Studies on Condensed Pyrimidine Systems. XXIV. The Condensation of 2,4,6-Triaminopyrimidine with Malondialdehyde Derivatives

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2,4,6-Triaminopyrimidine does not condense with 3-alkoxy- or 3-dimethylaminoacroleins to give products in useful yields under most conditions, but the compound formed by the reaction of 3-dimethylaminoacrolein with phosgene does condense with 2,4,6-triaminopyrimidine to give 6-substituted 2,4-diaminopyrido[2,3-*d*]pyrimidines. Some new alkyl- and aryl-substituted 3-dimethylaminoacroleins and 2,4-diaminopyrido[2,3-*d*]pyrimidines are reported.

The activity of 5,6-disubstituted 2,4-diaminopyrido-[2,3-*d*]pyrimidines[1,2] as inhibitors of specific dihydrofolate reductases made it desirable to prepare similar compounds which were monsubstituted in the 6 position. The necessary intermediates became available through the work of Arnold, *et al.*,[3] from 1957 onward, on a modification of the Vilsmeier reaction. They obtained the product (II) by the reaction of N,N-dimethylformamide (DMF) with phosgene. From the reaction of II with acetals Arnold and Šorm[3a] isolated three types of compounds, 2-alkyl-3-dimethylaminoacroleins (III), 2-alkyl-3-alkoxyacroleins (IV), and the quaternary salts (V). Part of this work has been repeated and a number of new 3-dimethylaminoacroleins have been prepared.

The reactions of 3-alkoxy- and 3-dimethylaminoacroleins with 2,4,6-triaminopyrimidine were studied. No condensation occurred with 3-alkoxyacroleins under any conditions investigated. Very low yields of 2,4-diaminopyrido[2,3-*d*]pyrimidines were obtained on heating 3-dimethylaminoacroleins with 2,4,6-triaminopyrimidine either alone or in a high-boiling, inert solvent such as diphenyl ether. Arnold and Žemlička[3b] found that 3-dimethylaminoacroleins undergo reaction with phosgene to give the quaternary salts VI. Rylski, *et al.*,[3c] reported that these quaternary salts condense with urea and with thiourea to give pyrimidines. In the present work these salts were found to give, with 2,4,6-triaminopyrimidine in absolute alcohol, 6-substituted 2,4-diaminopyrido[2,3-*d*]pyrimidines (I).

Although vinyl ethers and compounds which can be readily transformed into vinyl ethers will undergo reaction with II, enol acetates (VII) prepared by the method of Scriabine[4] were recovered unchanged after treatment with II under the same conditions which caused acetals to react. In 1960, Lorette and Howard[5] reported that acetals could be interconverted, and aldehydes could be converted to their acetals by means of an acid-catalyzed exchange with 2,2-dimethoxypropane and an appropriate alcohol. In this work it was found that enol acetates could be converted in one step to the corresponding acetals under the same conditions.

The elemental analyses indicate that the products of the condensation of 2,4,6-triaminopyrimidine with compounds of type VI are bicyclic, aromatic systems. They could possibly be 6-substituted 2,4-diaminopyrido[2,3-*d*]pyrimidines (I), 7-substituted 4-amino-2-imino-2H-pyrimido[1,2-*a*]pyrimidines (VIII), or 3-substituted 6-amino-8-imino-8H-pyrimido[1,2-*c*]pyrimidines (IX). By analogy with the condensations of 2,4,6-triaminopyrimidines with β-ketoaldehydes, β-diketones, and β-keto esters, which give 2,4-diaminopyrido[2,3-*d*]pyrimidines in every case, the condensation with the malondialdehyde derivatives VI would be expected to give I. This structure assignment is supported by the ultraviolet and pmr spectra. The uv spectra and pK_a values of representative compounds are shown in Table I. The spectra of the butyl derivative are shown in Figure 1. The uv spectra of the other alkyl and aralkyl derivatives are very similar to those of the butyl derivative.

The pyrimidopyrimidines VIII and IX would be expected to be quite strong bases. The thermodynamic

TABLE I

REPRESENTATIVE ULTRAVIOLET SPECTRA AND pK_a's OF 6-SUBSTITUTED 2,4-DIAMINOPYRIDO[2,3-*d*]PYRIMIDINES

Compd	λ_{max}, mμ (ε × 10^{-3}) pH 2	pH 11	pK_a
10	322 (8.8)	248 (19.9)	6.8
	332[a] (7.6)	268 (9.8)	
		348 (6.9)	
15	253 (34.0)	232 (19.7)	
	335 (8.6)	253 (23.9)	
		291 (20.4)	
		356 (7.7)	
16	322 (9.4)	225 (26.5)	6.6
		248 (21.5)	
		270 (11.3)	
		347 (6.6)	

[a] Inflection.

TABLE II

PMR SPECTRUM OF **11** IN TRIFLUOROACETIC ACID (Me_4Si AS INTERNAL STANDARD)

Chemical shift, ppm (δ)	*J*, cps	Integrated no. of protons	Type of peak	Assignment
1.06	6.5	6	Doublet	$CH_2CH(CH_3)_2$
2.08	?	1	Multiplet	$CH_2CH(CH_3)_2$
2.88	7.5	2	Doublet	$CH_2CH(CH_3)_2$
10.52	2.0	1	Doublet	Heterocyclic CH
10.98	2.0	1	Doublet	Heterocyclic CH

(1) (a) B. S. Hurlbert, K. W. Ledig, P. Stenbuck, B. F. Valenti, and G. H. Hitchings, *J. Med. Chem.*, **11**, 703 (1968), preceding paper; G. H. Hitchings and J. J. Burchall, *Advan. Enzymol.*, **27**, 417 (1965); G. H. Hitchings, T. A. Herrmann, B. S. Hurlbert, and S. R. M. Bushby, Proceedings of the IIIrd International Congress of Chemotherapy, Stuttgart, 1963, p 1363.

(2) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958).

(3) (a) Z. Arnold and F. Šorm, *Chem. Listy*, **51**, 1082 (1957); (b) Z. Arnold and J. Žemlička, *Collection Czech. Chem. Commun.*, **24**, 2378 (1959); (c) L. Rylski, F. Šorm, and Z. Arnold, *ibid.*, **24**, 1667 (1959).

(4) I. Scriabine, *Bull. Soc. Chim. France* 1194 (1961).

(5) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

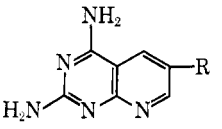
TABLE III

$(CH_3)_2NCH{=}CCHO$
|
R

No.	R	Yield, %	Mp (bp (1 mm)), °C	Formula	Analyses	$\lambda_{max}^{95\%\ EtOH}$, mμ ($\epsilon \times 10^{-3}$)	ν_{max}, cm^{-1}	Solvent[a]
1	$CH_2CH(CH_3)_2$	66	(110)	$C_9H_{17}NO$	H; C[b]		1600	A
							1605	B
2	C_6H_{13}	67	(125)	$C_{11}H_{21}NO$	H, N; C[c]		1602	A
3	C_9H_{19}	59	(140)	$C_{14}H_{27}NO$	N		1600	A
4	p-$CH_2C_6H_4OCH_3$	30	74	$C_{13}H_{17}NO_2$	C, H, N	225 (12.7)	1580	C
						292 (31.8)		
5	p-$CH_2C_6H_4CH_3$	26	95	$C_{13}H_{17}NO$	C, H, N	292 (31.2)	1575	C
6	p-$CH_2C_6H_4Cl$	19	124	$C_{12}H_{14}NOCl$	N	220 (15.6)	1580	C
						292 (35.4)		
7	o-$CH_2C_6H_4Cl$	16	137	$C_{12}H_{14}NOCl$	C, H, N	290 (32.8)	1580	C
8	$CH_2CH_2C_6H_5$	36	100	$C_{13}H_{17}NO$	C, H, N	292 (31.2)	1595	C

[a] Ir sample phases: A, $CHCl_3$; B, thin film; C, KBr pellet. [b] C: calcd, 69.63; found, 68.90. [c] C: calcd, 72.08; found, 71.59.

TABLE IV



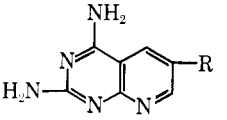
No.	R	Yield, %	Mp, °C[a]	Formula	Analyses
9	C_3H_7	33	275	$C_{10}H_{13}N_5 \cdot HCl \cdot H_2O$	C, H, N
				$C_{10}H_{13}N_5 \cdot C_2H_6O_4S$[b]	C, H, N
10	C_4H_9	79	278	$C_{11}H_{15}N_5 \cdot HCl$	C, H, N
11	$CH_2CH(CH_3)_2$	36	286	$C_{11}H_{15}N_5 \cdot HCl \cdot H_2O$	C, H, N
12	C_5H_{11}	21	252	$C_{12}H_{17}N_5 \cdot C_2H_6O_4S$[b]	C, H, N
13	C_6H_{13}	19		$C_{13}H_{19}N_5 \cdot C_2H_6O_4S$[b]	C, H, N
14	C_9H_{19}	29		$(C_{16}H_{25}N_5)_2 \cdot C_2H_6O_4S$[c]	C, H, N
15	C_6H_5	30	385	$C_{13}H_{11}N_5$	C, H, N
				$C_{13}H_{11}N_5 \cdot C_2H_6O_4S \cdot H_2O$[b]	C, H, N
16	$CH_2C_6H_5$	21	324	$C_{14}H_{13}N_5$	C, H, N
17	p-$CH_2C_6H_4OCH_3$	12	288	$C_{15}H_{15}N_5O \cdot C_2H_6O_4S$[b]	C, H, N
18	p-$CH_2C_6H_4CH_3$	14	286	$(C_{15}H_{15}N_5)_2 \cdot C_2H_6O_4S$[c]	C, H, N
19	p-$CH_2C_6H_4Cl$	7.8		$C_{14}H_{12}N_5Cl \cdot HCl$	C, H, N
20	o-$CH_2C_6H_4Cl$			$(C_{14}H_{12}N_5Cl)_2 \cdot C_2H_6O_4S \cdot 2H_2O$[c]	C, H, N
21	p-$CH_2C_6H_4NO_2$	51	276	$(C_{14}H_{12}N_6O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$	C, H, N
22	$CH_2CH_2C_6H_5$	30	199	$C_{15}H_{15}N_5 \cdot HCl$	C, H, N

[a] Where no melting point is given, compound decomposed without melting. [b] Isethionate salt. [c] Basic isethionate salt.

pK_a values of the butyl (**10**) and benzyl (**16**) derivatives were determined[6] spectrometrically in dilute phosphate buffers. These values are close to the pK_a values obtained for other 2,4-diaminopyrido[2,3-*d*]pyrimidines[1] and lower than would be expected for structures VIII and IX.

The pmr spectrum of the isobutyl derivative (**11**) is shown in Table II. This is consistent with the spectrum to be expected for 2,4-diamino-6-isobutylpyrido[2,3-*d*]pyrimidine, particularly in that it has two heterocyclic protons. The pyrimidopyrimidines VIII and IX would each be expected to show three heterocyclic protons.

The biological activities of these compounds will be reported in the following paper.[7]



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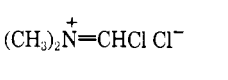
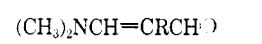


II



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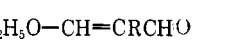

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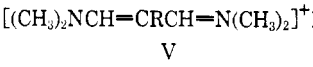
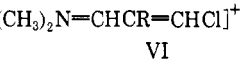
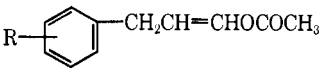


V



VI



VII

Experimental Section

Uv spectra were determined on the Beckman Model DU and Cary Model 15 spectrophotometers, pmr spectra on a Varian A-60 spectrometer. The acetals used as starting materials were purchased or were prepared by the exchange reaction of aldehydes with 2,2-dimethoxypropane, by reaction of a suitable Grignard reagent with triethyl orthoformate, or by the following sequence.

1,1-Dimethoxy-3-*p*-tolylpropane.—$TiCl_4$ (190 g, 1.0 mole) and 2–3 ml of BF_3–Et_2O were dissolved in 1 l. of toluene and cooled to −15° in an ice–salt bath, and 1,1-diacetoxy-2-propene (158 g, 1.0 mole) was added dropwise with stirring at −15 to −10°. When the addition was complete, the reaction mixture was stirred 1 hr at −10°, poured into 1500 g of ice and 170 ml of 12 *M* HCl, stirred, and separated. The toluene layer was washed

(6) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

(7) B. S. Hurlbert, R. Ferone, T. A. Herrmann, G. H. Hitchings, M. Barnett, and S. R. M. Bushby, *J. Med. Chem.*, **11**, 711 (1968).

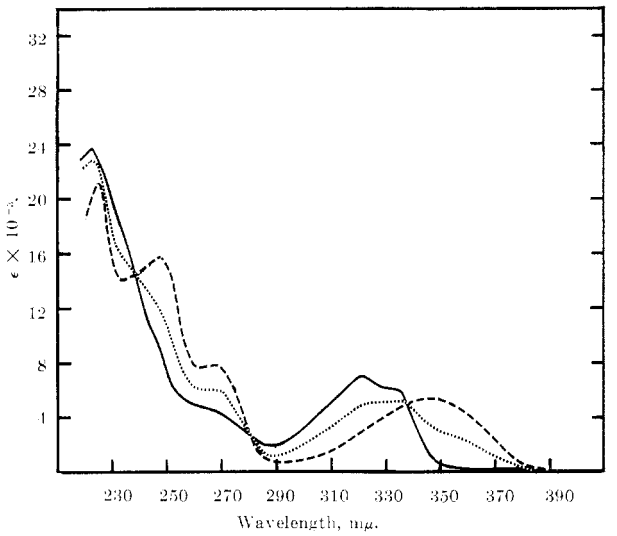


Figure 1.—Ultraviolet spectra of 6-butyl-2,4-diaminopyrido[2,3-*d*]pyrimidine (**10**): ———, spectrum of protonated form: - - - - - - - - -, spectrum of neutral molecule: . . . . . , spectrum at $pK_a = 6.90$.

(H_2O, saturated $NaHCO_3$, H_2O) and dried (Na_2SO_4), the solvents were removed on a rotary evaporator, and the residue was distilled to give 142 g (75%) of 1-acetoxy-3-*p*-tolylpropene, bp 80–86° (0.5 mm), having ir bands at 1765 (C=O), 1682 (C=C), and 1227 (C–O–C) cm^{-1}. Vpe analysis showed it to be more than 90% pure. It formed a 2,4-dinitrophenylhydrazone, mp 115–117°. *Anal.* ($C_{16}H_{16}N_4O_4$) N.

A mixture of the above enol acetate (142.7 g, 0.75 mole), 2,2-dimethoxypropane (156 g, 1.5 moles), 1100 ml of absolute MeOH, and 200 mg of *p*-toluenesulfonic acid was slowly distilled through a 30-cm column packed with glass helices to remove Me_2CO, bp 56.5°, MeOAc, bp 57°, MeOH, bp 64.5°, and some of a dimethoxypropane–MeOH azeotrope. The undistilled portion was then made basic with NaOMe and distilled through the same column to give 121 g (83%) of 1,1-dimethoxy-3-*p*-tolylpropane, bp 82° (0.5 mm). This compound has no ir absorption between 1530 and 1850 cm^{-1} and gives a 2,4-dinitrophenylhydrazone, mp 115–117° alone or when mixed with that obtained above.

2-Alkyl and 2-phenyl-3-dimethylaminoacroleins were prepared by the known procedure[3a] (Table III).

3-Dimethylamino-2-isobutylacrolein.—From 109 g (1.1 moles) of $COCl_2$, 150 g (2 moles) of DMF, and 174 g (1.0 mole) of 1,1-diethoxy-4-methylpentane was obtained an oil which gave two fractions when distilled at 1 mm: (1) 2-isobutyl-3-ethoxyacrolein, bp 80–90°, 28.5 g (18%), $\nu_{max}^{CHCl_3}$ 1660 and 1644 cm^{-1}, and (2) 3-dimethylamino-2-isobutylacrolein, bp 105–115°, 74.0 g (48%), $\nu_{max}^{CHCl_3}$ 1608 cm^{-1} (see Table II).

3-Dimethylamino-2-*p*-tolylacrolein.—1,1-Dimethoxy-3-*p*-tolylpropane (58.3 g, 0.3 mole) was treated with $COCl_2$ (59.4 g, 0.6 mole) and DMF (43.8 g, 0.6 mole), and the reaction mixture was hydrolyzed as above. The aqueous phase was extracted with $(CH_2Cl)_2$ and the extracts were combined, washed (H_2O), and dried (Na_2SO_4). The solvent was distilled on a steam bath, and the residue was recrystallized from a C_6H_6–C_6H_{14} mixture to give 16 g (26%) of near-white crystals. In runs in which the product could not be crystallized directly from C_6H_6–C_6H_{14} it was isolated from funnels 2–6 of a nine-funnel, countercurrent distribution between $CHCl_3$ and 2 *N* HCl and was then recrystallized as above.

In none of these cases was any 3-alkoxyacrolein isolated. However, both the starting aldehyde and its aldol-condensation product were obtained from the countercurrent distributions, and it is possible that the 3-alkoxyacroleins were formed and either were not crystalline or did not survive the acid conditions.

2,4-Diamino-6-isobutylpyrido[2,3-*d*]pyrimidine.—A solution of $COCl_2$ (13 g, 0.13 mole) in 100 ml of $(CH_2Cl)_2$ was added slowly with stirring and cooling to a solution of 2-isobutyl-3-dimethylaminoacrolein (20 g, 0.129 mole) in 50 ml of $(CH_2Cl)_2$. When CO_2 evolution ceased, the solvent was distilled *in vacuo* on a steam bath, and to the residue was added 2,4,6-triaminopyrimidine (16.26 g, 0.13 mole) and 250 ml of absolute EtOH. This mixture was heated under reflux on a steam bath for 18 hr, made strongly basic with NaOMe, and heated 1 hr more. It then was cooled, and the precipitated pyridopyrimidine base was filtered and recrystallized from 70% EtOH–H_2O which was acidified with HCl. 2,4-Diamino-6-isobutylpyrido[2,3-*d*]pyrimidine hydrochloride (**16**, 16.3 g, 50%) was obtained. This compound could also be crystallized as the isethionate.

2,4-Diamino-6-(*p*-nitrobenzyl)pyrido[2,3-*d*]pyrimidine.—2,4-Diamino-6-benzylpyrido[2,3-*d*]pyrimidine (3.0 g, 0.01 mole) was dissolved in 50 ml of cold, concentrated H_2SO_4. Powered KNO_3 (1.01 g, 0.01 mole) was added, and the solution was stirred at 0° for 1.5 hr. It then was poured into 400 ml of 50% ice and EtOH and brought to a pH of 3 by addition of 17 *N* NaOH. This mixture was filtered, and the precipitate was recrystallized from 800 ml of 70% EtOH–H_2O to yield 2.0 g (51%) of the half-sulfate dihydrate (Table IV).

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