SYNTHESIS AND PROPERTIES OF SOME PYRIMIDO[5,4-d]PYRIMIDINE DERIVATIVES

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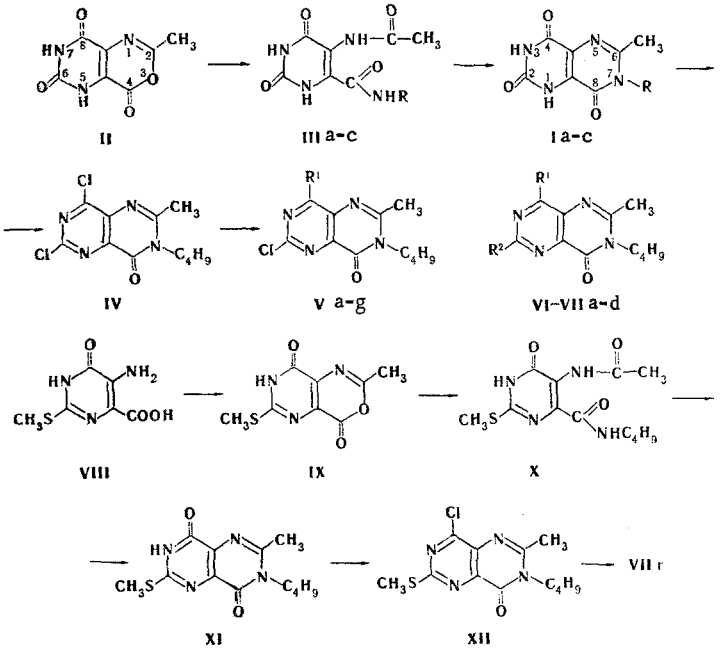
A method for the preparation of 2,4,8-trioxo-6-methyl derivatives of pyrimido[5,4-d]pyrimidine with various alkyl residues in the 7 position is described. It is shown that the chlorine in the 4 position of the 2,4-dichloro derivative of pyrimido[5,4-d]pyrimidine is the most labile in nucleophilic substitution reactions.

Substances having high biological activity are found among pyrimido[5,4-d]pyrimidine derivatives. Of these, the medicinal preparation persantine is of particular interest [1]. The starting compounds for the synthesis of derivatives of this sort are 2,4,6,8-tetraoxo and 2,4,8-trioxo derivatives of pyrimido[5,4-d]-pyrimidine, which were obtained by condensation of 5-aminoorotic acid with urea or formaldehyde [2]. We have developed a new method for the preparation of previously undescribed trioxo derivatives of pyrimido-[5,4-d]pyrimidine with various alkyl residues in the 7 position (Ia-c). It consists in the reaction of 4,6,8-trioxo-2-methyl-4H-5,6,7,8-tetrahydropyrimido[5,4-d]-1,3-oxazine (II) [3] with alkylamines and thermal cyclization of the resulting 5-acetamidoorotic acid alkylamides (IIIa-c). 2,4-Dichloropyrimidopyrimidine IV was synthesized by the action of phosphorus oxychloride on oxo derivative Ia. The different capacities of the chlorine atoms in the 2 and 4 positions of IV with respect to nucleophilic substitution reactions enabled us to accomplish their successive substitution. Replacement of one chlorine atom to give amines Va-f occurs in the reaction of chloro derivative IV with an equimolar amount of amine at 20-25°. Derivative Vg was obtained from IV by reaction with sodiomalonic ester.



I, III a $R=C_4H_9$; b $R=CH_3$; c $R=CH_2CH_2OH$; V a R^1=piperidino b $R^1=N(C_2H_5)_2$; c $R^1=NH_2$; d $R^1=NHCH_2C_6H_5$; e R^1=2-$\Delta^{1,2}$ cyclohexenylethylamino f $R^1=NHCH(CH_3)_2$; g $R^1=CH(COOC_2H_5)_2$; VI a $R=R^2=NHC_4H_9$; b $R^1=R^2=OCH_3$; c $R^1=R^2=SH$; d $R^1=R^2=SCH_3$; VII a R^1=piperidino $R^2=N(CH_2CH_2OH)_2$; b $R^1=NH_2$, $R^2=OCH_3$; c $R^1=NH_2$, $R^2=SH$; d $R^1=NH_2$, $R^2=SCH_3$

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C*	Found, %					Emperical formula	Calc. %					Yield, %
		C	H	Cl	N	S		C	H	Cl	N	S	
Ia	300—302	52,9	5,6		22,4		$C_{11}H_{14}N_4O_3$	52,8	5,6		22,4		50
Ib	>300	46,0	3,9		26,6		$C_8H_8N_4O_3$	46,1	3,8		26,9		47
Ic	320	45,0	4,2		23,6		$C_9H_{10}N_4O_4$	45,4	4,2		23,5		61
IV	117—119	46,0	4,2	24,4	19,4		$C_{11}H_{12}Cl_2N_4O$	46,0	4,2	24,7	19,5		71
Va	146—149	57,2	6,5	10,7	20,4		$C_{16}H_{22}ClN_5O$	57,2	6,5	10,6	20,9		77
Vb	127—129	55,6	6,8	11,4			$C_{15}H_{22}ClN_5O$	55,6	6,8	11,3			72
Vc	233—235	49,3	5,2	13,2	25,9		$C_{11}H_{14}ClN_5O$	49,3	5,2	13,3	26,2		94
Vd	180—181	60,4	5,7	9,6	19,6		$C_{18}H_{20}ClN_5O$	60,4	5,6	9,9	19,6		60
Ve	109—111	60,7	6,8	9,3	18,4		$C_{19}H_{26}ClN_5O$	60,7	6,9	9,4	18,6		73
Vf	121	54,3	6,3	11,4	22,7		$C_{14}H_{19}ClN_5O$	54,5	6,1	11,5	22,7		62
Vg	107—108	52,8	5,6	8,4	13,6		$C_{18}H_{22}ClN_4O_5$	52,8	5,4	8,7	13,6		74
VIa	194—196	63,3	9,0		23,7		$C_{19}H_{32}N_6O$	63,3	8,9		23,3		57
VIb	165—167	56,1	6,2				$C_{13}H_{18}N_4O_3$	56,1	6,5				62
VIc	>340					21,9	$C_{11}H_{14}N_4OS$					22,0	96
VId	145—147	50,1	5,9		17,9	20,6	$C_{13}H_{18}N_4OS_2$	50,3	5,8		18,1	20,6	79
VIIa	238	59,4	7,8		20,8		$C_{20}H_{32}N_6O_3$	59,4	7,9		20,8		69
VIIb	181—182	54,7	6,3		27,0		$C_{12}H_{17}N_5O_2$	54,7	6,5		26,6		81
VIId	190—192	51,5	6,0		25,4	11,6	$C_{12}H_{17}N_5OS$	51,6	6,1		25,4	11,5	63
XI	233—235	51,3	5,8		20,0	11,5	$C_{12}H_{16}N_4O_2S$	51,4	5,7		20,0	11,4	61
XII	119—121	48,2	5,2	11,6	18,6	11,4	$C_{12}H_{15}ClN_4OS$	48,2	5,0	11,9	18,8	10,7	45

*The compounds were purified by crystallization: Ia from DMF, Ib,c and XI from water, IV, Va,d, and VIIa,b,d from alcohol, Vb,e-g and VIa,b,d, from 80% alcohol, Vc from aqueous DMF, and XII from aqueous alcohol.

The corresponding 2,4-disubstituted VIa-c were obtained from chloro derivative IV by reaction with excess amine or other nucleophilic reagents. The use of monochloro derivatives Va,c as the starting compounds in nucleophilic substitution reactions enabled us to obtain pyrimide[5,4-d]pyrimidines VIIa-c with various substituents in the 2 and 4 positions. Since it is known that the chlorine atom in the 4 position in the pyrimidine series is the most labile, we assigned monosubstituted Va-g and disubstituted VIIa-d structures to the synthesized pyrimido[5,4-d]pyrimidine derivatives. To confirm the structures of the compounds, we accomplished the synthesis of VIId by an alternative method from the previously described 2-methylthio-4-oxo-5-amino-3,4-dihydropyrimidine-6-carboxylic acid (VIII) [4]. Compound IX was obtained from acid VIII by reaction with acetic anhydride, and we subsequently obtained 2-methylthio derivative XI by the method that we developed; XI was converted to 4-chloro derivative XII by the usual method. 2-Methylthio-4-amino-6-methyl-7-butyl-8-exo-7,8-dihydropyrimido[5,4-d]pyrimidine, identical to VIId formed by methylation of 2-mercapto derivative VIIc, was obtained by heating XII with an alcohol solution of ammonia.

EXPERIMENTAL

Metal Silufol plates were used for thin-layer chromatography, which was accomplished with a butyl alcohol–acetic acid–water system (4:1:5). The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer.

2,4,8-Trioxo-6-methyl-7-butyl-1,2,3,4,7,8-hexahydropyrimido[5,4-d]pyrimidine (Ia). A 5-g (25.6 mmole) sample of II was added to a solution of 5 g (68.5 mmole) of n-butylamine in 50 ml of water, and the mixture was allowed to stand for 24 h. The resulting solution was acidified, and IIIa was separated and heated at 250-260°. The solidified melt was crystallized from dimethylformamide (DMF) to give 3.2 g of product Oxo derivatives Ib and Ic were obtained similarly, but the cyclization of the intermediately formed IIIb and IIIc was carried out by refluxing in DMF for 5 min. The characteristics of these and all of the subsequent compounds are presented in Table 1.

2,4-Dichloro-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (IV). A mixture of 7.5 g (26 mmole) of Ia, 300 ml of $POCl_3$, and 21 g (153 mmole) of $(C_2H_5)_3N \cdot HCl$ was refluxed for 8 h, after which the $POCl_3$ was removed by vacuum distillation. The residue was treated with ice, and the solution was neutralized with $NaHCO_3$ and extracted with chloroform. Evaporation of the chloroform yielded 6.2 g of IV.

2-Chloro-4-piperidino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (Va). A 0.6-g (7 mmole) sample of piperidine was added to mixture of 1 g (3.5 mmole) of IV in 30 ml of alchol, and the mixture was stirred at 20-25° for 6 h. The resulting solution was vacuum evaporated, and the residue was triturated

with aqueous alcohol. The solid was removed by filtration to give 0.9 g of Va with R_f 0.6. Amines Vb,d-f were similarly obtained. Compound Vb had R_f 0.87, Vd had R_f 0.8, Ve had R_f 0.9, and Vf had R_f 0.8.

2-Chloro-4-amino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (Vc). A mixture of 1 g (3.5 mmole) of IV, 15 ml of alcohol, and 25 ml of 23% ammonium hydroxide was stirred at 20-25° for 48 h, after which the precipitate was removed by filtration to give 0.65 g of Vc with R_f 0.75.

2-Chloro-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidin-4-ylmalonic Ester (Vg). A solution of 1.8 g (6.3 mmole) of IV in 10 ml of toluene was added to sodiomalonic ester obtained from 0.35 g (15 g-atom) of sodium and 2.4 ml (15.8 mmole) of ethyl malonate in 20 ml of toluene, and the mixture was stirred at 40° for 1 h. Water (30 ml) was added to the suspension, and the aqueous layer was separated, acidified to pH 2, and extracted with chloroform. The chloroform was vacuum evaporated, and the residue was triturated with petroleum ether. The yield of Vg was 1.9 g.

2,4-Dibutylamino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIa). A mixture of 0.7 g (2.5 mmole) of IV and 1.5 g (20 mmole) of butylamine in 10 ml of alcohol was refluxed for 4 h, after which the resulting solution was evaporated to give 0.5 g of IVa with R_f 0.39.

2,4-Dimethoxy-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIb). A 0.5-g (1.7 mmole) sample of IV was added to a solution of sodium methoxide obtained from 0.14 g (6 g-atom) of sodium and 15 ml of methanol, and the mixture was allowed to stand at 20-25° for 6 h. The solution was vacuum evaporated to give 0.3 g of VIb with R_f 0.35.

2,4-Dimercapto-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIc). A 5-ml sample of a 10% aqueous solution (9 mmole) of NaSH was added to a solution of 1.2 g (4.2 mmole) of IV in 25 ml of chloroform, and the mixture was stirred for 5 h. The precipitated sodium salt was separated and dissolved in 100 ml of water, and the solution was acidified with acetic acid. Workup gave 1.1 g of VIc.

2,4-Dimethylthio-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VId). A solution of 0.25 g (4.4 mmole) of KOH in 20 ml of water and 0.4 ml (4.3 mmole) of dimethyl sulfate were added successively to 0.6 g (2 mmole) of VIc, and the mixture was stirred at 20-25° for 4 h. The precipitate was removed by filtration to give 0.5 g with R_f 0.65.

4-Piperidino-2-diethanolamino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIIa). A 1.2-g (3.6 mmole) sample of Va was heated in 10 ml of diethanolamine at 100-110° for 2 h, after which the mixture was treated with water, and the precipitate was removed by filtration to give 1 g of VIIa with R_f 0.15.

2-Methoxy-4-amino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIIb). A 1-g (3.7 mmole) sample of Vc was added to solution of sodium methoxide obtained from 0.12 g (5.2 mmole) of sodium and 25 ml of alcohol, and the mixture was refluxed for 5 h. The resulting solution was vacuum evaporated, and the residue was washed with water. The yield of VIIb, with R_f 0.42, was 0.8 g.

2-Mercapto-4-amino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIIc). A mixture of 0.5 g (1.87 mmole) of Vc, 17 ml of alcohol, and 2 ml of 10% aqueous (3.6 mmole) NaSH solution was refluxed for 2 h, after which it was acidified to pH 1 with hydrochloric acid. The precipitate was removed by filtration and reprecipitated from aqueous alkali solution by the addition of hydrochloric acid. The yield was 0.3 g.

2-Methylthio-4-amino-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (VIId). A) A solution of 0.3 g (1 mmole) of XII in 28 ml of a 10% solution of ammonia in alcohol was heated at 100° for 6 h, after which it was vacuum evaporated. Workup gave 0.2 g of VIId with R_f 0.52.

B) A 0.1-ml (1.2 mmole) sample of dimethyl sulfate was added at 20-25° to a solution of 0.3 g (1.2 mmole) of VIIc and 0.06 g (1.1 mmole) of KOH in 15 ml of water, and the mixture was stirred at 20-25° for 4 h. The precipitate was removed by filtration to give 0.2 g of VIId. The product was identical to the product obtained by method A. IR spectrum: 3320, 3500 (NH_2), 1680 (C = O), and five bands at 1400-1600 cm^{-1} (pyrimidine C = C and C = N).

2-Methylthio-4,8-dioxo-6-methyl-7-butyl-3,4,7,8-tetrahydropyrimido[5,4-d]pyrimidine (XI). A solution of 5.8 g of VIII [4] in 100 ml of acetic anhydride was refluxed for 2 h. The resulting IX [4.5 g (23.3 mmole)] was added to 2.4 g (33 mmole) of butylamine in 25 ml of water, and the solution was allowed to stand at 20-25° for 24 h. It was then acidified, and the precipitated X was removed by filtration. The latter was cyclized by dissolving it in 20 ml of 2 N KOH and allowing the solution to stand at 20-25° for 30 min. The precipitated potassium salt of XI was removed by filtration, washed with acetone, dissolved in a small amount of water, and acidified. The yiled of XI, with R_f 0.51, was 3.4 g.

2-Methylthio-4-chloro-6-methyl-7-butyl-8-oxo-7,8-dihydropyrimido[5,4-d]pyrimidine (XII). A 1.2-g (3.8 mmole) sample of XI was refluxed with 20 ml of $POCl_3$, after which the resulting solution was vacuum evaporated, and the residue was treated with ice. The aqueous solution was neutralized with dry $NaHCO_3$ and extracted with chloroform. The chlorofom was vacuum evaporated, and the residue was triturated with petroleum ether to give 0.5 g of XII.

LITERATURE CITED

1. H. Spitzbarth, Arzneimittel-Forsch., 9, 59 (1959).
2. F. G. Fischer and J. Roch, Ann., 572, 217 (1951).
3. N. E. Britikova, L. A. Belova, K. A. Chkhikvadze, and O. Yu. Magidson, Khim. Geterotsikl. Soedin., No. 2, 270 (1973).
4. Masuo Murakami, Shigemi Kawahara, Sanae Ishida, Mikio Ohno, and Hiroshi Horigychi, US patent No. 3,562,265 (1971); Ref. Zh. Khim., 21N, 470 (1971).

REACTIVITIES AND TRANSFORMATIONS OF PHENAZYL RADICALS

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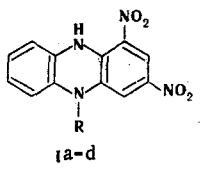
The kinetics of the recombination of phenazyl radicals and their reaction with secondary amines were studied by ESR spectroscopy. A relationship between the reactivities of the radicals and the character of the substituent in the 5 position was observed. The possibility of the addition of secondary amines to the dihydrophenazine system was shown during a study of the reaction of phenazyl radicals with the former.

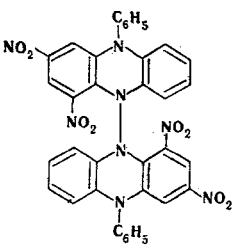
Continuing our study of the free radicals of a number of 5-substituted dihydrophenazines [1], we made a kinetic study of their recombination and reaction with secondary amines.

The radicals were generated by oxidation of dihydrophenazines Ia-d with lead dioxide in benzene, and the formation of paramagnetic particles was recorded with an RÉ-1301 radiospectrometer. The observed decrease in the intensities of the ESR signals with time (Fig. 1) provided evidence for recombination of the free radical particles and was accompanied by conversion of the green color characteristic for a solution of the free radical to violet.



Ia-d

I a R = n-C_4H_9; b R = C_6H_5; c R = 2,4-$(NO_2)_2C_6H_3$; d R = 2,4,6-$(NO_2)_3C_6H_2$



II

To study the structure of the transformation product we undertook the preparative oxidation of Ib with subsequent exhaustive recombination of the generated radical and chromatographic separation of the resulting solution on Al_2O_3.

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