PYRIMIDINES

XIII. SYNTHESIS AND BIOLOGICAL PROPERTIES OF ALKOXYBENZYL-SUBSTITUTED PYRIMIDYLACETIC ACIDS

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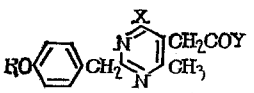
In the search for new carcinolytic drugs, we have undertaken the synthesis of some derivatives of pyrimid-5-ylacetic acids, of general formula I-IV:



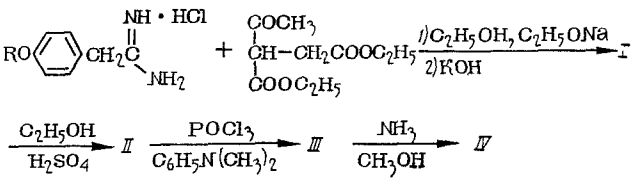
I-IV a-e

I: X=Y=OH
II: X=OH, Y=OC_2H_5
III: X=Cl, Y=OC_2H_5
IV: X=Y=NH_2

R = a) CH_3, b) C_2H_5, c) C_3H_7, d) iso-C_3H_7, e) C_4H_9

Compounds I-IV differ from those obtained previously [1] in the presence of a methoxycarbonyl group in the 5 position of the pyrimidine ring (reports have recently appeared describing the biological activity of pyrimidyl-5-acetic acids as hypocholesteremics and antitumor compounds [2, 3]).

Compounds I-IV were synthesized as follows:



When 4-alkoxyphenylacetamidines [4] were condensed with ethyl acetylsuccinate [5] under the usual conditions (heating for 6 h in absolute alcohol in the presence of sodium ethoxide), a mixture of the acid I and ester II was obtained. Changes in the temperature and duration of the reaction did not lead to the formation of I or II alone. In order to obtain I, the reaction mixture was completely hydrolyzed to the acid by treatment with 10% aqueous potassium hydroxide. Esterification of I in the presence of concentrated sulfuric acid afforded 5-ethoxycarbonylmethylpyrimidines (II), which on treatment with phosphoryl chloride in the presence of dimethylaniline were converted into the corresponding chloro derivatives (III).

It has been shown that on heating the chloropyrimidines (III) with an excess of methanolic ammonia in an autoclave at 140°, in addition to amination, amidation takes place with the formation of the corresponding 2-(4-alkoxybenzyl)-4-amino-5-carbamoylmethyl-6-methylpyrimidines (IV). Other workers have observed a similar formation of aminoamides [6].

The purity of compounds I-IV was established by thin-layer chromatography on Silufol UV-254, and their structures were confirmed by NMR, IR, and mass spectrometry.

The IR spectra of compounds I-IV in the double-bond region showed absorption at 1600 (benzene ring), 1580 (pyrimidine ring), and 1035 cm^{-1} (alkoxy group). The carboxyl group in the acetic acid residue showed typical absorption at 1680-1705 cm^{-1}.

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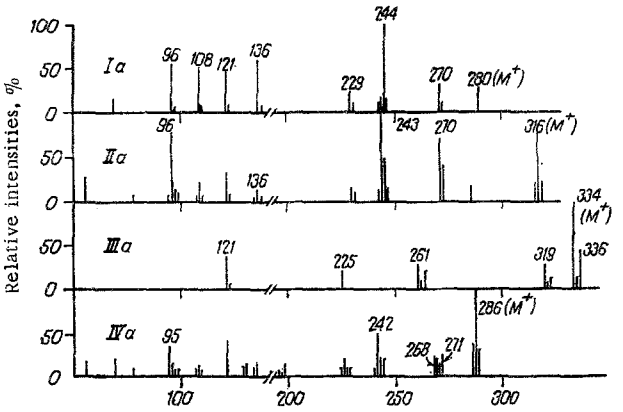

Fig. 1. Mass spectra of compounds Ia-IVa.

In the NMR spectra, the aromatic protons of compounds I-III (R = CH_3) formed an AB quartet (6.80-7.00 ppm). The methyl group protons in the CH_3O group appeared at 3.66-3.70 ppm. A singlet at 3.80-4.00 ppm was assigned to the methylene protons of the $-CH_2COY$ group. The methylene protons of the benzyl group resonated at 3.50-3.62 ppm. The methyl group in the 6 position of the pyrimidine ring gave a singlet at 2.22-2.42 ppm.

Figure 1 shows the mass spectra of compounds of I-IVa, in which there occur, in addition to the intense molecular ion peaks, peaks for the characteristic ions: $[M-COY]^+$, $[M-COY-C_6H_4OCH_3]^+$ and $[M-COY-CNCH_2C_6H_4OCH_3]^+$, where Y = OH, OC_2H_5, and NH_2 with masses in the case of I and II of 243, 136, and 96 respectively. The last two ions were not formed from III, and in the case of IV the peaks for the corresponding ions were shifted by one mass unit towards lower m/e (see Fig. 1).

The toxicity and antitumor activity of the compounds were determined by a method described in the literature [7] (Table 1).

The compounds were of low toxicity. Thus, the LD_{100} values for compounds Ia-e (cf. Table 1) averaged 2100 mg/kg. Replacement of the hydrogen atom of the carboxyl group by ethyl reduced the toxicity considerably (cf. IIa-IIe, Table 1). Replacement of the 4-hydroxy group by chlorine resulted in a slight increase in toxicity (IIIa-IIIe, Table 1).

In their antitumor properties these compounds were similar to other alkoxybenzylpyrimidines which we have previously investigated [8]. Most of them possessed moderate inhibitory activity towards sarcomas 45, M-1, and 180 (inhibiting growth by 30-59%), but they were inactive towards Ehrlich ascites carcinoma.

TABLE 1. Combined Toxicity and Antitumor Activity Data for Ia-IVe

Compound	Acute toxicity to mice			Antitumor activity				
				rats			mice	
	LD_{100}, mg/kg	MLD, mg/kg	MTD, mg/kg	dose, mg/kg	sarcoma 45	sarcoma M-1	dose, mg/kg	sarcoma 180
Ia	2565	2090	1315	80	±	±	125	+
Ib	2745	1985	1365	90	+	+	125	+
Ic	1375	1012	725	40	±	+	75	+
Id	2200	1377	1052	70	+	+	100	+
Ie	1647	1024	520	50	0	±	75	+
IIa	3750	—	—	100	+	+	150	0
IIb	3750	—	—	100	+	+	150	+
IIc	3750	—	—	100	±	+	150	+
IId	2700	2295	1585	90	+	—	125	+
IIe	3750	—	—	100	+	+	150	+
IIIa	2630	1795	1026	80	+	+	125	+
IIIb	2120	1346	789	70	±	—	100	0
IIIc	3750	—	—	100	++	0	200	0
IIId	2104	1410	1080	70	+	0	100	+
IIIe	3750	—	—	100	±	+	200	0
IVa	1841	1325	790	60	+	0	100	+
IVb	1026	650	256	35	0	0	50	0
IVc	2120	1466	785	70	+	—	100	+
IVd	3120	2565	1620	80	+	—	150	+
IVe	1865	1315	799	50	+	+	100	+

Note. 0) No effect; ±) up to 30% inhibition of tumor growth; +) 30-59% inhibition; ++) 60-79% inhibition.

TABLE 2. Pyrimid-5-ylacetic Acids Ia-IVe

Compound	Yield, %	Melting point, deg	R_f	Found, %				Molecular formula	Calculated, %			
				C	H	N	Cl		C	H	N	Cl
Ia	67,4	220—1	0,85	62,75	5,83	9,97		$C_{15}H_{16}N_2O_4$	62,49	5,59	9,72	
Ib	85,1	215—6	0,88	63,21	6,24	9,08		$C_{16}H_{18}N_2O_4$	63,56	6,00	9,27	
Ic	63,3	212—3	0,89	64,86	6,10	9,06		$C_{17}H_{20}N_2O_4$	64,54	6,37	8,86	
Id	75,2	195—6	0,81	64,82	6,61	9,13		$C_{17}H_{20}N_2O_4$	64,54	6,37	8,86	
Ie	61,2	189—90	0,91	65,71	7,05	8,62		$C_{18}H_{22}N_2O_4$	65,44	6,71	8,48	
IIa	88,7	184—5	0,26	64,81	6,45	9,01		$C_{17}H_{20}N_2O_4$	64,54	6,37	8,86	
IIb	84,6	192—3	0,30	65,36	7,01	8,23		$C_{18}H_{22}N_2O_4$	65,44	6,71	8,48	
IIc	72,8	165—6	0,33	66,43	7,21	8,31		$C_{19}H_{24}N_2O_4$	66,26	7,03	8,14	
IId	77,5	150—1	0,36	65,96	7,33	8,11		$C_{19}H_{24}N_2O_4$	66,26	7,03	8,14	
IIe	73,5	153—4	0,39	66,70	7,60	7,58		$C_{20}H_{26}N_2O_4$	67,01	7,31	7,82	
IIIa	67,2	42—3	0,34	61,18	5,72	8,52	10,34	$C_{17}H_{19}ClN_2O_3$	60,99	5,72	8,37	10,59
IIIb	60,6	66—7	0,44	62,32	6,22	7,95	10,32	$C_{18}H_{21}ClN_2O_3$	62,55	6,07	8,03	10,16
IIIc	63,5	56—7	0,42	62,58	6,16	7,91	9,47	$C_{19}H_{23}ClN_2O_3$	62,89	6,39	7,72	9,77
IIId	55,2	230†	0,40	62,60	6,27	8,07	9,45	$C_{19}H_{23}ClN_2O_3$	62,89	6,39	7,72	9,77
IIIe	55,7	49—50	0,46	63,91	6,95	7,72	9,33	$C_{20}H_{25}ClN_2O_3$	63,70	6,69	7,43	9,41
IVa	61,9	226—227	0,26	62,71	6,11	19,29		$C_{15}H_{18}N_4O_2$	62,92	6,34	19,57	
IVb	59,4	207—208	0,27	63,70	6,43	18,42		$C_{16}H_{20}N_4O_2$	63,98	6,71	18,65	
IVc	63,7	170—171	0,29	65,13	7,02	18,02		$C_{17}H_{22}N_4O_2$	64,95	7,05	17,82	
IVd	62,3	201—202	0,33	65,02	7,25	17,75		$C_{17}H_{22}N_4O_2$	64,95	7,05	17,82	
IVe	65,1	164—165	0,37	65,58	7,41	16,82		$C_{18}H_{24}N_4O_2$	65,83	7,37	17,06	

*Chromatographed on Silufol in systems ether—methanol, 4:1 (for I); ether—acetone, 49:1 (for II); ether—light petroleum (for III); methanol—water, 4:1 (for IV). Visualized in UV light.

†Boiling point (1 mm Hg).

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument as suspensions in vaseline oil, and the NMR spectra on a Varian T-60, working frequency 60 MHz. Spectra of I and II were obtained under the usual conditions (7% solutions in hexadeuteroethanol), and of III in carbon tetrachloride. The internal standard was hexamethyldisiloxane. Mass spectra were obtained on an MX-1303 instrument with direct insertion of the sample into the ion source.

2-(4-Alkoxybenzyl)-4-hydroxy-5-methoxycarbonyl-6-methylpyrimidines (I). A mixture of 0.1 mole of 4-alkoxyphenylacetamidine hydrochloride, 0.1 mole of ethyl acetylsuccinate, and sodium ethoxide prepared from 4.6 g (0.2 mole) of sodium and 100 ml of absolute ethanol was heated with stirring on the water bath for 6-8 h. The alcohol was removed by distillation, 100 ml of 10% aqueous potassium hydroxide was added, and the mixture was boiled for 1 h. After cooling to 10-15°C, the mixture was acidified with concentrated hydrochloric acid to pH 5.0-4.0, and the precipitate was filtered off, washed with water, and dried. The resulting I were colorless, crystalline solids, insoluble in benzene, ether, and acetone. They could be crystallized from methanol (Table 2).

2-(4-Alkoxybenzyl)-4-hydroxy-5-ethoxycarbonylmethyl-6-methylpyrimidines (II). A mixture of 0.1 mole of I, 150 ml of ethanol, and 20 ml of concentrated sulfuric acid was boiled for 5-6 h. The alcohol was removed by distillation, 100 ml of water was added, and the mixture was neutralized with a concentrated aqueous solution of sodium bicarbonate. The solid was filtered off, washed with water, and dried to give colorless crystalline solids, soluble in chloroform. Recrystallization was carried out from ethanol (cf. Table 2).

2-(4-Alkoxybenzyl)-4-chloro-5-ethoxycarbonylmethyl-6-methylpyrimidines (III). A mixture of 0.01 mole of II, 6.12 g (0.04 mole) of freshly distilled phosphoryl chloride, and 3 ml of dimethylaniline was heated on the water bath until the solid had dissolved completely (approximately 1 h). The excess of phosphoryl chloride was removed by distillation, ice water was added, the mixture was extracted with chloroform, and the extract dried over anhydrous sodium sulfate. After removal of the solvent, the residue was crystallized by treatment with cold alcohol, and recrystalliezd from ethanol (cf. Table 2).

2-(4-Alkoxybenzyl)-4-amino-5-carbamoylmethyl-6-methylpyrimidine (IV). A steel autoclave of capacity 100 ml was charged with 0.01 mole of III and 50 ml of a methanolic solution of ammonia (containing 0.025-0.03 mole of ammonia) and the mixture was heated at 140° for 8-10 h. After cooling, the crystalline produce was filtered off, washed with water followed by ether, and dried. Recrystallized from 75% methanol (cf. Table 2).

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