Synthesis of Pyrimido[4,5-*e*][1,4]oxazepin-5-ones

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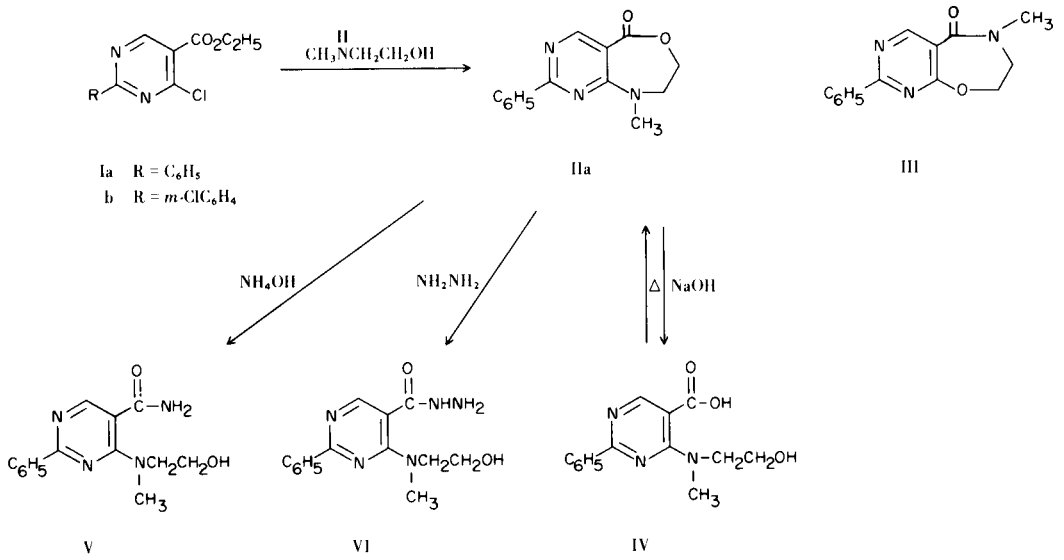
Eighteen novel pyrimido[4,5-*e*][1,4]oxazepin-5-ones were prepared directly *via* the reaction of either ethyl 4-chloro-2-phenyl-5-pyrimidinecarboxylate (Ia) or ethyl 4-chloro-2-*m*-chlorophenyl-5-pyrimidinecarboxylate (Ib) with a variety of substituted 2-(alkylamino)ethanols. A typical example was the preparation of 8,9-dihydro-9-methyl-2-phenylpyrimido[4,5-*e*][1,4]-oxazepin-5(7*H*)-one (IIa) from the reaction of Ia with 2-(methylamino)ethanol. Hydrolytic cleavage of the lactone ring in IIa with sodium hydroxide solution, followed by acidification with hydrochloric acid afforded 4-[(2-hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic acid (IV). Reactions of IIa with concentrated ammonium hydroxide or hydrazine also caused cleavage of the lactone ring, giving the corresponding amide (V) or hydrazide (VI), respectively. Structural assignments were supported by infrared and nuclear magnetic resonance spectra.

Previously, we reported on the use of ethyl 4-chloro-2-phenyl-5-pyrimidinecarboxylate (Ia) and related derivatives as intermediates for the preparation of several condensed pyrimidine systems (1a-d). Further interest in the chemistry and general pharmacologic action of such structural types prompted additional work in this area. As a result of that effort we now report the preparation of a new heterocyclic class, the pyrimido[4,5-*e*][1,4]oxazepin-5-ones (IIa-r) obtained directly *via* the reaction of Ia-b with a variety of substituted 2-(alkylamino)ethanols (2,2a).

In a typical example, treatment of Ia with 2-(methylamino)ethanol in refluxing ethanol containing sodium carbonate gave the lactone 8,9-dihydro-9-methyl-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5(7*H*)-one (IIa, Scheme I). The possibility that the reaction afforded instead, the isomeric lactam III, was considered unlikely on the basis of the infrared carbonyl absorption, which appeared at 5.88 μ. A similar lactone, 1-methyl-2,3-dihydro-4,1-benzoxazepin-5(1*H*)-one, has its carbonyl absorption at 5.86 μ (3). The lactam carbonyl band for III might be

SCHEME I



expected to appear in the region of 6.1 μ since we observed the carbonyl absorption of a closely related lactam analog, 6,9-dimethyl-6,7,8,9-tetrahydro-2-phenyl-5*H*-pyrimido[4,5-*e*][1,4]diazepin-5-one at this wavelength (1d). Further confirmatory evidence to support the lactone nature of IIa was obtained by an examination of ring cleavage products and their spectra. For example, hydrolysis of IIa with sodium hydroxide, followed by acidification, afforded 4-[(2-hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic acid (IV). As expected, IV when heated to 180° underwent cyclodehydration to give back the starting lactone IIa.

Some noteworthy nmr spectral changes which accompanied the transformation of IIa to IV are the following. In IIa, apart from the aromatic protons, the methyl protons are found as a sharp singlet at 3.28 δ. The two sets of methylene groups bridging the hetero atoms appear as triplets in an A_2X_2 pattern. The triplet of the methylene protons adjacent to the ring nitrogen atom is centered at 3.80 δ, while the methylene protons adjacent to the ring oxygen atom appear further downfield, centered at 4.56 δ (J = 2.5 cps). In the acid, IV, the methyl group protons again are found as a sharp singlet at 3.25 δ. The two sets of methylene group protons, however, now appear as a complex multiplet centered at 3.82 δ. The chemical shift of the methylene protons adjacent to the nitrogen atom remains essentially unchanged, while a substantial upfield shift of the methylene protons adjacent to the oxygen atom is observed. A paramagnetic shift of these protons might be expected, since in the open-chain acid they no longer experience the deshielding effect of the contiguous pyrimidine carbonyl moiety (4). The methylene protons next to the nitrogen atom, however, remain essentially in the same magnetic environment.

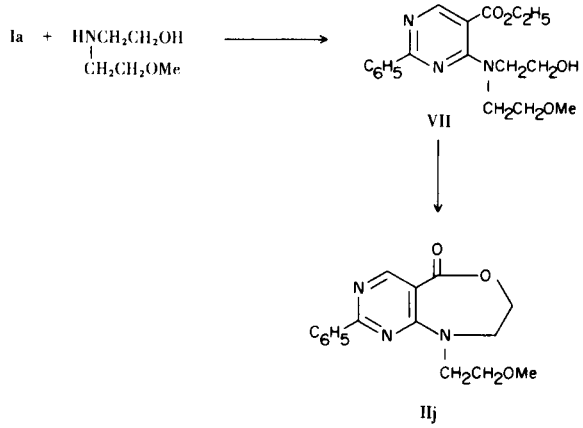
When IIa was treated with concentrated ammonium hydroxide or with hydrazine, cleavage of the lactone ring resulted affording the amide V or hydrazide VI, respectively.

Several other pyrimido[4,5-*e*][1,4]oxazepin-5-ones (IIb-r) were prepared directly by the reaction of suitably substituted aminoethanols with Ia or Ib. These are summarized in the table. The lactone carbonyl absorption bands for these compounds ranged from 5.83-5.97 μ.

In one example, the reaction of Ia with 2-(2-methoxyethylamino)ethanol in refluxing ethanol, a reaction time of 2.5 hours was insufficient for ring closure to the lactone to occur (Scheme II). The open chain hydroxy ester (VII) was obtained instead. The lactone, IIj, was obtained directly when the reaction was repeated with extended reflux time. It was shown that VII is an intermediate in the reaction by the fact that it could be readily converted to IIj under identical conditions. These observations indicate that the reaction proceeds in a stepwise fashion, *i.e.* dechloroamination followed by lactonization.

Several of the pyrimido[4,5-*e*][1,4]oxazepin-5-ones prepared for this study were found to be central nervous system depressants in test animals.

SCHEME II



EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in potassium bromide discs using a Perkin-Elmer (Model 21) spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer using dimethyl sulfoxide (DMSO-d_6). The chemical shifts are measured in ppm (δ) with respect to tetramethylsilane. The observed spectra are in accord with assigned structures, only essential spectral features being given for key compounds. The yields are the results of single experiments and are not considered optimal.

Most of the 2-(alkylamino)ethanols used for the preparation of the compounds in the table were commercially available.

2-Phenethylaminoethanol (5), 2-(3-diethylaminopropylamino)-ethanol (6) and 2-(2-methoxyethylamino)ethanol (7) were previously described.

8,9-Dihydro-9-methyl-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5-(7*H*)-one (IIa).

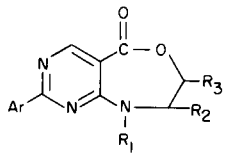
A stirred mixture of 12 g. of ethyl 4-chloro-2-phenyl-5-pyrimidinecarboxylate (Ia), 3.75 g. of 2-(methylamino)ethanol and 5.3 g. of powdered sodium carbonate in 50 ml. of ethanol was heated under reflux for 3.5 hours. The mixture was evaporated to dryness *in vacuo* in a rotary evaporator. Water (50 ml.) was added to the residue and the mixture was filtered. The collected crystals were washed with cold ethanol, affording 9.3 g. of product, m.p. 170-172°. The analytical sample, prepared by recrystallization from ethanol, had m.p. 170-173°; ir 5.88 μ (C=O); nmr δ 3.28 (s, 3H, CH_3), 3.80 (t, 2H, CH_2N), 4.56 (t, 2H, CH_2O, J = 2.5 cps).

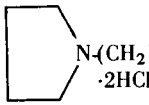
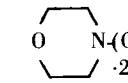
Alternatively, 1.5 g. of IV (described below) was heated for a period of 1 hour in an oil bath maintained at 180°. On cooling the reaction mixture to room temperature a solid was obtained which upon recrystallization from ethanol gave 0.85 g. of IIa, m.p. 168-172°. No depression of melting point was observed upon admixture with the sample prepared by the first method.

4-[(2-Hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic Acid (IV).

TABLE I

Pyrimido[4,5-*e*][1,4]oxazepin-5-ones



Compound	Ar	R_1	R_2	R_3	M.p., °C	% Yield	Recryst. Solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
IIa	C_6H_5	CH_3	H	H	170-173	80	ethanol	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46	65.70	5.16	16.63
b	C_6H_5	C_2H_5	H	H	126-128	15	ethanol	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.61	66.81	5.56	15.64
c	C_6H_5	$CH_3C(H)CH_3$	H	H	154-155	32	ethanol	$C_{16}H_{17}N_3O_2$	67.82	6.05	14.83	67.64	5.79	14.65
d	C_6H_5	$CH_3(CH_2)_3$	H	H	127-129	64	ethyl acetate	$C_{17}H_{19}N_3O_2$	68.66	6.44	14.13	68.38	6.06	14.23
e	*m*-ClC_6H_4	$CH_3(CH_2)_3$	H	H	98-100	8	ethanol	$C_{17}H_{18}ClN_3O_2$	61.54	5.47	12.66	61.84	5.37	12.45
f	C_6H_5	$HOCH_2CH_2$-	H	H	150-152	53	ethanol	$C_{15}H_{15}N_3O_3$	63.15	5.30	14.73	63.02	5.15	14.75
g	C_6H_5	$C_6H_5CH_2$	H	H	218-219	88	ethanol	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.63	5.17	12.39
h	*m*-ClC_6H_4	$C_6H_5CH_2$	H	H	150-153	44	methanol	$C_{20}H_{16}ClN_3O_2$	65.66	4.41	11.49	65.52	4.35	11.42
i	C_6H_5	$C_6H_5CH_2$	CH_3	H	169-171	61	methanol	$C_{21}H_{19}N_3O_2$	73.02	5.55	12.17	72.86	5.35	11.95
j	C_6H_5	$MeOCH_2CH_2$	H	H	94-96	54	cyclohexane	$C_{16}H_{17}N_3O_3$	64.20	5.72	14.04	64.41	5.66	13.86
k	C_6H_5	$C_6H_5CH_2CH_2$	H	H	150-152	67	ethanol	$C_{21}H_{19}N_3O_2$	73.02	5.55	12.17	73.14	5.65	11.97
l	C_6H_5	cyclo-C_6H_{11}	H	C_6H_5	177-178	35	benzene-petroleum ether	$C_{25}H_{25}N_3O_2$	75.16	6.31	10.52	75.14	6.09	10.62
m	C_6H_5	cyclo-C_6H_{11}	H	H	200-202	6	ethanol	$C_{19}H_{21}N_3O_2$	70.56	6.55	13.00	70.49	6.81	12.88
n	C_6H_5	CH_3	H	C_6H_5	204-205	21	ethanol	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.51	5.04	12.44
o	C_6H_5		H	H	254-257	61	95% ethanol	$C_{19}H_{22}N_4O_2 \cdot 2HCl$	55.48	5.88	13.62	55.42	5.68	13.82
p	C_6H_5	$Et_2N(CH_2)_2 \cdot 2HCl$	H	H	240-242	55	methanol-acetone	$C_{19}H_{24}N_4O_2 \cdot 2HCl$	55.20	6.34	13.55	54.97	6.18	13.65
q	C_6H_5	$Et_2N(CH_2)_3 \cdot 2HCl$	H	H	223-224	34	ethanol-petroleum ether	$C_{20}H_{26}N_4O_2$ 2HCl	56.21	6.60	13.11	55.99	6.62	13.22
r	C_6H_5		H	H	248-250	61	95% ethanol	$C_{19}H_{22}N_4O_3$ 2HCl	53.40	5.66	13.11	53.44	5.60	13.40

Ethanol (10 ml.) was added to a mixture of 1.1 g. of IIa in 20 ml. of 25% sodium hydroxide solution. The reaction mixture was allowed to stand at room temperature for 3 days, after which it was cooled in ice and acidified with concentrated hydrochloric acid to *p*H 3. The crystalline product that deposited was collected on a filter and recrystallized from ethanol, affording 0.6 g. of product, m.p. 179-181°; ir 2.96 (OH), 3.54 (carboxyl OH, broad), 5.82 μ (C=O); nmr δ 3.25 (s, 3H, CH_3), 3.82 (m, 4H, OCH_2CH_2N).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.44; H, 5.68; N, 15.26.

4-[(2-Hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxamide (V).

A mixture of 2.0 g. of IIa in 50 ml. of concentrated ammonium hydroxide solution was heated on a steam bath for 1.5 days and then cooled in ice, giving 0.5 g. of product, m.p. 186-188°. The analytical sample, m.p. 190-191°, was obtained by recrystallization from water; ir 3.06, 3.21 (NH_2, OH), 6.04 μ (C=O).

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.85; H, 5.85; N, 20.45.

4-[(2-Hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxhydrazide (VI).

To a solution of 1 g. of IIa in 50 ml. of ethanol was added 5 ml. of hydrazine hydrate (99%). The reaction mixture was heated under reflux for 3 hours and the ethanol was removed in a rotary evaporator. The resulting residue was recrystallized from benzene, affording 0.6 g. of product, m.p. 146-148°; ir 3.13 (NH, OH), 3.24 (NH shoulder), 6.20 μ (C=O).

Anal. Calcd. for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.12; H, 6.05; N, 24.24.

2-(2-Methoxyethylamino)ethanol.

To an ice cold solution of 15 g. of 2-methoxyethylamine in 100 ml. of methanol was added, dropwise over a period of 25 minutes, 11.0 g. of ethylene oxide. The reaction mixture was allowed to warm to room temperature and stand for 16 hours. The ethanol was removed in a rotary evaporator and the residue (18.3 g.) was distilled through a Claisen head. The fraction having b.p. 83-88° (0.6 mm.) (Lit. [7] 155-165°/3 mm.) amounted to 6.6 g.; ir 3.11 (OH, NH, broad), 3.56 (CH), 9.01 (ether C-O), 9.46 μ (C-OH).

Anal. Calcd. for $C_5H_{13}NO_2$: C, 50.39; H, 11.00; N, 11.76. Found: C, 50.41; H, 10.87; N, 11.77.

2-(1-Pyrrolidinylethylamino)ethanol.

This compound was prepared using the same procedure as described above. From 22.8 g. of 2-(1-pyrrolidinyl)ethylamine and 11 g. of ethylene oxide in 100 ml. of ethanol was obtained 5.1 g. of product, b.p. 110-113° (0.25 mm.); ir 3.20 (OH, NH, broad), 3.48 (CH), 3.65 (CH-N), 9.45 μ (C-OH).

Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.72; H, 11.47. Found: C, 60.54; H, 11.62.

Ethyl 2-(*m*-Chlorophenyl)-4-hydroxy-5-pyrimidinecarboxylate.

To a stirred solution of 15.6 g. of sodium dissolved in 1200 ml. of ethanol was added 64 g. of *m*-chlorobenzamidine hydrochloride (8), followed by the slow addition of 73.5 g. of diethyl ethoxymethylenemalonate (total addition time, 20 minutes). The reaction mixture was heated under reflux for 40 minutes, chilled in ice and filtered under suction. The sodium salt of the product thus obtained was dissolved in one liter of water and acidified with concentrated hydrochloric acid. The precipitate that deposited was collected on a filter and dried, yielding 61 g. of product, m.p. 178-182°. The analytical sample, m.p. 180-181°, was obtained by recrystallization from ethanol; ir 5.87 (C=O), 6.02 μ (lactam C=O).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3$: C, 56.03; H, 3.98; Cl, 12.72; N, 10.05. Found: C, 56.33; H, 4.00; Cl, 12.60; N, 10.12.

Ethyl 4-Chloro-2-(*m*-chlorophenyl)-5-pyrimidinecarboxylate (Ib).

A mixture of 46 g. of ethyl 2-(*m*-chlorophenyl)-4-hydroxy-5-pyrimidinecarboxylate in 400 ml. of thionyl chloride was heated under reflux for 48 hours. The thionyl chloride was removed in a rotary evaporator, leaving 39.7 g. of product, m.p. 64-69°. The sample was used directly without purification, since great difficulty was experienced in obtained analytically pure material; ir 5.79 μ (C=O), no absorption in lactam region.

Ethyl 4-[(2-hydroxyethyl)(2-methoxyethyl)amino]-2-phenyl-5-pyrimidinecarboxylate (VII).

A mixture of 2.6 g. of Ia, 1.2 g. of 2-(2-methoxyethylamino)-ethanol and 1.1 g. of sodium carbonate was heated under reflux for 2.5 hours. The reaction mixture was filtered and the solvent was removed under rotary evaporation *in vacuo*. The residual oil solidified on scratching, giving 3.4 g. of product, m.p. 82-85°. An analytical sample (m.p. 83-85°) was obtained by recrystallization from cyclohexane; ir 3.18 (OH), 5.88 (C=O), 8.99 (ether C-O), 9.41 μ (C-OH).

Anal. Calcd. for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.83; H, 6.56; N, 12.24.

8,9-Dihydro-9-(2-methoxyethyl)-2-phenylpyrimido[4,5-*e*][1,4]-oxazepin-5(7*H*)-one (IIj).

This compound was prepared in the same manner as VII, using the same quantities of reagents except the reaction time was extended to 5 hours of refluxing. After recrystallization from cyclohexane there was obtained 1.6 g. of product, m.p. 94-96°; ir 5.97 μ (C=O).

Alternatively, 0.7 g. of VII and 0.5 g. of sodium carbonate in 25 ml. of ethanol was heated under reflux for 5 hours. The reaction mixture was filtered and the filtrate was taken to dryness giving 0.3 g. of a product. The melting point and infrared spectrum after recrystallization from cyclohexane were identical with IIj.

8,9-Dihydro-2-phenyl-9-[2-(1-pyrrolidinyl)ethyl]pyrimido[4,5-*e*]-[1,4]oxazepin-5(7*H*)-one Dihydrochloride (IIo).

A mixture of 2.6 g. of Ia, 1.7 g. of 2-(1-pyrrolidinoethylamino)ethanol and 1.1 g. of sodium carbonate in 50 ml. of ethanol was heated under reflux for 4 hours. The reaction mixture was filtered and the filtrate was taken to dryness on a rotary evaporator. The residual oil was dissolved in 50 ml. of ethanol. The solution was chilled in ice and hydrogen chloride gas was bubbled into it for a few minutes. A crystalline material was deposited which was collected on a filter. Recrystallization from 95% ethanol afforded 2.5 g. of product, m.p. 254-257°; ir 3.80-4.30 (broad salt bands), 5.84 μ (C=O).

Similarly prepared were the dihydrochlorides IIp-r given in the Table.

Acknowledgment.

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(2) A Japanese patent (Takeda Chemical Industries, Ltd., 16995 [1971] recently appeared concurrently with our own patent (A. A. Santilli and D. H. Kim, U. S. Patent 3,594,372 [1971]) describing the same type of reaction.

(2a) Note added in proof. See also S. Yurugi, M. Hieda, T. Fushimi, and M. Tomimoto, *Chem. Pharm. Bull.*, 19, 2354 (1971) which subsequently appeared while our manuscript was in preparation for press.

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