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IMIDAZOLE DERIVATIVES.

XXIII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 4-NITRO-5-THIOIMIDAZOLE

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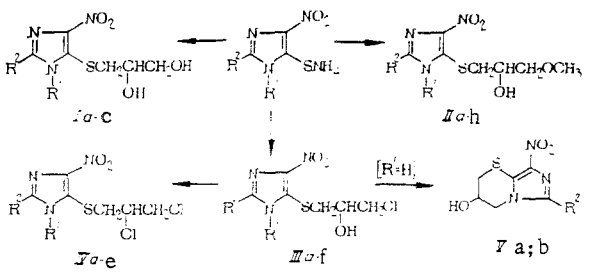
Imidazole and certain of its derivatives are known to protect living organisms from the destructive action of ionizing radiation [7, 10]. Substituted 2-nitroimidazoles such as 1-(2-hydroxy-3-methoxypropyl-1)-2-nitroimidazole (mizonidazole), give a high degree of protection against radiation [6, 8].

The present work is part of continuing research into biologically active derivatives of 4-nitro-5-thioimidazoles [1, 2]. In order to study their radiation-protection and antitumor properties, compounds I-IV have been synthesized by reacting the corresponding ammonium mercaptide with 1,2-dihydroxy-3-chloropropane, 3-methoxy-, and 3-chloro-1,2-epoxypropane. The reaction of 1,2-epoxypropane with a thiol or its salt gives a secondary alcohol [9].



R^1 = H (Ia—IIIa), CH_3 (Ib—IIIb, IVa), $CH_2C_6H_5$ (IIc, IIIc, IVb), $CH_2C_6H_4Cl$-4 (IIId IVc), $CH_2C_6H_3NO_2$-3-OMe-4 (Ic, IId), $CH_2C_6H_3NO_2$-3-OEt-4 (IIe, IIIe, IVd), $CH_2C_6H_3NO_2$-3-OPr-4 (IIf), $CH_2C_6H_3NO_2$-3-OBu-4 (IIg), $CH_2C_6H_3NO_2$-3-OAm-4 (IIh, IIIf, IVe);
R^2 = H (Ib—IIIb, IVa, Va), CH_3 (Ia—IIIa, Ic, IIc-h, IIIc-f, IVc-e, Vb).

The reaction of the mercaptoammonium salt of 2-methyl-4(5)-nitro-5(4)-thioimidazole with 3-chloro-1,2-epoxypropane in absolute ethanol gives a mixture of 2-methyl-4(5)-nitro-5(4)-(2-hydroxy-3-chloropropyl-1)thioimidazole (IIIa) and its cyclization product, imidazo-[5,1-b](1,3)thiazine (Vb), a bicyclic compound of a type not previously described in the literature. The latter was obtained in 82% yield when the reaction was carried out in water.

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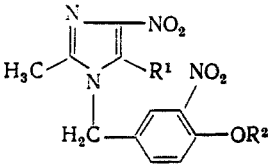
A similar intramolecular condensation has been observed for 2-methyl-4(5)-nitro-5(4)-(2-chloroethyl)thioimidazole [2].

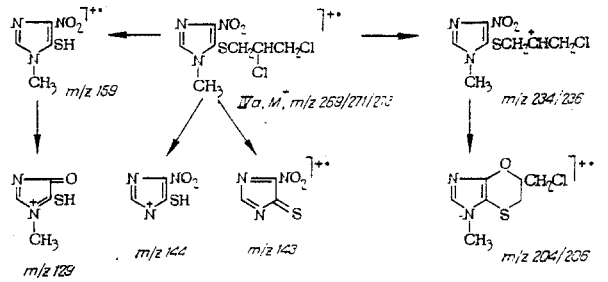
Several starting ammonium mercaptides are described in [1, 2]. The ammonium salts of 1-(4-alkoxy-3-nitrobenzyl)-2-methyl-4-nitro-5-thioimidazoles (VIII) were obtained by the replacement of the bromine in 5-bromoimidazole (VII) by a thioammonium group.



VIa-d — VIIIa-d

R^1 = H (VIad), Br (VIIad), SNH_4 (VIIIad); R^2 = Et (VIa—VIIIa), Pr (VIb—VIIIb), Bu (VIc—VIIIc), Am (VId—VIIId).

The structures of compounds I-V were confirmed from PMR and mass-spectral data. The principle fragments produced by the electron bombardment of 1-methyl-4-nitro-5-(2, 3-dichloropropyl-1)thioimidazole (IVa) are shown. Ions with mass numbers 143 and 144 undergo rearrangement and are seen in the mass spectrum as 1-methyl-4-nitro-5-thioimidazole derivatives [2].



In the same way, compound IVa decays to give Ia and IIb. In these compounds, H_2O, CH_2OH (Ia), and CH_3OCH_2 (IIb) are eliminated first.

The mass spectra of the benzyl derivatives IIIc, and IVb (R^1 = $C_6H_5CH_2$, R^2 = CH_3) are characterized by the splitting off of HCl (IIIc), chlorine (IVb), substituents from position 5 of the imidazole ring (m/Z 217), and the tropyl cation (m/Z 91).

The mass spectrum of the imidazothiazine Vb contains a molecular ion peak (m/Z 215), and ion peaks resulting from the loss of oxygen (m/Z 199), NO (m/Z 185), NO_2 (m/Z 169) from M^+.

EXPERIMENTAL (CHEMICAL)

Mass spectra were taken on an MX-1303 spectrometer with direct introduction of the sample into the ion source at 30-40°C below the melting point of the material; PMR spectra were obtained on a Varian T-60 (internal standard, TMS).

Compounds I, II, and V were chromatographed on Silufol UV-256 plates in the solvent system n-butanol—acetic acid—water 4:1:5, III, IV, VI, VII in ethyl acetate—absolute ether 1:1. The spots were visualized in UV light.

Substituted 4-Nitro-5-thioimidazoles (I, II, III). A mixture of 0.01 mole of the corresponding ammonium mercaptide, 0.013 mole of 2,3-dihydroxy-3-chloropropane (3-methoxy- or 3-chloro-1,2-epoxypropane) and 50 ml of absolute ethanol refluxed for 6-7 hours. The reaction mixture was then filtered and the filtrate evaporated to remove most of the ethanol. Compound I was precipitated by the addition of water, compound II by the addition of ether, and compound III crystallized when the mixture was left in the refrigerator. The precipitated material was filtered off and recrystallized from absolute ethanol. Compounds IIg and h crystallized on trituration with n-hexane (Table 1).

PMR spectra, δ, ppm: Ia (CD_3OH): 2.38 s (CH_3), 3.22 m (CH_2S), 3.60 m (CH_2OH), 3.88 m (CH), IIa: 2.40 s (CH_3), 3.25 m (CH_2S), 3.37 s (OCH_3), 3.48 m (CH_2O), 4.0 m (CHOH); IIb: 3.08 m (SCH_2), 3.33 s (OCH_3), 3.37 m (CH_2O), overlapped OCH_3), 3.82 s (NCH_3), 3.86 m (CHOH, overlapped NCH_3), 7.85 s (H); IIc: 2.37 s (CH_3), 3.03 m (SCH_2), 3.30 s (OCH_3), 3.35 m (CH_2O, overlapped OCH_3), 3.77 m (CHOH), 5.53 s (CH_2), 7.0-7.60 m (Ph); IIIb: 3.13 m (SCH_2), 3.57 m

TABLE 1. Substituted 4-Nitro-5-thioimidazoles

Compound	Yield, %	mp, °C	R_f	Found, %					Empirical formula	Calculated, %				
				C	H	Cl(Br)	N	S		C	H	Cl(Br)	N	S
Ia	65	90—2	0,64	35,93	4,60	—	18,26	13,35	$C_7H_{11}N_3O_4S$	36,04	4,75	—	18,02	13,75
Ib	67	116—7	0,46	36,20	4,80	—	18,00	14,08	$C_7H_{11}N_3O_4S$	36,04	4,75	—	18,02	13,75
Ic	72	165—7	0,55	45,51	4,34	—	14,22	8,32	$C_{15}H_{18}N_4O_7S$	45,22	4,55	—	14,06	8,05
IIa	68	134—6	0,75	39,13	5,59	—	17,28	13,08	$C_8H_{13}N_3O_4S$	38,86	5,30	—	16,99	12,97
IIb	71	116—8	0,53	39,10	5,50	—	17,20	13,24	$C_8H_{13}N_3O_4S$	38,86	5,30	—	16,99	12,97
IIc	77	115—6	0,75	53,29	5,55	—	12,20	9,21	$C_{15}H_{19}N_3O_4S$	53,40	5,68	—	12,45	9,50
IId	83	100—102	0,61	46,30	4,65	—	13,80	8,05	$C_{16}H_{20}N_4O_7S$	46,60	4,89	—	13,59	7,77
IIe	76	117—8	0,76	47,65	5,05	—	13,37	7,28	$C_{17}H_{22}N_4O_7S$	47,88	5,20	—	13,14	7,52
IIf	83	108—10	0,77	49,06	5,28	—	12,62	7,14	$C_{18}H_{24}N_4O_7S$	49,08	5,49	—	12,72	7,28
IIg	73	54—6	0,81	49,96	6,04	—	12,05	7,25	$C_{19}H_{26}N_4O_7S$	50,21	5,77	—	12,33	7,05
IIh	75	63—5	0,85	51,58	6,28	—	11,70	7,12	$C_{20}H_{28}N_4O_7S$	51,27	6,02	—	11,96	6,84
IIIa	45	168—70	0,60	33,66	4,22	13,89	16,54	12,47	$C_7H_{10}ClN_3O_3S$	33,40	4,00	14,09	16,70	12,74
IIIb	63	75—6	0,32	33,12	4,13	14,40	16,97	12,52	$C_7H_{10}ClN_3O_3S$	33,40	4,00	14,09	16,70	12,74
IIIc	65	118—20	0,72	49,20	4,79	10,60	12,50	9,13	$C_{14}H_{16}ClN_3O_3S$	49,19	4,72	10,37	12,29	9,38
IIId	76	145—6	0,68	44,90	3,80	18,61	10,95	8,80	$C_{14}H_{15}Cl_2N_3O_3S$	44,69	4,02	18,84	11,17	8,52
IIIe	80	134—5	0,56	44,80	4,56	8,10	13,30	7,56	$C_{16}H_{19}ClN_4O_6S$	44,60	4,44	8,23	13,00	7,44
IIIf	62	105—6	0,66	48,15	5,30	7,23	11,60	7,00	$C_{19}H_{25}ClN_4O_6S$	48,25	5,33	7,50	11,85	6,78
IVa	65	161—3	0,55	31,40	3,32	26,51	15,29	11,63	$C_7H_9Cl_2H_3O_2S$	31,12	3,36	26,25	15,56	11,87
IVb	78	94—5	0,75	46,83	4,01	19,60	11,40	8,65	$C_{14}H_{15}Cl_2N_3O_2S$	46,67	4,20	19,68	11,66	8,90
IVc	73	74—6	0,79	42,84	3,71	27,25	10,60	8,10	$C_{14}H_{14}Cl_3N_3O_2S$	42,60	3,58	26,95	10,65	8,12
IVd	85	131—3	0,70	42,97	4,32	15,60	12,18	6,95	$C_{16}H_{18}Cl_2N_4O_5S$	42,77	4,04	15,78	12,47	7,14
IVe	66	117—8	0,78	46,70	4,80	14,60	11,67	6,80	$C_{19}H_{24}Cl_2N_4O_5S$	46,44	4,92	14,43	11,40	6,52
Va	75	129—30	0,30	51,24	4,60	—	18,10	—	$C_{13}H_{14}N_4O_5$	50,98	4,61	—	18,29	—
Vb	78	114—6	0,40	52,30	4,97	—	17,20	—	$C_{14}H_{16}N_4O_5$	52,50	5,03	—	17,49	—
Vc	79	122—4	0,42	54,01	5,33	—	16,47	—	$C_{15}H_{18}N_4O_5$	53,89	5,43	—	16,76	—
Vd	76	121—2	0,50	55,00	5,85	—	15,84	—	$C_{16}H_{20}N_4O_5$	55,16	5,79	—	16,08	—
VIa	80	138—40	0,48	40,82	3,22	20,59	14,51	—	$C_{13}H_{13}BrN_4O_5$	40,54	3,40	20,74	14,55	—
VIb	81	108—10	0,68	41,87	3,74	20,11	13,80	—	$C_{14}H_{15}BrN_4O_5$	42,12	3,79	20,02	14,04	—
VIc	83	98—100	0,58	43,46	4,10	19,12	13,41	—	$C_{15}H_{17}BrN_4O_5$	43,60	4,15	19,34	13,56	—
VId	77	94—6	0,60	44,85	4,24	19,00	13,32	—	$C_{16}H_{19}BrN_4O_5$	44,98	4,48	18,70	13,11	—
VIIa	83	170—2	—	43,80	4,74	—	19,78	9,22	$C_{13}H_{17}N_5O_5S$	43,94	4,82	—	19,71	9,02
VIIb	81	182—5	—	45,36	5,10	—	19,06	8,83	$C_{14}H_{19}N_5O_5S$	45,52	5,18	—	18,96	8,68
VIIc	79	168—9	—	46,81	5,35	—	17,94	8,51	$C_{15}H_{21}N_5O_5S$	46,99	5,52	—	18,27	8,36
VIId	80	163—5	—	48,39	6,10	—	17,35	7,83	$C_{16}H_{23}N_5O_5S$	48,35	5,83	—	17,62	8,07

(CH_2Cl), 3.83 s (NCH_3), 3.90 m (CHOH, overlapped NCH_3), 7.78 s (H); IIIc acetone-d_6: 2.33 s (CH_3), 3.12 m (SCH_2), 3.62 m (CH_2Cl), 3.90 m (CHOH), 5.50 s (CH_2), 7.0-7.5 m (Ph).

Mass spectrum, m/z (%): Ib: 233 (39) M^+, 215 (13), 202 (26), 192 (14), 191 (10), 159 (19), 144 (19), 143 (26), 142 (19), 129 (24), 128 (21), 127 (16), 121 (17), 116 (26), 90 (100); IIb: 247 (33) M^+, 202 (25), 186 (12), 159 (14), 144 (25), 143 (41), 142 (16), 140 (14), 129 (20), 128 (20), 116 (44), 104 (39), 89 (31), 71 (59), 45 (100); IIIc: 343 (17), 341 (38) M^+, 311 (8), 309 (15), 305 (8), 234 (23), 233 (17), 232 (21), 218 (33), 217 (19), 216 (35), 202 (23), 201 (19), 163 (23), 127 (23), 110 (35), 108 (73), 91 (100), 73 (72).

Substituted 4-Nitro-5-(2,3-dichloropropyl-1)thioimidazoles (IV). A mixture of 0.01 mole of III and 30 ml of thionyl chloride was refluxed for 5-6 hours, and the excess thionyl chloride was distilled off using an aspirator. Water was then added, and the precipitated material filtered off and recrystallized from ethanol (see Table 1).

PMR spectra, δ, ppm: (DMSO-d_6) IVa: 3.33 m (CHCl), 3.73 s (CH_3), 3.93 m (SCH_2, CH_2Cl), 8.03 s (H); IVb (acetone-d_6): 2.37 s (CH_3), 3.37 m (CHCl), 3.90 m (SCH_2, CH_2Cl), 5.53 s (CH_2),, 6.92-7.48 m (Ph).

Mass spectrum, m/z (%): IVa: 273 (26), 271 (71), 269 (100) M^+, 236 (23), 234 (44), 206 (5), 204 (15), 159 (32), 144 (23), 143 (26), 142 (29), 140 (21), 129 (40), 128 (22), 116 (43), 102 (22), 89 (26); IVb: 364 (22), 362 (80), 360 (100) M^+, 327 (10), 325 (23), 235 (12), 234 (11), 233 (19), 219 (14), 218 (19), 217 (70), 202 (9), 192 (7), 186 (4), 185 (7), 176 (10), 175(7), 150(6), 144(6), 128(21), 127(10), 106(8), 91(74).

3-Hydroxy-6-methyl-8-nitroimidazo[5,1-b](1,3) (thiazine (Vb). A mixture of 2 g (11 mmole) of mercaptoammonium 2-methyl-4(5)-nitro-5(4)thioimidazole, 1.2 g (13 mmole) of 3-chloro-1,2-epoxypropane, and 50 ml of water was refluxed for 6-7 hours and then allowed to stand overnight. The precipitated material was filtered off and recrystallized from water to give 2 g (82%) of product with mp 239-240°C. Found, %: C 38.87; H 4.12; N 19.32; S 14.80. $C_7H_9N_3O_3S$. Calculated, %: C 39.06; H 4.21; N 19.52; S 14.90. PMR spectrum of Vb (DMSO-d_6), δ, ppm: 2.27 s (CH_3), 3.08 m (CH_2S), 3.92 d (CH_2N, J 4 Hz), 4.4 m (CHOH), 5.68 d (OH, J 4 Hz). Mass spectrum of Vb, m/z (5): 215 (100) M^+, 199 (6), 185 (9), 169 (11), 164 (11), 121 (13), 116 (30).

3-Hydroxy-8-nitroimidazo[5,1-b](1,3)thiazine (Va) was obtained by the same method as Vb in 79% yield, mp 237-238°C (from water). Found, %: C 36.06; H 3.80; N 21.15; S 15.69. $C_6H_7N_3O_3S$. Calculated, %: C 35.82; H 3.51; N 20.88; S 15.93.

2-Methyl-4(5)-nitro-5(4)-(2-hydroxy-3-chloropropyl-1)thioimidazole (IIIa). A mixture of 2 g (11 mmole) of mercaptoammonium 2-methyl-4(5)-nitro-5(4)thioimidazole, 1.2 g (13 mmole) of 3-chloro-1,2-epoxypropane, 50 ml of absolute ethanol was refluxed for 5-6 hours. After standing overnight, the precipitated material was filtered off to give 0.7 g (29%) of Va. The filtrate was concentrated, and placed in the refrigerator until IIIa precipitated out; it was then filtered off and recrystallized from ethanol (see Table 1).

1-(4-Alkoxy-3-nitro-benzyl)-2-methyl-4-nitroimidazoles (VIa-d), 1-(4-alkoxy-3-nitrobenzoyl)-5-bromo-2-methyl-4-nitroimidazoles (VIIa-d) and mercaptoammonium 1-(4-alkoxy-3-nitrobenzyl)-2-methyl-4-nitro-5-thioimidazoles (VIIIa-d) were synthesized by the same method [1]. Physicochemical data and elemental analysis for VI-VIII are given in Table 1. Compounds VIIIa-d melted with decomposition.

EXPERIMENTAL (PHARMACOLOGICAL)

The mutagenic and antimutagenic action of compounds I-V was studied on auxotrophic strains of Escherichia coli P-678 thr^- and Actinomyces rimosus 222 lys^- by the dose-effect method [3, 4].

The mutagenic activity was determined from the rate of mutation from the auxotrophic to prototrophic state according to the locus correlating the synthesis of threonine and lysine. Spontaneous mutations were used as controls: these comprised 6 ± 0.4 cells per 10^6 surviving cells for E. coli, and 9.5 ± 0.65 cells per 10^5 surviving spores for actinomyces. The compounds were studied at a concentration of 0.1 M and treatment times of approximately 120 minutes.

The antimutagenic action was evaluated from the effect of the test compounds on mutations, produced either spontaneously or by irradiation with UV light. The compounds were

TABLE 2. Acute Toxicity and Antitumor Activity (% suppression of tumor growth) of 4-Nitro-5-thioimidazoles

Compound	Toxicity		Antitumor activity			
	LD_{100}, mg/kg	MED, mg/kg	dose, mg/kg	sarcoma 45	dose mg/kg	sarcoma 180
IIa	1000	800	50	37.5	100	0
IIb	1000	800	50	0	100	35
IId	1500	1000	80	47.5	150	50
IIh	>2500	...	150	46	250	45
IIIc	>2500	...	150	35	250	0
IIId	2000	1500	120	53	200	33
IIIf	1500	1250	80	45	150	47
IVa	1500	1250	80	48	150	38
IVb	>2500	...	150	53	250	60
IVc	>2500	...	150	0	250	45
IVe	>2500	...	150	37	250	41
Vb	1500	750	70	23*	150	20*
VIIIa	750	500	40	46	50	45
VIIId	500	300	25	50	35	42

*Confidence level, $p > 0.05$.

studied at low molar concentration – 0.01 M – and treatment times of approximately 10 minutes.

Studies showed that in the majority of cases the compounds exhibited no mutagenic action of either of the test systems. Against E. coli, derivatives Ib, IId, IIh, and IVd, with a higher survival rate of the cell to reverse induced mutation, were 2.6, 4.5, 3.7, and 3.3 times more effective than the control.

The 2,3-dichloropropylthioimidazoles IVb and IVe exhibited antimutagenic action of 25-42%, while 1-(4-amyloxy-3-nitrobenzyl-2-methyl-4-nitro-5-(2,3-dichloropropyl-1)thioimidazole (IVe) showed some protective action (35%) on UV-induced mutations.

The acute toxicity and antitumor activities of the test compounds were determined by standard methods [5]. Toxicity studies were carried out on non-pedigree white mice using a single dose, administered either intraperitoneally (IIa, b, d, h, IIf, IVa, e, Vb, VIIa, d) or orally (IIc, d, IVb, c). For each compound, the absolute lethal dose (LD_{100}) and maximum endurable dose (MED) were determined. The antitumor action of the substances was studied on rats and mice with the following transplanted tumors: sarcoma 45 and 180, and Walker's carcinosarcoma. Based on the therapeutic action of the compounds, the most active were tested on a number of other models: sarcoma 37, Pliss' lymphosarcoma, Swedish leucosis, and Erlich's ascitic carcinoma. All the compounds were tested at doasges of 1/10-1/20 of their LD_{100}.

It was found that the absolute lethal dose for the ammonium mercaptides VIIIa and d was 500-750 mg/kg, for the 2-hydroxy-3-methoxypropyl derivatives (IIa, b, and d) it was 1000-1500 mg/kg, while for the remaining compounds, the lethal dose was 1500-2500 mg/kg (Table 2). Chemotherapeutic experiments showed that compounds IId, h, IIIf, IVb, and VIIIa, d showed average antitumor activity in tests with sarcoma 45 and 180, suppressing their growth by 45-60%. A number of other analogs (IIId, IVa, c, e) showed similar therapeutic action against only one of the models. All the compounds except IIh, IIIf, and IVb were found to be ineffective in tests with Walker's carcinosarcoma. Of the 4-nitro-5-thioimidazole derivatives tested, the most active was 1-benzyl-2-methyl-4-nitro-5-(2,3-dichloropropyl-1)thioimidazole (IVb), which in therapeutic doses (150-250 mg/kg) caused a 50-60% inhibition of the growth of sarcoma 45, 180, and 37, and of Walker's carcinosarcoma and Pliss' lymphosarcoma; however it did not affect the growth of Ehrlich's ascitic carcinoma or Swedish leucosis.

Biological tests showed that even though the molecule of the test compound contains a group which is present both in the antitumor preparation prospidin and the radiation-protecting agent misonidazole, derivatives of 4-nitro-5-thioimidazole have a relatively narrow spectrum of therapeutic action.

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SYNTHESIS AND MUTAGENIC ACTION OF TETRAHYDROPYRANYL- AND TETRAHYDROTHIOPYRANYL PYRAZOLES AND PYRIMIDINES

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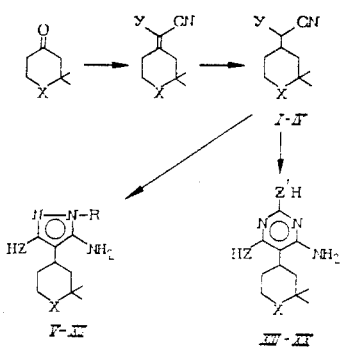
Derivatives of pyrazoles and pyrimidines are generally recognized to be of considerable interest because of their biological action, and they are widely used in medicine as therapeutic drugs. Moreover, compounds with diversified biological properties have been found among the bicyclic derivatives of tetrahydropyran [1]. In that connection we felt it would be of interest to synthesize the tetrahydropyranyl- and tetrahydrothiopyranyl-substituted derivatives of pyrazoles and pyrimidines. The indicated bicyclic compounds with C–C linked rings can be obtained by using the functional substituted tetrahydropyrans and tetrahydrothiopyrans in function position 4 that are capable of heterocyclization. Selected for this purpose were the β-carethoxynitrile and β-dinitrile groups. We then devised a method for synthesizing the tetrahydropyranyl- and tetrahydrothiopyranyl substituted esters of cyanoacetic acid (I, II) and malonic acid dinitriles (III, IV) which were obtained for the first time by the sodium borohydride reduction of the appropriate ilidene derivatives [3]. Compounds I-IV were reacted with 1,2- and 1,3-binucleophiles, i.e., hydrazine, phenylhydrazine, urea, and thiourea, in order to synthesize the target pyrazoles and pyrimidines (V-XX).



X = O (I, III, V, V , IX, X, XIII, XIV, XVII, XVIII), S (II, IV, VII, VIII, XI, XII, XV, XVI, XIX, XX); Y = COOEt (I, II), CN (III, IV); Z = O (V—VIII, XIII—XVI), NH (IX—XII, XVII—XX); Z^1 = O (XIII, XV, XVII, XIX), S (XIV, XVI, XVIII, XX); R = H (V, VII, IX, XI), Ph (VI, VIII, X, XII).

The IR spectra of the resultant pyrazoles V-XII exhibited absorption bands at 1530 and 1560 cm^{-1} that are characteristic of the aromatic pyrazole ring, at 1600 cm^{-1} which is characteristic of an aromatic benzene ring (for compounds VI, VII, X, and XII), at 1630 cm^{-1}

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