphorus pentachloride (0.20 g, 0.96 mmol) in chloroform (2 ml) was added a solution of **3** (0.20 g, 1.1 mmol) in chloroform (2 ml) with stirring at room temperature. After stirring was continued for 1 day, a mixture of sodium azide (0.20 g, 3.1 mmol) and sulfuric acid (0.1 ml) in benzene (10 ml) was added to the mixture. The resulting mixture was stirred for 10 hr at room temperature, basified with 10% aqueous potassium hydroxide, and extracted with chloroform (five 30-ml portions). The washed and dried (Na_2SO_4) extract was evaporated to give a solid residue which was purified on a silica gel column, eluting with chloroform to afford the tetrazole **5** as colorless crystals from acetone: mp 173–174°; ir (KBr) 1530 cm^{-1}; mass spectrum m/e (rel intensity) 204 (M^+, 20), 176 (15), 163 (30), and 149 (100).

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.49; H, 8.01; N, 27.14.

Schmidt Reaction of Homoadamantan-4-one (1). A. In CH_3SO_3H.—To an ice-cooled solution of **1** (0.50 g, 3.0 mmol) in CH_3SO_3H (5 ml) was added portionwise solid sodium azide (0.20 g, 3.1 mmol) during 4 hr with stirring. After stirring was continued for an additional 20 hr, the mixture was poured onto ice–water (30 ml), and the resulting mixture was neutralized with solid sodium bicarbonate and extracted with chloroform (five 30-ml portions). Work-up in the usual way afforded a solid product which was purified on a silica gel column, eluting with chloroform to give recovered **1** (0.145 g, 29% recovery), a 1:1 mixture of the tetrazoles **5** and **6** (0.30 g, 48%), mp 188–189°, and a 1:1 mixture of the lactams **3** and **4** (0.040 g, 7%), mp 153–160°.

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.44; H, 8.00; N, 27.04. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.40; H, 9.57; N, 7.83.

A similar reaction of **1** (0.50 g, 3.0 mmol) with sodium azide (0.41 g, 6.3 mmol) in CH_3SO_3H (8 ml) afforded a 1:1 mixture of the tetrazoles **5** and **6** (0.58 g, 93.5%).

B. In CH_3SO_3H–AcOH.—A similar reaction of **1** (0.50 g, 3.0 mmol) with sodium azide (0.20 g, 3.1 mmol) in CH_3SO_3H (2 ml)–AcOH (2 ml) and work-up as above afforded the tetrazole mixture (0.15 g, 24%), the lactam mixture (0.19 g, 34%), and recovered **1** (0.085 g, 17% recovery).

Registry No.—**2**, 26770-89-8; **3**, 29863-86-3; **4**, 29863-87-4; **5**, 29863-88-5; **6**, 29863-89-6.

Pyridazines. XXXVII. Pyrimido[1,2-*b*]pyridazines

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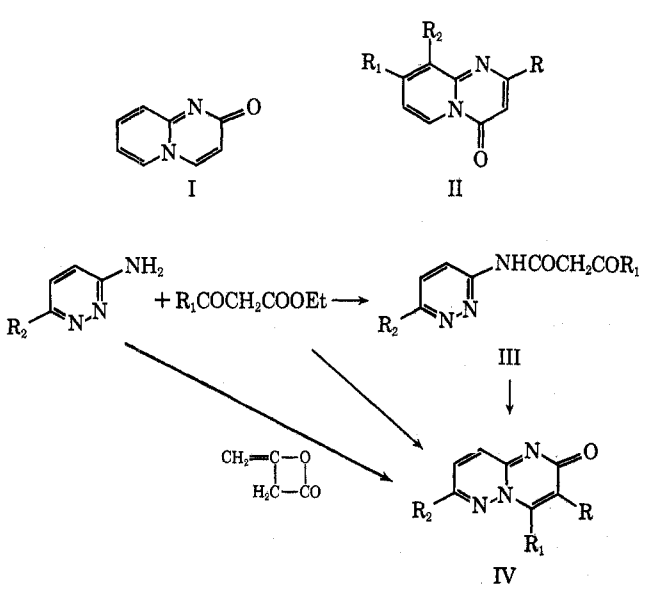
3-Aminopyridazines condense with 1,3-dicarbonyl compounds in polyphosphoric acid to give pyrimido[1,2-*b*]-pyridazines. With β-keto esters pyrimido[1,2-*b*]pyridazin-2-ones are formed, in contrast to 2-aminopyridines which give pyrido[1,2-*a*]pyrimidin-4-ones.

The intriguing structural problem concerning condensation products of amino heterocycles with β-keto esters and related compounds has recently received further interest. In the pyridine series, the controversy regarding the bicyclic products as pyrido[1,2-*a*]-pyrimidin-2-ones (I) or pyrido[1,2-*a*]pyrimidin-4-ones (II) has been solved in favor of the latter ones.[1] The 2-ones were prepared by cyclization of the addition products of the Michael type, formed from aminopyridines and acetylenic compounds.[2] Moreover, mechanism for the formation of 4-ones has been discussed[3] and the reaction was applied to 2-aminothiazoles.[4]



We have extended the reaction to 3-aminopyridazines and with several β-keto esters, derivatives of the recently described pyrimido[1,2-*b*]pyridazine system[5,6] were obtained. 3-Aminopyridazines do not condense with β-keto esters to acylamino derivatives III unless a base, such as triethylamine, is added. On the other hand, the formation of crotonates as intermediates is very unlikely. 3-Acetoacetylaminopyridazine, when heated in polyphosphoric acid (PPA), afforded 4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = Me) which can be obtained also from 3-aminopyridazine and diketene or in a straightforward

(1) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," part II, Interscience, New York, N. Y., 1961, p 1141.
(2) J. G. Wilson and W. Bottomley, *J. Heterocycl. Chem.*, **4**, 360 (1967).
(3) M. Shur and S. S. Israelstam, *J. Org. Chem.*, **33**, 3015 (1968).
(4) G. T. F. Galasko and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **22**, 121 (1969).
(5) B. Stanovnik and M. Tišler, *Tetrahedron Lett.*, 33 (1968).
(6) S. Ostovernšik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **41**, 135 (1969).

TABLE I

π BOND ORDERS FOR THE PYRIMIDINE PART

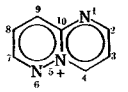
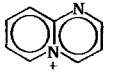
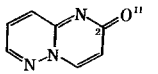
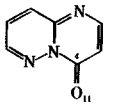
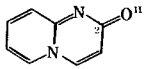
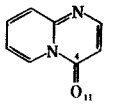
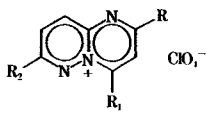
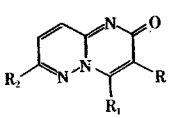
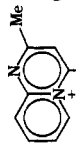
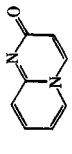
Bond						
1–2	0.683	0.703	0.499	0.651	0.505	0.639
2–3	0.612	0.583	0.485	0.661	0.489	0.663
3–4	0.715	0.761	0.806	0.492	0.814	0.542
4–5	0.497	0.409	0.416	0.371	0.386	0.321
2–11			0.630		0.618	
4–11				0.682		0.727

TABLE II

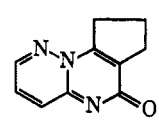
NMR DATA

	Registry no.	H_2	H_3	H_4	H_7	H_8	H_9	J_{23}	J_{34}	J_{24}	J_{78}	J_{89}	J_{79}	J_{49}	2Me	4Me	$J_{3,4Me}$
																	
R = R_1 = R_2 = H[a]	30247-51-9	0.21 (dd)	1.52 (dd)	0.0 (ddd)	0.34 (dd)	1.48 (dd)	0.97 (ddd)	4.5	6.7	1.8	4.5	9.4	1.8	0.9			
R = R_2 = H; R_1 = Me[a]	30247-52-0	0.45 (d)	1.54 (dd)		0.42 (dd)	1.66 (dd)	1.11 (dd)	4.2			4.3	9.0	1.8			6.96 (d)	0.8
R = R_1 = Me; R_2 = H[a]	30318-64-0		1.62 (q)		0.41 (dd)	1.52 (dd)	1.17 (dd)				4.5	9.2	1.8		7.08 (s)	6.95 (d)	0.9
R = Me; R_1 = Ph; R_2 = H[a]	30247-53-1		1.57 (s)		0.59 (dd)	1.60 (dd)	1.12 (dd)				4.2	9.0	1.8		7.03 (s)	2.30 (m, Ph)	
R = R_1 = Me; R_2 = Cl[a]	30247-54-2		1.70 (q)			1.48 (d)	1.18 (d)					9.0			7.13 (s)	7.07 (d)	0.4
																	
R = R_1 = R_2 = H[b]	30247-55-3		3.36 (d)	1.78 (d)	1.32 (dd)	2.48 (dd)	2.10 (dd)		6.3		4.9	8.9	2.1	0.1			
R = R_2 = H; R_1 = Me[b] (b)	30247-56-4		3.43 (q)		1.38 (dd)	2.46 (dd)	2.12 (dd)				3.9	9.0	2.0			7.51 (d)	0.8
R = H; R_1 = Me; R_2 = Cl[b]	30347-57-5		3.43 (q)			2.55 (d)	2.19 (d)					9.4				7.53 (d)	0.8
R = H; R_1 = Ph; R_2 = H[b]	30247-58-6		2.82 (s)		1.25 (dd)	2.42 (dd)	1.96 (dd)				3.8	8.8	1.8				
R = Br; R_1 = Me; R_2 = H[b]	30247-59-7				1.42 (dd)	2.60 (dd)	2.24 (dd)				3.9	9.7	1.8			7.38 (s)	

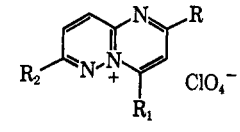
	Registry no.	H_2	H_3	H_4	H_6	H_7	H_8 ⌒ H_9	J_{23}	J_{34}	J_{67}	J_{78}	J_{89}	J_{68}	J_{79}	J_{49}	Me groups
	30247-60-0		2.0 (q)		0.80 (dd)	1.95 (ddd)	1.55 (m)	0	0.8 (H_3Me_4)	6.7	6.6	8.9	0.8	1.9		7.20 (s) 7.03[b] (d)
	16075-67-5		3.42 (d)	1.70 (dd)	1.88 (dd)		2.80 (m) 2.22 (dd)		7.5	6.5	6.6	8.3	1.0	1.6	0.1	*c*
	23443-10-9	1.74 (d)	3.60 (d)		0.93 (dd)	2.83 (ddd)	2.30 (m)	6.2		6.7	6.6	8.5	1.0	1.5		*b, d*
	1693-94-3		3.57 (s)		0.86 (dd)	2.75 (ddd)	2.25 (m)			6.7	6.6	8.5	1.0	2.0		7.43 (s) *b*
	30247-64-4		3.78 (s)		1.12 (d)	3.10 (dd)	2.69 (dq)			7.2		1.2 (H_9 8Me)		1.8		7.57 (s, 2Me) 7.52[b] (d)
	30247-65-5		3.65 (s)		1.08 (dd)	3.02 (t)[e]	2.41 (m)			6.6	6.6	0.8	0.9			7.54 (s, 2Me) 7.43[b] (s)

[a] In DMSO. [b] In $CDCl_3$. [c] In D_2O. [d] Prepared according to R. Adams and I. J. Pachter, *J. Amer. Chem Soc.*, **74**, 5491 (1952). [e] Degenerated quartet.

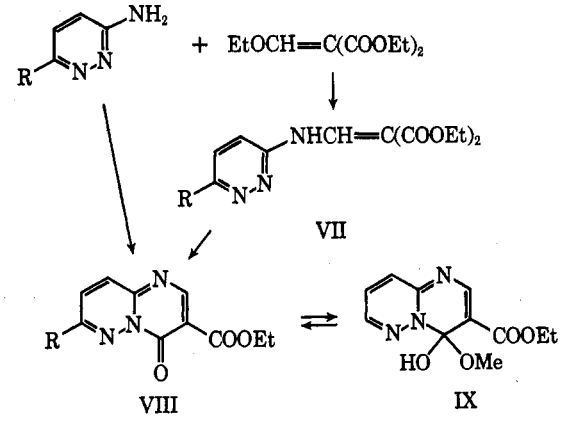
reaction with acetoacetic ester in the presence of PPA. The last-mentioned method proved to be the most convenient reaction for the synthesis of these and related bicyclic compounds V.



V



VI



VII VIII IX

We have assigned to pyrimido[1,2-*b*]pyridazinones the structure of 2-ones rather than 4-ones on the basis of chemical evidence and of nmr spectroscopic correlations and π bond orders. The empirical relation between J_{ortho} and π bond order which was applied for a series of carbocyclic aromatic compounds[7] and recently redefined for six-membered carbocyclic aromatic molecules[8] was extended to several bicyclic heteroaromatic systems[9] and discussed in connection with the partial bond fixation. Table I presents the calculated values for p_{ij} for the pyrimidine part of the isomeric pyrimido[1,2-*b*]pyridazin-2-ones and -4-ones as well as of pyrido[1,2-*a*]pyrimidin-2-ones and -4-ones.[10] There is an increase in bond order for $p_{3,4}$ of 2-ones as compared to $p_{2,3}$ of the isomeric 4-ones. As anticipated, this is reflected also in J_{ortho}. For an authentic pair of the isomeric pyrido[1,2-*a*]pyrimidin-2-one and -4-one, the observed $J_{3,4}$ and $J_{2,3}$, respectively, are in agreement with the aforementioned differences (Table II).

Similar regularities apply to pyrimido[1,2-*b*]pyridazinium perchlorate, prepared from 3-aminopyridazine and 1,1,3,3-tetraethoxypropane in the presence of PPA. The product (VI, R = R_1 = R_2 = H) is the first example of this fully aromatic bicyclic system and with other 1,3-dicarboxyl compounds related azinium perchlorates VI were synthesized.

As condensing agent PPA was found advantageous in the reaction between 3-aminopyridazines and ethoxymethylenemalonate to give the isomeric 4-ones (VIII). The previously reported[5] unsuccessful thermal cycliza-

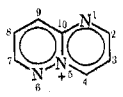
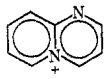
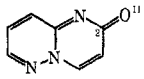
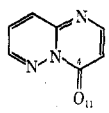
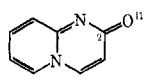
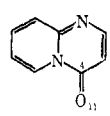
(7) N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.*, **36**, 2443 (1962).

(8) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **91**, 6325 (1969).

(9) A. J. Boulton, P. J. Halls, and A. R. Katritzky, *Org. Magn. Resonance*, **1**, 311 (1969).

(10) The authors are grateful to Professor Paudler, Ohio University, Athens, for a copy of the program according to which the reported values were calculated by Hückel method. The parameters used were in general those suggested by Streitwieser ("Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 135).

TABLE III
CALCULATED TOTAL π-ELECTRON DENSITIES

Position						
1	1.165	1.186	1.297	1.262	1.316	1.359
2	0.842	0.845	0.833	0.887	0.839	0.966
3	0.975	0.992	1.025	1.076	1.029	1.113
4	0.807	0.816	0.860	0.798	0.870	0.975
5	1.568	1.595	1.527	1.544	1.516	1.564
6	1.070	0.856	1.076	1.071	0.887	0.872
7	0.920	0.991	0.946	0.945	1.017	1.043
8	0.887	0.883	0.901	0.901	0.906	0.904
9	0.940	0.993	0.962	0.956	1.021	1.038
10	0.826	0.844	0.843	0.850	0.865	0.875
11			1.730	1.710	1.733	1.292

tion of VII (R = Cl) was now easily accomplished in PPA and VIII (R = Cl) was obtained.

It is noteworthy that compound VIII (R = H) underwent an acid-catalyzed addition of MeOH to the 4-carbonyl group and the formed adduct IX is upon heating reconverted to the starting 4-one. A nmr examination in $CDCl_3$ solution disclosed an equilibrium of about equal amounts of the 4-one VIII (R = H) and the adduct IX.

4-Methylpyrimido[1,2-*b*]pyridazin-2-one was brominated to form the 3-bromo derivative IV (R = Br; R_1 = Me; R_2 = H). The attack of the electrophile at position 3 is in agreement with the observed nmr data and was anticipated on hand of the calculated electron densities for this system (Table III).

In the pyrido[1,2-*a*]pyrimidone series nmr spectra permit distinction between the 2-one (I) and the 4-one (II, R = R_1 = R_2 = H), the $J_{3,4}$ being larger than $J_{2,3}$ of the 4-one. Moreover, a long-range coupling constant, $J_{4,9}$, was observed with the 2-ones of the pyrido[1,2-*a*]pyrimidine (I) or pyrimido[1,2-*b*]pyridazine (IV) series as well as with pyrimido[1,2-*b*]pyridazinium perchlorate (VI, R = R_1 = R_2 = H). Furthermore, only 4-methyl derivatives of all these systems display a small coupling constant between the 4-methyl group and H_3, whereas with 2-methyl derivatives such interactions with H_3 were not observed. According to previous[3] and these observations, pyrido[1,2-*a*]pyrimidones, obtained from 2-aminopyridines and acetoacetic ester, are in fact 4-ones and not 2-ones.[11]

The different reactivity of 3-aminopyridazines to give the bicyclic 2-ones as compared to 2-aminopyridines which gave the corresponding 4-ones may account for a lower basicity of 3-aminopyridazines. It is noteworthy that 5-nitro-2-aminopyridine failed to give a bicyclic product.[3]

Experimental Section

Melting points were taken on a Kofler melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord; ultraviolet spectra were recorded on a Beckman DU spectrophotometer and nmr spectra on a JEOL JNM-C-60HL spectrometer, using tetramethylsilane as internal standard.

3-Acetoacetylaminopyridazine (III, R = CH_3).—3-Aminopyridazine (1.9 g), acetoacetic ester (10 ml), and anhydrous Et_3N (1.0 ml) were heated under reflux for 2 hr at 135–140°. Upon standing overnight at room temperature diethyl ether (20 ml) was added, and the product was separated and washed with some ether (yield 2.0 g, 54%). For analysis a sample was recrystallized from methanol to give colorless needles: mp 179–180°; ir (KBr) 1721 and 1692 cm^{-1} (CO); nmr (CD_3SOCD_3) τ 1.80 (dd, H_4), 2.42 (dd, H_5), 1.12 (dd, H_6), 6.30 (s, CH_2), 7.78 (s, CH_3) ($J_{4,5}$ = 8.6, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.3).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.66; H, 4.95; N, 23.66.

In essentially the same manner the following compounds were prepared.

3-Benzoylacetylaminopyridazine (III, R_1 = C_6H_5) was prepared from ethyl benzoylacetate in 82% yield: mp 209–210° (from ethanol); nmr (CD_3SOCD_3) τ 1.69 (dd, H_4), 2.00 (dd, H_5), 1.03 (dd, H_6), 5.68 (s, CH_2), 2.40 (m, C_6H_5) ($J_{4,5}$ = 8.4, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.2).

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.98; H, 4.69; N, 17.35.

Cyclopentan-2-onecarboxylic acid 3-pyridazinylamide was obtained in 78% yield from ethyl cyclopentan-2-onecarboxylate: mp 186–187° (from methanol); nmr spectrum (CD_3SOCD_3) τ 1.75 (dd, H_4), 2.38 (dd, H_5), 1.10 (dd, H_6), 7.80 (m, cyclopentanonyl part) ($J_{4,5}$ = 8.6, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.2).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.65; H, 5.16; N, 20.57.

Pyrimido[1,2-*b*]pyridazin-5-ium Perchlorate (VI, R = R_1 = R_2 = H).—A solution of 3-aminopyridazine (2.85 g) in PPA[12] (50 g) was prepared at 110° and then cooled to 50°. Under stirring 1,1,3,3-tetraethoxypropane (6.6 g) was added and the mixture was left at this temperature for 3 hr. Upon 48 hr at room temperature the mixture was treated with crushed ice (50 g) and perchloric acid (5.0 g of 70%) was added. The product was crystallized from methanol and water (2:1) to give colorless crystals (3.4 g, 49%): mp 315–316°; uv (methanol) λ_{max} 240 and 296 nm (ε 6090 and 5850); ir (KBr) 1616 and 1517 cm^{-1} (C=C and C=N).

Anal. Calcd for $C_7H_6ClN_3O_4$: C, 36.33; H, 2.16; N, 18.21. Found: C, 36.60; H, 2.85; N, 18.37.

4-Methylpyrimido[1,2-*b*]pyridazin-5-ium Perchlorate (VI, R = R_2 = H; R_1 = CH_3).—3-Aminopyridazine (2.85 g) in PPA (40 g) at 75° was treated with 3-ketobutanal dimethyl acetal (4.0 g). The mixture was kept at 75° for 3 hr and then treated with ice (40 g) and perchloric acid (5.0 g, 70%). The product (5.2 g, 71%) was crystallized from 66% methanol: mp 278–279°; uv (methanol) λ_{max} 270 nm (ε 4950).

Anal. Calcd for $C_8H_8ClN_3O_4$: C, 39.12; H, 3.28; N, 17.11. Found: C, 39.44; H, 3.55; N, 17.07.

General Procedure for the Synthesis of Other Pyrimido[1,2-*b*]-pyridazin-5-ium Perchlorates (VI).—A 3-aminopyridazine (0.01–0.03 mol) and the 1,3-dicarbonyl compound (0.01–0.03 mol) were mixed with a sevenfold (by weight) quantity of PPA and the mixture was heated at 110–115°. After 1–1.5 hr when foaming has subsided, heating was discontinued and the clear reddish-

(11) G. Stöckelmann, H. Specker, and W. Riepe, *Chem. Ber.*, **102**, 455 (1969).

(12) Polyphosphoric acid (PPA) containing 83% P_2O_5 was used throughout this paper.

brown solution was cooled to room temperature and treated with ice (the same weight as PPA) and perchloric acid (0.012–0.035 mol, 70%). The precipitate was filtered off, washed with some water and methanol, and dried. In this manner the following compounds were synthesized.

2,4-Dimethylpyrimido[1,2-*b*]pyridazin-5-ium perchlorate (VI, R_2 = H; R_1 = CH_3) was obtained from acetylacetone in 74% yield: mp 227–228° (from 66% methanol); uv (methanol) λ_{max} and 260 nm (ϵ 32,250 and 5480).

Anal. Calcd for $C_9H_{10}ClN_3O_4$: C, 41.63; H, 3.88; N, 16.18. Found: C, 41.87; H, 4.04; N, 16.30.

2-Methyl-4-phenylpyrimido[1,2-*b*]pyridazin-5-ium perchlorate (VI, R = CH_3; R_1 = C_6H_5; R_2 = H) was prepared from benzoylacetone in 80% yield: mp 202–203° (from acetic acid); uv (methanol) λ_{max} 217 and 314 nm (ϵ 30,150 and 3870).

Anal. Calcd for $C_{14}H_{12}ClN_3O_4$: C, 52.27; H, 3.76; N, 12.92. Found: C, 52.51; H, 3.89; N, 13.02.

7-Chloro-2,4-dimethylpyrimido[1,2-*b*]pyridazin-5-ium perchlorate (VI, R = R_1 = CH_3; R_2 = Cl) was prepared from 3-amino-6-chloropyridazine and acetylacetone in 84% yield: mp 278–279° (from 66% methanol); uv (methanol) λ_{max} 232 nm (ϵ 43,500).

Anal. Calcd for $C_9H_9Cl_2N_3O_4$: C, 36.76; H, 3.08; N, 14.29. Found: C, 36.63; H, 3.26; N, 14.55.

7-Chloro-2,4-dimethylpyrido[3,2-*d*]pyrimido[1,2-*b*]pyridazin-5-ium perchlorate was obtained from 5-amino-8-chloropyrido-[2,3-*d*]pyridazine[13] and acetylacetone in 68% yield: mp 275–276° (from 50% methanol); uv (methanol) λ_{max} 241 nm (ϵ 45,500).

Anal. Calcd for $C_{12}H_{10}Cl_2N_4O_4$: C, 41.76; H, 3.50; N, 16.23. Found: C, 42.01; H, 3.29; N, 16.19.

Pyrido[1,2-*a*]pyrimidin-5-ium Perchlorate.—A solution of 2-aminopyridine (0.96 g) in methanol (10 ml), 1,1,3,3-tetraethoxypropane (2.2 g), and hydrobromic acid (2.0 g, 48%) was heated under reflux for 2 hr. The cooled mixture was treated with perchloric acid (2.5 g, 70%) and the obtained salt (1,3 g, 60%) was recrystallized from aqueous methanol to give colorless needles: mp 222–223°; uv (methanol) λ_{max} 226, 268, and 316 nm (ϵ 13,100, 4060, and 5150); ir (KBr) 1634 and 1504 cm^{-1} (C=C and C=N).

Anal. Calcd for $C_8H_7ClN_2O_4$: C, 41.67; H, 2.85; N, 12.15. Found: C, 41.69; H, 3.07; N, 12.19.

2,4-Dimethylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate was obtained in the same manner in 78% yield: mp 229–230° (from 50% methanol); uv (methanol) λ_{max} 228, 274, and 312 nm (ϵ 35,000, 3050, and 5100).

Anal. Calcd for $C_{10}H_{11}ClN_2O_4$: C, 46.42; H, 4.28; N, 10.83. Found: C, 46.60; H, 4.25; N, 10.87.

General Procedure for the Synthesis of Pyrimido[1,2-*b*]pyridazin-2-ones (IV).—The corresponding 3-aminopyridazine (0.01–0.03 mol), an equivalent amount of a β-keto ester, and PPA (a sevenfold amount by weight) were heated under stirring at 110–120° for 1–2 hr until foaming subsided. The cooled mixture was diluted with water (double the weight of PPA) and solid sodium bicarbonate was added until pH 5–6. The mixture was repeatedly extracted with chloroform and from this solution the crude product was obtained after evaporation to dryness *in vacuo*. In this manner the following were prepared.

7-Chloro-4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = H; R_1 = CH_3; R_2 = Cl) in 72% yield from 3-amino-6-chloropyridazine and acetoacetic ester: mp 223–224° (from ethanol and ethyl acetate); uv (ethanol) λ_{max} 252 and 316 nm (ϵ 10,500 and 6000).

Anal. Calcd for $C_8H_6ClN_3O$: C, 49.12; H, 3.09; N, 21.48. Found: C, 49.29; H, 3.40; N, 21.37.

Cyclopenta-5,6-pyrimido[1,2-*b*]pyridazin-4-one (V) from ethyl cyclopenta-2-one carboxylate in 70% yield: mp 194–195° [sublimed at 160° (0.1 mm)]; uv (ethanol) λ_{max} 236 and 320 nm (ϵ 13,100 and 7200); nmr ($CDCl_3$) τ 2.15 (dd, H_6), 2.53 (dd, H_7), 1.24 (dd, H_8), 7.80 (m), and 6.95 [m, both for $(CH_2)_3$] ($J_{7,8}$ = 4.5, $J_{6,7}$ = 9.5, $J_{6,8}$ = 2.0).

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.20; H, 4.86; N, 22.06.

4-Phenylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = C_6H_5) was obtained from ethyl benzoylacetate in 78% yield: mp 204–205° (ethanol); uv (ethanol) λ_{max} 269 and 335 nm (ϵ 27,200 and 7100).

(13) Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.*, **13**, 586 (1965).

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.89; H, 4.11; N, 18.54.

4-Methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = CH_3). **A.**—According to the above method it was obtained in 83% yield from acetoacetic ester and sublimed at 160° (0.1 mm): mp 179–180°; uv (ethanol) λ_{max} 228 and 314 nm (ϵ 12,200 and 6800).

Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.45; H, 4.65; N, 26.36.

B.—A solution of 3-aminopyridazine (1.9 g) in water (20 ml) was treated under vigorous stirring with diketene (2.0 g) dropwise during 30 min. Temperature was held at about 30° and after addition was complete, stirring was continued for 1 hr. The mixture was then extracted with chloroform and the crude product (1.1 g, 34%) crystallized from ethyl acetate, mp 179–180°. Ir and mixture melting point showed identity with the product obtained as described under A.

C.—Compound III (R = CH_3, 0.5 g) and PPA (5.0 g) were heated at 120° for 2 hr. Upon cooling water (20 ml) was added and the mixture neutralized with sodium bicarbonate to pH 6. Extraction with chloroform and evaporation of the solvent yielded a residue (0.2 g) which was sublimed at 140° (0.1 mm), mp 178–179°. Ir and mixture melting point showed identity with the specimen obtained under A.

4-Carbethoxypyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = $COOC_2H_5$).—A stirred mixture of 3-aminopyridazine (0.95 g), potassium salt of the enolic form of diethyl oxaloacetate (2.3 g), and PPA (20 g) was heated at 115° for 2 hr. The cooled mixture was treated with water (60 ml) and neutralized with sodium bicarbonate to pH 6. Extraction with chloroform (four times with 30 ml) gave upon evaporation the crude product (1.7 g, 78%). Upon sublimation at 160° (0.1 mm) the compound had mp 223–224°; uv (ethanol) λ_{max} 340 nm (ϵ 7300); ir (KBr) 1736 and 1695 cm^{-1} (CO); nmr ($CDCl_3$) τ 2.63 (s, H_3), 1.28 (dd, H_7), 2.46 (dd, H_8), 1.92 (dd, H_9), 5.52 (q, CH_2), 8.56 (t, CH_3) (J = 6.8, $J_{7,8}$ = 3.9, $J_{8,9}$ = 9.3, $J_{7,9}$ = 1.7).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 55.03; H, 4.31; N, 18.95.

Pyrimido[1,2-*b*]pyridazin-2-one-4-carboxylic Acid (IV, R = R_2 = H; R_1 = COOH).—The above ester (2.2 g) was left to stand at room temperature in aqueous KOH (15 ml, 10%) for 1 hr. Acidification with concentrated hydrochloric acid to pH 1 yielded colorless crystals (1.5 g, 79%): mp 280° dec (from water); uv (ethanol) λ_{max} 225 and 330 nm (ϵ 14,400 and 7200).

Anal. Calcd for $C_8H_5N_3O_3$: C, 50.27; H, 2.64; N, 21.98. Found: C, 50.03; H, 2.59; N, 21.93.

Pyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_1 = R_2 = H).—The above acid was thoroughly mixed with copper bronze (0.2 g). Portions of 100 mg of this mixture were sublimed at 270–275° (0.1 mm). The combined sublimates (210 mg) were resublimed and the pure compound (56%) had mp 169–170°; uv (ethanol) λ_{max} 228 and 318 nm (ϵ 12,250 and 7300); ir (KBr) 1709 cm^{-1} (CO).

Anal. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.13; H, 3.13; N, 28.40.

3-Bromo-4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = Br; R_1 = CH_3; R_2 = H).—A stirred solution of IV (R = R_2 = H; R_1 = CH_3; 1.6 g) in glacial acetic acid (15 ml) was treated with bromine (1.6 g) and the mixture was heated for 5 min on a water bath. The separated product was washed with some acetic acid, suspended in a solution of sodium bicarbonate (25 ml, 10%). The remaining solid was filtered off, washed with water, and dried (1.7 g, 71%): mp (of colorless needles) 230–231° (ethanol); ir (KBr) 1701 cm^{-1} (CO).

Anal. Calcd for $C_8H_6BrN_3O$: C, 40.19; H, 2.59; N, 17.57. Found: C, 40.47; H, 2.55; N, 17.30.

3-Carbethoxypyrimido[1,2-*b*]pyridazin-4-one (VIII, R = H). **A.**—3-Aminopyridazine (1.9 g), diethyl ethoxymethylenemalonate (4.35 g), and PPA (40 g) were heated at 120° for 2 hr. Upon dilution with water (100 ml) and neutralization with sodium bicarbonate to pH 6, the product was filtered off, washed with some water, and dried *in vacuo* over KOH (3.7 g, 84%), mp 169–170° (ethanol).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 54.57; H, 3.91; N, 19.11.

B.—Compound VII (R = H) when heated in a sevenfold quantity of PPA at 120° for 2 hr afforded a product which was identical in all respects with the specimen under A (yield 80%).

3-Carbethoxy-7-chloropyrimido[1,2-*b*]pyridazin-4-one (VIII, R = Cl).—The compound was prepared according to the above

procedure from 3-amino-6-chloropyridazine in 76% yield: mp 154–155° (ethanol); uv (ethanol) λ_{max} 254 and 340 nm (ϵ 11,000 and 8850); nmr ($CDCl_3$) τ 1.04 (s, H_2), 2.38 (d, H_8), 2.02 (d, H_9) ($J_{8,9}$ = 9.2), 5.56 (q, CH_2), 8.58 (t, CH_3) (J = 6.6).

Anal. Calcd for $C_{10}H_8ClN_3O_3$: C, 47.35; H, 3.17; N, 16.57. Found: C, 47.39; H, 3.09; H, 3.09; N, 16.80.

3-Carbethoxy-4-hydroxy-4-methoxypyrimido[1,2-*b*]pyridazine (IX).—Compound VIII (R = H; 0.5 g), methanol (10 ml), and few drops of concentrated hydrochloric acid were heated under reflux for 3 hr. Upon evaporation *in vacuo* to half of the original volume and after standing on ice overnight, the separated product (0.35 g) had mp 158–160° (at 150° on a preheated melting point apparatus); ir (Nujol) 2247 (hydrogen bonded OH) and 1754 cm^{-1} (CO). From the melt a new compound separated and had mp 168–170° (identical with the starting pyrimidopyridazinone): nmr of IX ($CDCl_3$) τ 0.95 (s, H_2), 6.00 (s, OCH_3), 1.14 (dd, H_7), 2.28 (dd, H_8), 1.95 (dd, H_9) ($J_{7,8}$ = 5.5, $J_{8,9}$ = 8.5, $J_{7,9}$ = 2.5), 5.55 (q, CH_2), 8.58 (t, CH_3).

From the nmr spectrum it is evident that the adduct is in equilibrium with the starting compound (ratio of about 1:1). When heated *in vacuo* the adduct is reconverted to the starting bicyclic compound.

2,9-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (II, R_1 = H; R = R_2 = CH_3).—The procedure for the synthesis of IV was followed, but using 2-amino-3-methylpyridine and acetoacetic ester (yield 71%), mp 131–132° (from *n*-hexane and ethyl acetate) (lit.[3] mp 131–132°).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.98; N, 16.08.

2,8-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (II, R_2 = H; R = R_1 = CH_3).—The compound was prepared as the above analog from 2-amino-4-methylpyridine in 74% yield, mp 136–137° (from *n*-hexane and ethyl acetate).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.64; H, 5.57; N, 16.20.

Registry No.—III (R_1 = CH_3), 30247-66-6; III (R_1 = C_6H_5), 30247-67-7; IV (R = R_2 = H; R_1 = $COOC_2H_5$), 30247-68-8; IV (R = R_2 = H; R_1 = COOH), 30247-69-9; V, 30247-70-2; VIII (R = H), 19111-57-2; VIII (R = Cl), 30247-72-4; IX, 30247-73-5; cyclopentan-2-onecarboxylic acid 3-pyridazinyl amide, 30318-65-1; 7-chloro-2,4-dimethylpyrido[3,2-*d*]-pyrimido[1,2-*b*]pyridazin-5-ium perchlorate, 30247-74-6; pyrido[1,2-*a*]pyrimidin-5-ium perchlorate, 30247-75-7; 2,4-dimethylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate, 30247-60-0.

Reaction of 4,6-Dimethoxy-5-nitropyrimidine with Methylhydrazine. Formation of 4-Hydrazino-6-hydroxypyrimidine

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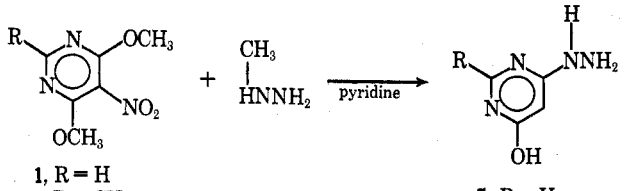
The reaction of 4,6-dimethoxy-5-nitropyrimidine (1) with methylhydrazine in refluxing pyridine or butanol is very complex involving the methylation of the solvent by 1 and the nucleophilic substitution and demethylation of the methylhydrazino substituent in the 5 position to yield 4-hydrazino-6-hydroxypyrimidine. The first step in this sequence of reactions involves the methylation of the solvent, followed by nucleophilic substitution of methylhydrazine in the 4 position, migration of its methyl substituent to form a carbon to oxygen bond with the adjacent nitro substituent, and eventual elimination of methyl nitrite from the 5 position as one of the reaction products. 4,6-Dimethoxy-5-nitropyrimidine reacts with pyridine (in the absence of methylhydrazine) to yield an insoluble methylpyridium salt which is not a precursor of 4-hydrazino-6-hydroxypyrimidine. The mother liquor from this reaction on acid hydrolysis yields 4-hydroxy-6-methoxy-5-nitropyrimidine and reacts with methylhydrazine to yield 4-hydroxy-6-hydrazinopyrimidine. Both 4-chloro-6-hydroxy-5-nitropyrimidine and 4,6-dichloro-5-nitropyrimidine react with methylhydrazine in ethanol to yield the corresponding methylhydrazino derivatives.

In previous work,[1] the reaction of methylhydrazine with 4,6-dimethoxy-5-nitropyrimidine (**1**) in an alcoholic solvent was found to be unexpectedly complex. We have continued the investigations of the reactions of **1** and the 2-methyl and 2-phenyl analogs (**2** and **3**) and 4,6-diethoxy-5-nitropyrimidine (**4**) and have established that the products are the 4-hydrazino-6-hydroxypyrimidines **5**–**7**.

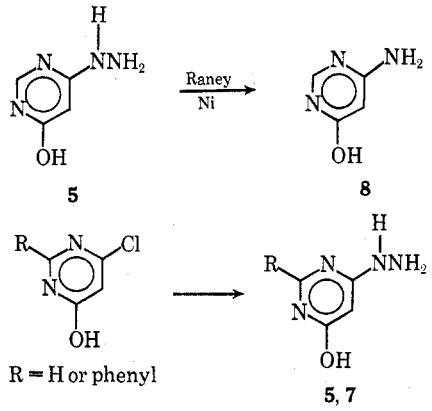


1, R = H
2, R = CH_3
3, R = C_6H_5

5, R = H
6, R = CH_3
7, R = C_6H_5

The structures were initially inferred from the spectral data which showed the probable presence of either a hydrazino, amino, or hydroxyl substituent and the absence of the methoxy and nitro substituents of the original starting material **1**. High-resolution mass spectral measurements gave apparent molecular formulas $RC_4H_5N_4O$, R = H or phenyl.

The hydrazino structures were finally established by hydrogenolysis of **5** to give 4-amino-6-hydroxypyrimidine[2] (**8**) and by the synthesis of **5** and **7** from the reac-



5

8

5, 7

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(2) D. J. Brown, *J. Soc. Chem. Ind., London*, **69**, 353 (1950).