SYNTHESIS OF METHYL ESTERS OF 6-DIALKYLAMINO-2-(CARBETHOXY)-METHYLTHIOPYRIMIDINE-4-CARBOXYLIC ACIDS

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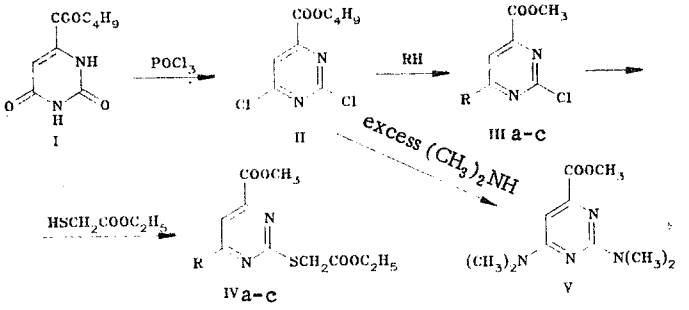
A preparative method is proposed for the synthesis of methylesters of 6-dialkylamino-2-(carbethoxy)methylthiopyrimidine-4-carboxylic acids form the butyl ester of orotic acid.

2-Pyrimidylthioacetic acid derivatives, having an amino group in the 4-position of the pyrimidine ring and chlorine [1] or methyl [2] at position 6, possess hypolipidemic activity. However, the dependence of this activity on the nature of the 6-substituent has been little investigated. Hence we have studied methods of synthesis of methyl esters of 6-dialkylamino-2(carbethoxy)methylthiopyrimidine-4-carboxylic acids (IVa-c) as part of our search for compounds with novel biological activity. In contrast to previously reported materials [3] these have an electron acceptor ester group in the 6-position. These compounds are of interest not only as potentially active substances but also in chemical terms. Because they can react with nucleophiles at several active centers they serve as intermediates in the synthesis of a variety of pyrimidine derivatives.



III, IV a R = $(CH_3)_2N$, b R = piperidino c R = morpholino

Refluxing the butyl ester(I) with excess phosphorus oxychloride gave II which was treated with equimolar amounts of secondary amines in methanol at 0°C (in the presence of anhydrous sodium carbonate) to form the methyl esters of 6-dialkylamino-2-chloropyrimidine-4-carboxylic acids (IIIa-c). The reaction course depends upon the reagent ratios. Use of excess dimethylamine leads to substitution of both chlorine atoms in II with formation of the methyl ester of 2,6-bis(dimethylamino)pyrimidine-4-carboxylic acid (V). Such facile substitution of both chlorines in II may be explained by the electron acceptor influence of the ester group in position 4 of the pyrimidine ring.

On heating esters IIIa-c with ethyl thioglycolate in triethylamine there were formed IVa-c respectively. The structures of compounds IVa-c were confirmed by elemental analytical data (Table 1) and by PMR spectra (Table 2) in which there were observed signals for the ester group, the pyrimidine 5-proton, protons of the R substituent, and the characteristic thiomethylene group at 4.18-4.30 ppm.

In view of the comparative ease of substituents of both chlorines in II by dimethylamine there arose the need to show that the substitution in the pyrimidine ring of IIIa-c is at the 6- and not the 2- position (despite literature data showing the predominance of 4- amino derivative formation in reactions of 2,4-dichloropyrimidines with amines in polar solvents [4, 5]).

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TABLE 1. Data for Compounds II, IIIa-c, IVa-c, V, VII, and IX

Compound	mp* or bp (mm) in °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
II	177—178 (7)	43,2	4,4	11,7	$C_9H_{10}Cl_2N_2O_2$	43,4	4,1	11,3	83
IIIa	137,5—138,5	44,9	4,8	19,6	$C_8H_{10}ClN_3O_2$	44,6	4,7	19,5	64
IIIb	88—89	51,3	5,6	16,1	$C_{11}H_{14}ClN_3O_2$	51,7	5,5	16,4	59
IIIc	139,5—140,5	46,7	4,5	16,6	$C_{10}H_{12}ClN_3O_3$	46,6	4,7	16,3	91
IVa	93—95	48,4	5,9	14,2	$C_{12}H_{17}N_3O_4S$	48,2	5,7	14,0	80
IVb	87—89	52,8	6,4	12,7	$C_{15}H_{21}N_3O_4S$	53,1	6,2	12,4	45
IVc	126—127	49,5	5,7	12,2	$C_{14}H_{19}N_3O_5S$	49,3	5,6	12,3	62
V	79—81	53,7	7,1	24,7	$C_{10}H_{16}N_4O_2$	53,6	7,2	25,0	80
VII	145,5—147,5	41,6	4,2	10,9	$C_9H_{10}N_2O_5S$	41,9	3,9	10,9	65
IX	124—125	47,9	5,0	12,9	$C_{13}H_{17}N_3O_5S$	47,7	5,2	12,8	43 (A) 63 (B)

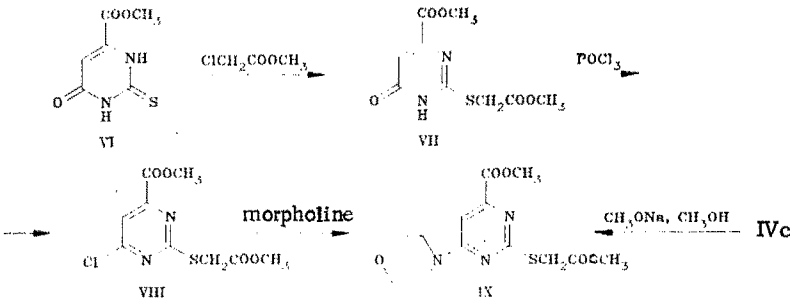
*Compounds IIIa, b, V were crystallized from hexane; IIIc, IVa-c from ethanol; VII, IX from methanol.

TABLE 2. PMR Spectra of Compounds II, IIIa-c, IVa-c, V, VII, and IX

Compound	PMR spectrum, δ, ppm
II	1,04 (3H, t, J=6 Hz, CH_3), 1,30—2,13 (4H, m, $2CH_2$), 4,58 (2H, t, J=6 Hz, OCH_2), 8,16 (1H, s, CH)
IIIa	3,45 (3H, s, CH_3N), 3,54 (3H, s, CH_3N), 4,14 (3H, s, CH_3O), 7,46 (1H, s, CH)
IIIb	1,89 (6H, s, $3CH_2$), 3,75—4,35 (7H, m, $2CH_2N+CH_3O$), 7,53 (1H, s, CH)
IIIc	3,90—4,48 (11H, m, $2CH_2N+2CH_2O+CH_3O$), 7,58 (1H, s, CH)
IVa	1,35 (3H, t, J=7 Hz CH_3), 3,40 (6H, s, $2CH_3N$), 4,08 (3H, s, CH_3O), 4,18 (2H, s, CH_2S), 4,35 (2H, q, J=7 Hz, CH_2O), 6,90 (1H, s, CH)
IVb	1,35 (3H, t, J=6 Hz, CH_3), 1,83 (6H, s, $3CH_2$), 3,80 (4H, s, $2CH_2N$), 4,06 (5H, s, CH_3O+CH_2S), 4,34 (2H, q, J=6 Hz, CH_2O), 7,36 (1H, s, CH)
IVc	1,40 (3H, t, J=6Hz, CH_3), 3,93—4,50 (15H, m, $2CH_2N+3CH_2O+CH_3O+CH_2S$), 7,41 (1H, s, CH)
V	3,25 (12H, s, $4CH_3N$), 4,06 (3H, s, CH_3O), 6,95 (1H, s, CH)
VII	3,93 (3H, s, CH_3O), 4,13 (3H, s, CH_3O), 4,26 (2H, s, CH_2S), 7,34 (1H, s, CH)
IX	3,89 (3H, s, CH_3O), 3,98—4,38 (13H, m, $2CH_2N+2CH_2O+CH_2S+CH_3O$), 7,38 (1H, s, CH)

With this in mind we have studied other methods of preparing esters IV, e.g., the methyl ester of 6-morpholino-2-(carbomethoxy)methylthiopyrimidine-4-carboxylic acid (IX).

Alkylation of the methyl ester of thioorotic acid (VI) using methyl chloroacetate in the presence of sodium methoxide gave VII which was refluxed with phosphorus oxychloride to yield the chloro derivative VIII. Without further purification this was then treated with an equimolar amount of morpholine to give IX. The spectral and physical properties of IX were identical to those of the compound obtained by trans esterification of compound IVc.



Thus the methyl esters of 6-dialkylamino-2-(carbalkoxy)methylthiopyrimidine-4-carboxylic acids may be obtained by two alternative methods. Their synthesis from butyl orotate is to be preferred because the starting ester (I) and all intermediate compounds are formed in higher yields. Additionally the second method has an important drawback in that VIII

(evolved in the form of an oil) is difficult to purify by crystallization or by vacuum distillation.

A study of the hypolipidemic activity of the synthesized compounds was carried out in the synthesis and medicinal studies problem solving laboratories of the V. Kapuskas State University, Vilnyus, under the direction of V.-S. M. Rochka. This has shown that only the methyl ester IIIc decreases the cholesterol level in rat blood serum by 14.3% when dosed at 200 mg/kg (LD_{50} on oral administration greater that 2000 mg/kg). For this compound the general lipids were reduced by 3.6% and triglycerides by 25% when compared with controls.

EXPERIMENTAL

Reaction following and compound purities were monitored by TLC on Silufol plates. PMR Spectra were recorded on a Tesla BS 487 C (80 MHz) instrument at 33°C with CH_3COOH solvent and TMS internal standard.

Butyl orotate (I) was prepared from orotic acid using [6] and methyl thioorotate (VI) from thioorotic acid [7] using [8].

The physicochemical and spectral characteristics of the synthesized compounds are given in Tables 1 and 2.

Butyl Ester of 2,6-Dichloropyrimidine-4-carboxylic Acid (II). A mixture of I (21.2 g, 100 mmole) and phosphorus oxychloride (214 ml, 2340 mmole) were refluxed for 2 h. Excess reagent was removed under reduced pressure and the residue was poured onto ice (150 g) and extracted with ether (5 × 60 ml). The extracts were washed with water (3 × 60 ml) and held over activated charcoal (15 min) with occasional shaking. The carbon was filtered off and the extract dried (anhydrous magnesium sulfate), filtered, the solvent removed, and the product vacuum distilled to give II.

Methyl Esters of 6-Dialkylamino-2-Chlorpyrimidine-4-carboxylic Acids (IIIa-c). The appropriate dialkylamine (16 mmole) in absolute methanol (5 ml) was added dropwise with stirring to a mixture of II (4 g, 16 mmole), absolute methanol (60 ml) and anhydrous sodium carbonate (3.2 g, 30 mmole). The reaction mixture was stirred at this temperature for 2 h and allowed to stand overnight. The inorganic salt was then filtered off, the filtrate reduced to dryness at reduced pressure, and the residue was recrystallized to give IIIa-c.

Methyl Esters of 6-Dialkylamino-2-(carbethoxy)methylthiopyrimidine-4-carboxylic Acids (IVa-c). A mixture of IIIa-c (3.1 mmole), triethylamine (0.35 g, 3.4 mmole) and ethyl thioglycolate (0.37 g, 3.1 mmole) was held in water bath at 110°C for 2 h and then poured into water (6 ml) and stirred thoroughly. In the case of IVc a precipitate was obtained which was filtered off and recrystallized. For IVa and b the aqueous solution was extracted with ether (3 × 20 ml), the extracts washed with water (40 ml), dried (anhydrous magnesium sulfate), filtered, ether removed by distillation, and the residue crystallized.

Methyl ester of 2,6-bis(dimethylamino)pyrimidine-4-carboxylic Acid (V). Obtained analogously to IIIa-c using the butyl ester of 2,6-dichloropyrimidine-4-carboxylic acid (II) with a fivefold excess of dimethylamine. For isolation of V the inorganic salt was filtered off, the filtrate concentrated at reduced pressure to one fifth volume, cooled to 0-5°C, and the solid filtered off and recrystallized.

Methyl Ester of 1,6-Dihydro-6-oxo-2-(carbethoxy)methylthiopyrimidine-4-carboxylic Acid (VII). A solution of sodium methoxide (40 ml, 1.25 N, in methanol) was added to a suspension of VI (9.3 g, 50 mmole) in absolute methanol (120 ml). To this solution there was added dropwise with stirring methyl chloroacetate (5.4 g, 50 mmole) such that the temperature did not exceed 30°C. The mixture was stirred at room temperature for 1 h, refluxed for 4 h (to a neutral reaction), filtered hot, the filtrate concentrated at reduced pressure to one third volume, cooled to 0-5°C, and the resultant solid filtered off and recrystallized to yield VII.

Methyl Ester of 2-(carbomethoxy)methylthio-6-chloropyrimidine-4-carboxylic Acid (VIII). A mixture of VII (4.0 g, 16 mmole) and phosphorous oxychloride (11 ml, 120 mmole) was refluxed for 1.5 h. Excess reagent was distilled off under reduced pressure and the residue poured onto ice (50 g). The solution obtained was extracted with ether (3 × 50 ml), dried with anhydrous calcium chloride, filtered, and the ether distilled off to give VIII (4.0 g, 93%).

Methyl Ester of 2-(Carbomethoxy)methylthio-6-morpholinopyrimidine-4-carboxylic Acid (IX). A. Anhydrous sodium carbonate (12.7 g, 120 mmole) was added to a solution of crude VIII (11.1 g, 40 mmole) in absolute methanol (60 ml). Morpholine (3.5 g, 40 mmole) was added dropwise with stirring and the mixture obtained was stirred at room temperature for 4 h and allowed to stand overnight. The solid product was filtered off and recrystallized to give IX.

B. Compound IVc (1 g, 2.9 mmole) was added to a 0.035N solution of sodium methoxide (40 ml) and the mixture stirred for 3 h at room temperature until all of IVc had dissolved. The solution was then concentrated at reduced pressure to one third volume, poured into water (30 ml), and neutralized with dilute hydrochloric acid (1:5). The solid was filtered off and recrystallized to give IX.

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SYNTHESIS OF 2-ARYL- AND 2-HETARYLOXAZOLES FROM THE OXAZOLINES AND OXAZOLIDINES

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Treatment of 2-phenyl-, 2-(2-furyl)-, and 2-(2-thienyl)oxazolines with nickel peroxide has been found to give, in addition to the dehydrogenation products (2-substituted oxazoles), the fragmentation products (amides of benzoic, furan-2-carboxylic, and thiophen-2-carboxylic acids). This fragmentation appears to give initially the nitriles, which are then converted into the amides by the nickel peroxide. Catalytic dehydrogenation of 2-phenyloxazoline gives low yields of 2-phenyloxazole, the principal product being benzonitrile. Treatment of the Schiff's bases obtained from ethanolamine and aldehydes (benzaldehyde, furfural, and thiophen-2-aldehyde) with nickel peroxide gives trace amounts of the oxazoles, the principal products being the aldehydes, with smaller amounts of the nitriles.

It has been shown [1] that 1-phenyloxazoline (Ia) on treatment with nickel peroxide is converted to 2-phenyloxazole (IIa). We here describe an analogous syntheses of 2-(2-furyl)-oxazole (IIb) and 2-(2-thienyl)oxazole (IIc). In all cases, although the oxazolines reacted completely, the yields of oxazoles were around 50%. Attempts by us to carry out this dehydrogenation with other oxidants (lead tetraacetate, pyridinium chlorochromate, sulfur, and N,N'-bisbenzenesulfonyl-p-benzoquinoneimine) were successful. Further examination of the aromatization of oxazolines showed that substantial amounts of the amides of the acids (III) [benzoic acid (28%), furan-2-carboxylic (23%), and thiophen-2-carboxylic acid (45%)] remained adsorbed on the nickel peroxide as by-products.

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