INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXVI.* PROPERTIES OF PYRIMIDO[5,4-b][1,4]OXAZIN-7-ONES

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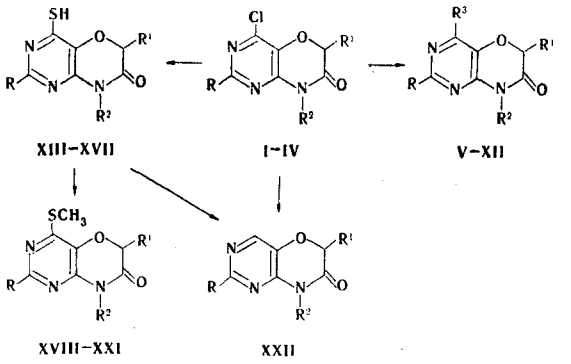
The chlorine atom in 4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4-oxazin-7-ones is replaced by amine residues and mercapto and methoxy groups and can also be removed in the presence of Pd/C. Pyrimidooxazin-7-ones are alkylated in the 8 position, while, depending on the conditions, the 4-mercapto derivatives are alkylated either at the mercapto group or simultaneously at the mercapto group and in the 8 position.

In a continuation of the study in [2], we have investigated the nucleophilic substitution of the chlorine atom in 2-methyl-4-chloro- (I) and 4-chloropyrimido[5,4-b][1,4]oxazin-7-ones (II) and the alkylation of some pyrimidooxazin-7-ones. The corresponding 4-morpholino(piperidino)pyrimidooxazin-7-ones (V-VIII) are formed in the reaction of I and II with morpholine or piperidine in refluxing n-butyl alcohol. The reaction of I with sodium methoxide in an autoclave at 110°C gives 2-methyl-4-methoxypyrimidooxazin-7-one (IX). Like most heterocyclic lactams, the pyrimidooxazin-7-ones (I and V) are alkylated by alkyl halides (methyl iodide and benzyl chloride) in the presence of sodium methoxide at the nitrogen atom of the lactam group to give 8-alkylpyrimidooxazin-7-ones (X-XII). The corresponding 4-mercaptopyrimidooxazin-7-ones (XIII-XV) are obtained in good yield when I, 2,6-dimethyl-4-chloro- (III), and 2-methyl-4-chloro-6-ethylpyrimidooxazin-7-ones (IV) are heated with thiourea in alcohol.

4-Mercaptopyrimidooxazin-7-one (XVI) was similarly synthesized from II and potassium iodide.



I R=CH_3, R^1=R^2=H; II R=R^1=R^2=H; III R=R^1=CH_3, R^2=H; IV R=CH_3, R^1=C_2H_5, R^2=H; V R=CH_3, R^1=R^2=H, R^3=morpholino; VI R=CH_3, R^1=R^2=H, R^3= piperidino; VII R=R^1=R^2=H, R^3=morpholino- VIII R=R^1=R^2=H, R^3= piperidino; IX R=CH_3, R^1=R^2=H, R^3=OCH_3; X R=R^2=CH_3, R^1=H, R^3=Cl; XI R=CH_3, R^1=H, R^2=$CH_2C_6H_5$, R^3=Cl; XII R=R^2=CH_3, R^1=H, R^3=morpholino; XIII R=CH_3, R^1=R^2=H; XIV R=R^1=CH_3, R^2=H; XV R=CH_3, R^1=C_2H_5, R^2=H; XVI R=R^1=R^2=H; XVII R=R^2=CH_3, R^1=H; XVIII R=CH_3, R^1=R^2=H; XIX R=R^1=R^2=H; XX R=R^2=CH_3, R^1=H; XXI R=R^2=CH_3, R^1=C_2H_5; XXII R=CH_3, R^1=R^2=H

*See [1] for communication XXV.

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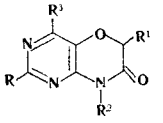
TABLE 1



V–XXII

Comp.	R	R¹	R²	R³	mp, °C[a]	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	N	S	C	H	N	S	
V	CH_3	H	H	morpholino	243—245	$C_{11}H_{14}N_4O_3$	53,1	5,6	22,7	—	52,8	5,6	22,4	—	95
VI	CH_3	H	H	piperidino	177,5—178,5	$C_{12}H_{16}N_4O_2$	58,4	6,8	22,3	—	58,1	6,5	22,6	—	92,7
VII	H	H	H	morpholino	242—243	$C_{10}H_{12}N_4O_3$	51,1	5,5	23,7	—	50,8	5,1	23,7	—	99
VIII	H	H	H	piperidino	179—180	$C_{11}H_{14}N_4O_2$	56,2	6,1	23,6	—	56,4	6,0	23,9	—	81
IX	CH_3	H	H	OCH_3	227—228	$C_8H_9N_3O_3$ [b]	49,0	4,9	21,2	—	49,2	4,7	21,5	—	92,5
X	CH_3	H	CH_3	Cl	145,5—146	$C_8H_8ClN_3O_2$ [c]	44,7	3,7	19,3	—	45,0	3,8	19,7	—	80
XI	CH_3	H	$CH_2C_6H_5$	Cl	87—88	$C_{14}H_{12}ClN_3O_2$	58,1	4,2	14,2	—	58,1	4,2	14,5	—	59
XII	CH_3	H	CH_3	morpholino	121—122	$C_{12}H_{16}N_4O_3$	54,3	5,9	21,0	—	54,5	6,1	21,2	—	91
XIII	CH_3	H	H	SH	>300	$C_7H_7N_3O_2S$	42,9	3,6	21,1	15,7	42,6	3,6	21,3	16,3	92,6
XIV	CH_3	CH_3	H	SH	>300	$C_8H_9N_3O_2S$	45,4	4,4	19,7	15,2	45,5	4,3	19,9	15,2	85
XV	CH_3	C_2H_5	H	SH	>300	$C_9H_{11}N_3O_2S$	47,6	4,9	19,0	13,9	48,0	4,9	18,7	14,2	85
XVI	H	H	H	SH	>300[d]	$C_6H_5N_3O_2S$	39,0	2,6	23,1	17,1	39,3	2,8	22,9	17,5	87
XVII	CH_3	H	CH_3	SH	281[e]	$C_8H_9N_3O_2S$	45,2	4,4	20,0	15,1	45,5	4,3	19,9	15,2	86
XVIII	CH_3	H	H	SCH_3	228—229	$C_8H_9N_3O_2S$	45,1	4,2	19,9	15,0	45,5	4,3	19,9	15,2	71
XIX	H	H	H	SCH_3	270—271	$C_7H_7N_3O_2S$	42,9	3,8	21,2	16,3	42,6	3,6	21,3	16,3	84
XX	CH_3	H	CH_3	SCH_3	127,5—128,5	$C_9H_{11}N_3O_2S$	48,1	5,0	18,4	14,1	48,0	4,9	18,7	14,2	86
XXI	CH_3	C_2H_5	CH_3	SCH_3	98—100	$C_{11}H_{15}N_3O_2S$	52,1	5,4	16,7	12,6	52,2	6,0	16,6	12,7	99
XXII	CH_3	H	H	H	267—268	$C_7H_7N_3O_2$	51,4	4,3	25,4	—	50,9	4,3	25,5	—	84 (A) 93 (B)

[a]Compounds V and XII were crystallized from water; VI, IX, XX, and XXII were crystallized from methanol; VII was crystallized from n-butyl alcohol; VIII and X were crystallized from alcohol; XI was crystallized from water–alcohol (1 : 1); XIII-XV were crystallized from acetic acid; XVII was crystallized from aqueous acetic acid; and XIX and XXI were crystallized from aqueous alcohol. [b]Found, %: Cl 16.6. Calculated, %: Cl 16. [c]Found, %: Cl 12.1. Calculated, %: Cl 12.2. [d]This compound was reprecipitated from NaOH solution by the addition of acetic acid. [e]This is the temperature at which the compound decomposed.

4-Methylthio derivatives XVIII and XIX were obtained by the action of methyl iodide on an aqueous alkali solution of XIII or XVI at about 20°. If the reaction of XIII and XV with methyl iodide is carried out in refluxing alcohol in the presence of two equivalents of sodium methoxide, the mercapto group and the nitrogen in the 8 position are simultaneously methylated to give 2,8-dimethyl-4-methylthio- (XX) and 2,8-dimethyl-4-methylthio-6-ethylpyrimidooxazin-7-one (XXI). Compounds with a free mercapto group in the 4 position of the two-ring system and substituents in the 8 position can be obtained by the action of thiourea on 8-alkyl-4-chloropyrimidooxazin-7-ones. This route was used to obtain XVII from X. The reaction of XVII with methyl iodide was used to synthesize XX.

2-Methyl-4-mercaptopyrimidooxazin-7-one (XIII) is smoothly desulfurized to 2-methylpyrimidooxazin-7-one (XXII) on treatment with Raney nickel. This compound is also obtained by dehalogenation of I in the presence of Pd/C.

The structures of the compounds obtained were confirmed by IR spectroscopy. Absorption bands characteristic for the amide CO group (1690-1720 cm^{-1}) and the amide NH group (3100-3170 cm^{-1}) are observed in the IR spectra of mineral oil suspensions of V, IX, XVIII, and XXII; the latter bands vanish in the spectra of X, XI, XVII, XX, and XXI, which are substituted in the 8 position.

EXPERIMENTAL

2-Methyl-4-morpholino-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (V). A 2.5-g (28 mmole) sample of morpholine was added to 2.3 g (11.5 mmole) of I in 60 ml of n-butyl alcohol, and the mixture was refluxed for 6 h and cooled to 20°. The precipitated V was separated and washed on the funnel with water. Compounds VI-VIII were similarly obtained.*

2-Methyl-4-methoxy-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (IX). A 0.62-g (3.1 mmole) sample of I was added to sodium methoxide, obtained from 0.29 g (12.4 mg-atom) of sodium in 30 ml of methanol, and the mixture was heated in an autoclave at 110° (bath temperature) for 6 h. It was then cooled, and the solvent was evaporated to dryness. The residue was dissolved in 15 ml of water, the solution was acidified to pH 6 with dilute HCl (1 : 4), and the precipitated IX was separated and washed with water.

2,8-Dimethyl-4-morpholino-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XII). A 0.5-g (2 mmole) sample of V and 1 ml of methyl iodide were added to sodium methoxide, prepared from 0.05 g (2 mg-atom) of sodium in 20 ml of methanol, and the solution was refluxed for 3 h. The alcohol was evaporated to dryness, and the residue was washed with water to give XII.

Compounds X and XI were similarly obtained.

2-Methyl-4-mercapto-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XIII). A mixture of 2.2 g (11.5 mmole) of I and 2.2 g (28.9 mmole) of thiourea in 60 ml of absolute alcohol was refluxed for 6 h, after which it was cooled and the precipitated XIII was separated and washed with water. Compounds XIV, XV, and XVII were similarly obtained.

Compound XIV was similarly obtained, but the reaction was carried out with a catalytic amount of potassium iodide.

2-Methyl-4-methylthio-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XVIII). A solution of 0.5 ml of methyl iodide in 2 ml of methanol was added in one batch to a solution obtained from 0.5 g (2.54 mmole) of XIII and 0.011 g (2.54 mmole) of NaOH in 10 ml of water. Immediately after the addition of the methyl iodide, a precipitate began to form. The reaction mass was held at about 20° for 24 h, after which the XVIII was separated and washed with water. Compounds XIX and XX were similarly obtained from XVII.

2,8-Dimethyl-4-methylthio-6,7-dihydro-8H-pyrimido[5,4-b][1,4-oxazin-7-one (XX). A 0.53-g (2.68 mmole) sample of XIII and 1 ml of methyl iodide were added to sodium methoxide obtained from 0.125 g (5.36 mg-atom) of sodium in 20 ml of methanol, and the resulting solution was refluxed for 3 h. The mixture was evaporated to dryness, and the residue was washed with water to give XX. Compound XXI was similarly obtained.

2-Methyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXII). A. A mixture of 1.04 g (5.21 mmole) of I, 0.21 g (5.21 mmole) of NaOH, and 0.3 g of 5% Pd on BAU carbon was hydrogenated in 30 ml of alcohol at about 20° and normal pressure for 3.5 h until the calculated amount (120 ml) of hydrogen had

*In the isolation of VI, the alcohol was removed by distillation to dryness.

been absorbed. A 10-ml sample of 1 N NaOH was added to the reaction mass, and the mixture was filtered to remove the carbon. The carbon was washed on the filter with alcohol, and the mother liquors were combined and evaporated in vacuo to 15 ml. This solution was neutralized with acetic acid, and the precipitated XXII was separated.

B. A 3-g sample of Raney nickel was added in portions to a solution of 0.93 g of XIII in 40 ml of water containing 3 ml of concentrated NH_4OH at 90-95°, and the mixture was heated at the same temperature for 1 h. The catalyst was removed and washed with hot water, and the mother liquors were combined and evaporated to dryness in vacuo. The residue was crystallized from a mixture of water and acetic acid to give XXII. The melting point of the product was not depressed by mixing it with the sample obtained via method A.

The IR spectra of mineral oil suspensions of samples of the compounds were recorded with a UR-10 double-beam spectrophotometer.

LITERATURE CITED

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2. N. V. Sazonov and T. S. Safonova, Khim. Geterotsikl. Soedin., 1285 (1972).