INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXIX.* SYNTHESIS AND PROPERTIES OF 6-CARBETHOXY-8H-PYRIMIDO[5,4-b][1,4]OXAZINES

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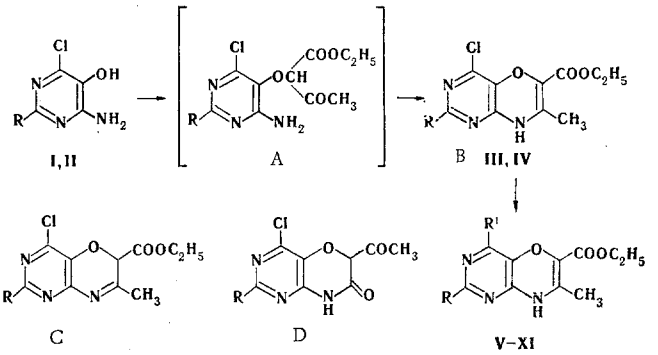
Reaction of 4-chloro-5-hydroxy-6-aminopyrimidine and its 2-methyl derivatives with α-chloroacetoacetic ester gave the corresponding 4-chloro-6-carbethoxy-8H-pyrimido-[5,4-b][1,4]oxazines, which were converted to 4-aminopyrimidooxazines by reaction with amines.

In developing the research in [2, 3] on the synthesis of pyrimidooxazines, we studied the reaction of 4-chloro-5-hydroxy-6-aminopyrimidine (I) and its 2-methyl derivative (II) with α-chloroacetoacetic ester. Reaction of II with α-chloroacetoacetic ester in the presence of sodium ethoxide gave 2,7-dimethyl-4-chloro-6-carbethoxy-8H-pyrimido[5,4-b][1,4]oxazine (III) in ~10% yield. If triethylamine is used in place of sodium ethoxide in the reactions of I and II with α-chloroacetoacetic ester, the yield of pyrimidooxazines III and IV reaches 80%.



I R=H; II R=CH_3; III R=CH_3; IV R=H; V R=CH_3, R^1=morpholino; VI R=H, R^1=morpholino; VII R=CH_3, R^1=piperidino; VIII R=H, R^1=piperidino; IX R=H, R^1=$=N(C_2H_5)_2$; X R=H, R^1=diethylcarbamoylpiperazino; XI R=H, R^1=$NHCH_2C_6H_5$.

The first step in this reaction is apparently alkylation of the hydroxyl group of pyrimidine, as a result of which intermediate esters A are formed. The cyclization of esters A may proceed at both the keto and carbethoxy groups to give, respectively, 8H(or 6H)-pyrimidooxazines B and C or pyrimidooxazine D. According to the data in [4], the pyrido[4,3-b][1,4]oxazine, obtained by reaction of 3-amino-4-hydroxypyridine with α-chloroacetoacetic ester, was assigned the 6H structure with the double bond in the oxazine ring at C_7–C_8.

The individuality of the III and IV that we obtained was proved by chromatography.

The structure of III and IV as derivatives of the 8H structure (B) was proved by the IR and PMR spectra. The absorption band of an NH group at 3140-3270 cm^{-1} and one band at 1670-1720 cm^{-1}, which can be

*See [1] for communication XXVIII.

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TABLE 1. 6-Carbethoxy-7-methyl-8H-pyrimido[5,4-b][1,4]oxazines

Compound	mp, °C[a]	Empirical formula	Found, %			Calc., %			IR spectrum, cm^{-1}		UV spectrum, nm	Yield, %
			C	H	N	C	H	N	ν_{CO}	ν_{NH}	λ_{max} (lg ε)	
III	229—230	$C_{11}H_{12}ClN_3O_3$	49,4	4,7	15,5	49,00	4,5	15,6	1670[b] 1705	3270[b] 3410 3140	236 (4,2); 253 (3,9); 328 (3,5); 390 (3,5)	81,5
IV	260[c]	$C_{10}H_{10}ClN_3O_3$[d]	47,1	4,4	16,3	47.00	3,9	16,4	1720	3200 3200	233 (4,2); 255 (4,0); 330 (3,6); 390 (3,6)	83,5
V	210—211	$C_{15}H_{20}N_4O_4$	56,0	6,3	17,6	56,2	6,3	17,5	1700	3250	241 (4,1); 272 (3,8); 384 (3,2)	90,3
VI	227—229	$C_{14}H_{18}N_4O_4$	55,2	6,0	18,4	54.9	5,9	18,3	1700	3160	241 (4,3); 274 (4,0); 380 (3,3)	97
VII	153—155	$C_{16}H_{22}N_4O_3$	60,6	7,1	17,3	60,4	7,0	17,6	1685	3300	244 (4,3); 280 (4,1); 384 (3,3)	95.3
VIII	200—202	$C_{15}H_{20}N_4O_3$	58,9	6,3	18,3	59,2	6,6	18,4	1700	3160	244 (4,3); 282 (4,1); 382 (3,3)	84
IX	177—179	$C_{14}H_{20}N_4O_3$	57,4	6,8	18,9	57,5	6,90	19,2	1705	3180	241 (4,3); 282 (4,1); 384 (2,9)	89,2
X	156—158	$C_{19}H_{28}N_6O_4$	56,7	6,9	20,8	56,4	7,0	20,8	1700	3160	243 (4,4); 273 (4,1); 384 (3,3)	92,3
XI	187—188	$C_{17}H_{18}N_4O_3$	62,6	5,6	17,2	62,7	5,60	17,1			231 (4,4); 273 (4,2); 402 (3,2)	31,4

[a] Compounds III, V, and VIII were recrystallized from ethyl acetate; IV, X, and XI were recrystallized from alcohol; VI was recrystallized from butyl alcohol; VII was recrystallized from aqueous methanol; and IX was recrystallized from aqueous alcohol. [b] This is the spectrum of a saturated solution in chloroform (1.03-ml layer). [c] Decomposition temperature. [d] Found: Cl 13.6%. Calculated: Cl 13.9%.

assigned to absorption of the CO group of an ester conjugated with a double bond, are detected in the IR spectra of III and IV; this is in agreement with structure B.

The signals of a proton attached to $C_{(6)}$ are absent in the PMR spectra of III and IV, but there are signals of protons of $COOC_2H_5$ and CH_3 groups attached to $C_{(2)}$; in addition, the spectrum of III contains signals of protons of a CH_3 group attached to $C_{(2)}$, while the spectrum of IV contains the signal of a proton attached to $C_{(2)}$. Thus the data from the IR and PMR spectra confirm the structures of III and IV as 8H derivatives (structure B) and exclude structures C and D.

It has been shown that 4-chloro-6-carbethoxypyrimidooxazines III and IV undergo nucleophilic substitution. Thus the reaction of III and IV with morpholine, piperidine, diethylamine, diethylcarbamoylpiperazine, and benzylamine gives 4-amino-6-carbethoxypyrimidooxazines V-XI, the structure of which was confirmed by the presence of the absorption band of an ester CO group in the IR spectra and by the presence of the absorption maxima characteristic for the pyrimidooxazine system in the UV spectra.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the synthesized compounds were recorded with Perkin-Elmer 457 and UR-10 spectrometers. The UV spectra of alcohol solutions were recorded with an EPS-3 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a C-60HL spectrometer with an operating frequency of 60 MHz and tetramethylsilane as the internal standard (the proton signals are presented on the δ scale). Chromatography was carried out on Silufol UV_{254} plates in benzene–alcohol (22 : 3).

2,7-Dimethyl-4-chloro-6-carbethoxy-8H-pyrimido[5,4-b][1,4]oxazine (III). A 15-mmole sample of α-chloroacetoacetic ester [5] was added all at once to a solution of 10 mmole of II and 15 mmole of triethylamine in 12 ml of absolute alcohol, and the mixture was refluxed for 7 h. It was then cooled, and 10 ml of water was added to the suspension. The precipitate was separated and washed on the filter with 10 ml of alcohol to give 2.2 g (81.5%) of III with mp 225-227°. PMR spectrum (in ppm): 1.45 (triplet, 3H, CH_3 from C_2H_5), 2.28 (singlet, 3H, 7-CH_3), 2.58 (singlet, 3H, 2-CH_3), 4.5 (quartet, 2H, CH_2 from C_2H_5).

4-Chloro-7-methyl-6-carbethoxy-8H-pyrimido[5,4-b][1,4]oxazine (IV). This compound was similarly obtained. PMR spectrum (in ppm): 1.45 (triplet, 3H, CH_3 from C_2H_5), 2.26 (singlet, 3H, 7-CH_3), 4.48 (quartet, 2H, CH_2 from C_2H_5), 8.26 (singlet, 1H, 2H).

4-Morpholino-7-methyl-6-carbethoxy-8H-pyrimido[5,4-b][1,4]oxazine (VI). A mixture of 0.4 g (1.56 mmole) of IV and 0.27 g (3.12 mmole) of morpholine in 10 ml of n-butyl alcohol was refluxed for 7 h, after which it was cooled, and the precipitate was separated and washed on the filter with 5 ml of alcohol and 10 ml of water to give 0.46 g (97%) of VI with mp 225-227°. A similar method was used to obtain V, VII, and XI (Table 1).

2,7-Dimethyl-4-piperidino-6-carbethoxy-8H-pyrimido[5,4-b][1,4]oxazine (VII). A mixture of 0.4 g (1.5 mmole) of III and 0.26 g (3 mmole) of piperidine in 10 ml of n-butyl alcohol was refluxed for 7 h, after which the solvent was removed by distillation, and 10 ml of water was added to the dry residue. The aqueous mixture was triturated, and the solid was removed by filtration to give 0.45 g (95.3%) of VII with mp 147-150°.

Compound X was similarly obtained.

4-Diethylamino-7-methyl-6-carbethoxy-8H-pyrimido[5,4-b][1,4]oxazine (IX). A mixture of 0.5 g (1.96 mmole) of IV and 0.6 g (4 mmole) of diethylamine in 25 ml of alcohol was heated in an autoclave at 130-140° (bath temperature) for 7 h. The alcohol was then evaporated to dryness, and the residue was washed with 10 ml of water to give 0.51 g (89.2%) of IX. The pyrimidooxazines were obtained as yellow crystalline substances that were quite soluble in chloroform.

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