Potential Antineoplastics II: 1-Thiocarbamoyl-3-methyl 4-arylhydrazono-2-pyrazolin-5-ones, 2-Amino-4-phenyl-5-arylazothiazoles, and *N*-Phenyl-*N'*-2(4-phenyl-5-arylazothiazolyl)thiocarbamides

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Abstract ☐ A series of 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones, 2-amino-4-phenyl-5-arylazothiazoles, and *N*-phenyl-*N'*-2(4-phenyl-5-arylazothiazolyl)thiocarbamides have been prepared for evaluation as antineoplastic agents. The 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones and 2-amino-4-phenyl-5-arylazothiazoles were synthesized by coupling of appropriate aryldiazonium salts with 1-thiocarbamoyl-3-methyl-2-pyrazolin-5-one and 2-amino-4-phenylthiazole, respectively. The *N*-phenyl-*N'*-2(4-phenyl-5-arylazothiazolyl)thiocarbamides were obtained by condensing phenylisothiocyanate with 2-amino-4-phenyl-5-arylazothiazoles. The hydrazone-keto structures to 1-thiocarbamoyl-3-methyl-4-arylazo-2-pyrazolin-5-ones have been based on the IR spectral data. The intermediates required in these syntheses are also described.

Keyphrases ☐ 1-Thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones—synthesis ☐ 2-Amino-4-phenyl-5-arylazothiazoles—synthesis ☐ *N*-Phenyl-*N'*-2(4-phenyl-5-arylazothiazolyl)thiocarbamides—synthesis ☐ IR spectrophotometry—structure

There has been a growing interest, during the last few years, in compounds containing the N*-N*-S* or O*-N*-S* tridentate ligand system (1–5) or arylazo grouping (6, 7). This interest stems mainly from certain interesting carcinostatic activities of heterocyclic carboxyaldehyde thiosemicarbazones and the interfering action of 5-arylazopyrimidines with nucleic acid synthesis. Moreover, various Schiff bases from benzaldehyde nitrogen mustards and thiazoleamines have been reported to possess antitumor activity (8–10). As a part of a general study[1] directed toward the development of antineoplastics (11), the above-mentioned rationale led to examination of the synthesis and properties of three series of compounds having these mixed structural features—*viz.*, 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones and 2-amino-4-phenyl-5-arylazothiazoles having N*-N*-S* ligand and arylazo grouping and *N*-phenyl-*N'*-2(4-phenyl-5-arylazothiazolyl)thiocarbamides having N*-N*-S* ligand and arylazo grouping and a modified azomethine linkage. It was hoped that these series might afford compounds that would be relatively less toxic to normal cells and have a better chemotherapeutic index.[2]

THEORETICAL

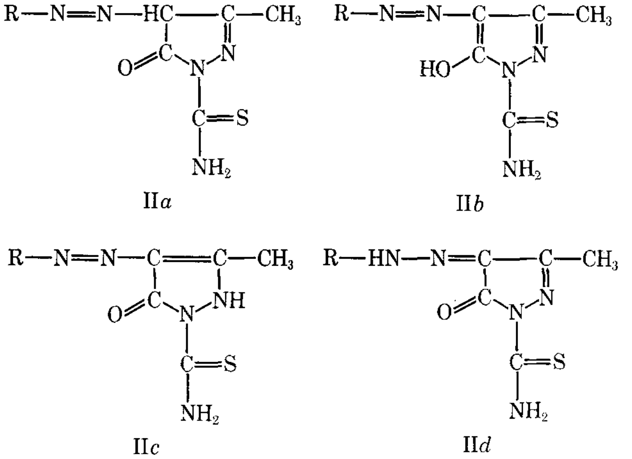
The most satisfactory route to 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones (II) has been found to be the prior synthesis of 1-thiocarbamoyl-3-methyl-2-pyrazolin-5-one (I) and its subsequent coupling with diazonium salts. The required intermediate (I) is obtained in excellent yield by the cyclization of ethyl 3-oxobutyrate-β-thiosemicarbazone in liquid ammonia at room temperature. This in turn is prepared from ethyl acetoacetate and thiosemicarbazide (12) (see Scheme I). The products are all highly colored crystalline derivatives which are summarized in Table I.

The precursor for 2-amino-4-phenyl-5-arylazothiazoles, 2-amino-4-phenylthiazole (III), has been obtained by the condensation of acetophenone and thiourea in presence of iodine (13). The arylazo group at C-5 has been introduced by the condensation of the corresponding diazonium salts with III. The different 2-amino-4-phenyl-5-arylazothiazoles so obtained are crystalline substances and are summarized in Table II.

Boiling equimolar quantities of phenylisothiocyanate, prepared according to the procedure of Dains *et al.* (14), and 2-amino-4-phenyl-5-arylazothiazoles in benzene on a steam bath gives the *N*-phenyl-*N'*-2(4-phenyl-5-arylazothiazolyl)thiocarbamides in yields exceeding 60% (Table III).

It is interesting to note that the 1-thiocarbamoyl group is thermolabile in 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones, and the cleavage of the thiocarbamoyl residue results in the products being the *N*-1-unsubstituted-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones (15).

The structures assigned to 1-thiocarbamoyl-3-methyl-4-arylazo-2-pyrazolin-5-ones need some comments as they can theoretically exist as one or more of the four possible structures (see structures of II).



II*a* II*b* II*c* II*d*

Possible Structures of Compound II

The IR spectra of all the compounds show bands characteristic of cyclic C=O frequency (16) (1660 cm.$^{-1}$ region) and C=C—NH—N=vibration (17) (1550 cm.$^{-1}$ region) (Table IV). This evidence unequivocally excludes Structures II*a*, II*b*, and II*c* from consideration and supports hydrazone-keto Structure II*d* for all 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones.

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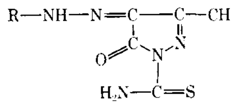
[1] A preliminary report of a portion of this work appeared in abstracts, Joint Convention of the Chemical Research Committee (C. S. I. R.) Institution of Chemists (India), and Society of Biological Chemists (India), Hyderabad-7 (India), 1969, p. 22.

[2] These compounds have been submitted for testing to Dr. H. B. Wood, Jr., National Institutes of Health, Bethesda, Md., the results of which will be reported elsewhere.

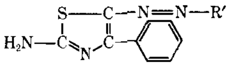
Table I—1-Thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones



Sample No.	R	Yield, %	M.p., °C.	Color	Formula	Anal., % Calcd.	Anal., % Found
1	Phenyl	75	224–225	Orange needles[a]	$C_{11}H_{11}N_5OS$	C, 50.5 H, 4.2 N, 26.8 S, 12.3	C, 50.1 H, 4.0 N, 26.4 S, 12.1
2	4-MePh	80	230–231	Orange needles	$C_{12}H_{13}N_5OS$	C, 52.3 H, 4.7 N, 25.4 S, 11.6	C, 52.0 H, 4.5 N, 25.7 S, 11.5
3	2-MePh	80	210–211	Yellow plates	$C_{12}H_{13}N_5OS$	C, 52.3 H, 4.7 N, 25.4 S, 11.6	C, 52.2 H, 4.2 N, 25.2 S, 11.7
4	2,4-Me_2Ph	70	223–224	Orange needles	$C_{13}H_{15}N_5OS$	C, 53.9 H, 5.1 N, 24.2 S, 11.1	C, 53.5 H, 4.9 N, 23.9 S, 11.0
5	2,5-Me_2Ph	86	174–175	Orange needles	$C_{13}H_{15}N_5OS$	C, 53.9 H, 5.1 N, 24.2 S, 11.1	C, 53.6 H, 4.7 N, 24.0 S, 11.3
6	2,6-Me_2Ph	84	187–188	Yellow needles	$C_{13}H_{15}N_5OS$	C, 53.9 H, 5.1 N, 24.2 S, 11.1	C, 53.4 H, 5.2 N, 24.4 S, 11.2
7	2-NO_2Ph	65	202–203	Orange needles	$C_{11}H_{10}N_6O_3S$	C, 43.1 H, 3.2 N, 27.4 S, 10.5	C, 42.9 H, 3.6 N, 27.6 S, 10.3
8	3-NO_2Ph	70	247–248	Yellow needles	$C_{11}H_{10}N_6O_3S$	C, 43.1 H, 3.2 N, 27.4 S, 10.5	C, 42.7 H, 3.1 N, 27.1 S, 10.4
9	4-NO_2Ph	72	241–242	Yellow needles	$C_{11}H_{10}N_6O_3S$	C, 43.1 H, 3.2 N, 27.4 S, 10.5	C, 42.9 H, 3.2 N, 27.5 S, 10.3
10	3-MeOPh	88	196–197	Brown fibers	$C_{12}H_{13}N_5O_2S$	C, 49.4 H, 4.4 N, 24.0 S, 11.0	C, 49.1 H, 4.0 N, 23.7 S, 10.8
11	2,6-Cl_2Ph	74	171–172	Brown plates	$C_{11}H_9Cl_2N_5OS$	C, 40.0 H, 2.7 N, 21.2 S, 9.7	C, 40.2 H, 2.5 N, 21.3 S, 9.8
12	3-ClPh	82	246–247	Orange needles	$C_{11}H_{10}ClN_5OS$	C, 44.5 H, 3.3 N, 23.6 S, 10.8	C, 44.8 H, 3.8 N, 23.2 S, 10.7
13	2,5-Cl_2Ph	83	226–227	Brown needles	$C_{11}H_9Cl_2N_5OS$	C, 40.0 H, 2.7 N, 21.2 S, 9.7	C, 40.3 H, 2.9 N, 21.2 S, 9.7
14	2-Cl-6-MePh	87	194–195	Yellow needles	$C_{12}H_{12}ClN_5OS$	C, 46.6 H, 3.5 N, 22.6 S, 10.4	C, 46.4 H, 3.1 N, 22.2 S, 10.2
15	4-ClPh	67	211–212	Brown fibers	$C_{11}H_{10}ClN_5OS$	C, 44.5 H, 3.3 N, 23.6 S, 10.8	C, 44.2 H, 3.6 N, 23.5 S, 10.5
16	2,5-MeO_2Ph	88	172–173	Brown needles	$C_{13}H_{15}N_5O_3S$	C, 48.7 H, 4.6 N, 21.6 S, 10.0	C, 48.5 H, 4.2 N, 21.6 S, 9.9
17	2-Cl-4-NO_2Ph	55	108–109	Pale-yellow needles	$C_{11}H_9ClN_6O_3S$	C, 38.8 H, 2.6 N, 24.7 S, 9.4	C, 38.3 H, 2.5 N, 24.5 S, 9.1
18	4-EtOPh	60	168(d)	Orange needles	$C_{13}H_{15}N_5O_2S$	C, 51.1 H, 4.9 N, 22.9 S, 10.5	C, 51.2 H, 4.4 N, 22.8 S, 10.3
19	4-SO_2NH_2Ph	76	229–230	Yellow needles	$C_{11}H_{12}N_6O_3S_2$	C, 38.8 H, 3.5 N, 24.7 S, 9.4	C, 38.4 H, 3.2 N, 24.9 S, 9.2

[a] Lit. m.p. 217°.

Table II—2-Amino-4-phenyl-5-arylazothiazoles



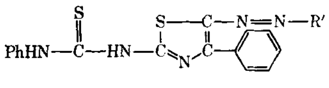
Sample No.	R′	Yield, %	M.p., °C.	Color	Formula	Anal., %	
						Calcd.	Found
1	2-MePh	78	159–160	Orange needles	$C_{16}H_{14}N_4S$	C, 65.3 H, 4.7 N, 19.0 S, 10.9	C, 65.2 H, 4.4 N, 18.5 S, 10.7
2	2-MeOPh	85	210–211	Deep-red needles	$C_{16}H_{14}N_4OS$	C, 61.9 H, 4.5 N, 18.0 S, 10.3	C, 61.4 H, 4.2 N, 18.2 S, 10.4
3	3-MeOPh	76	201–202	Red needles	$C_{16}H_{14}N_4OS$	C, 61.9 H, 4.5 N, 18.0 S, 10.3	C, 61.7 H, 4.6 N, 17.9 S, 10.3
4	4-MeOPh	82	204–205	Orange needles	$C_{16}H_{14}N_4OS$	C, 61.9 H, 4.5 N, 18.0 S, 10.2	C, 61.5 H, 4.2 N, 17.7 S, 10.3
5	3-ClPh	64	166–167	Orange plates	$C_{15}H_{11}ClN_4S$	C, 57.3 H, 3.5 N, 17.8 S, 10.0	C, 57.5 H, 3.1 N, 17.5 S, 10.0
6	4-ClPh	70	232–233	Violet needles	$C_{15}H_{11}ClN_4S$	C, 57.3 H, 3.5 N, 17.8 S, 10.2	C, 57.1 H, 3.4 N, 17.4 S, 10.1
7	2-NO_2Ph	71	210–211	Red needles	$C_{15}H_{11}N_5O_2S$	C, 55.3 H, 3.3 N, 21.5 S, 9.8	C, 55.0 H, 3.0 N, 21.2 S, 9.6
8	3-NO_2Ph	68	233–234	Orange plates	$C_{15}H_{11}N_5O_2S$	C, 55.3 H, 3.3 N, 21.5 S, 9.8	C, 55.5 H, 3.6 N, 21.0 S, 9.7
9	4-EtOPh	78	229–230	Brown needles	$C_{17}H_{16}N_4OS$	C, 62.9 H, 4.9 N, 17.2 S, 9.9	C, 62.5 H, 4.7 N, 17.5 S, 9.8
10	3-OHPh	65	181–182	Orange needles	$C_{15}H_{12}N_4OS$	C, 60.8 H, 4.0 N, 18.9 S, 10.8	C, 60.7 H, 4.2 N, 18.4 S, 10.5
11	2-COOHPh	60	268–269	Deep-red needles	$C_{16}H_{12}N_4O_2S$	C, 59.2 H, 3.7 N, 17.2 S, 9.9	C, 59.3 H, 3.5 N, 17.3 S, 9.7
12	2,4-Me_2Ph	90	184–185	Red needles	$C_{17}H_{16}N_4S$	C, 66.2 H, 5.1 N, 18.1 S, 10.4	C, 66.4 H, 5.2 N, 18.6 S, 10.2
13	2,5-Me_2Ph	86	204–205	Orange needles	$C_{17}H_{16}N_4S$	C, 66.2 H, 5.1 N, 18.1 S, 10.4	C, 66.0 H, 4.7 N, 18.2 S, 10.3
14	2,6-Me_2Ph	85	162–163	Deep-red needles	$C_{17}H_{16}N_4S$	C, 66.2 H, 5.1 N, 18.1 S, 10.4	C, 66.2 H, 4.9 N, 18.0 S, 10.1
15	2,5-MeO_2Ph	60	124–125	Orange needles	$C_{17}H_{16}N_4O_2S$	C, 60.0 H, 4.7 N, 16.4 S, 9.4	C, 60.4 H, 4.2 N, 16.2 S, 9.2
16	2,5-Cl_2Ph	75	227–228	Orange needles	$C_{15}H_{10}Cl_2N_4S$	C, 51.5 H, 2.8 N, 16.0 S, 9.2	C, 51.1 H, 2.5 N, 16.5 S, 9.0
17	2,6-Cl_2Ph	78	134–135	Orange fibers	$C_{15}H_{10}Cl_2N_4S$	C, 51.5 H, 2.8 N, 16.0 S, 9.2	C, 51.3 H, 2.7 N, 16.3 S, 9.1
18	2-Cl-6-MePh	70	180–181	Red needles	$C_{16}H_{13}ClN_4S$	C, 58.5 H, 3.9 N, 17.0 S, 9.8	C, 58.2 H, 3.4 N, 17.2 S, 9.6
19	2-Cl-4-NO_2Ph	72	272–273	Violet needles	$C_{15}H_{10}ClN_5O_2S$	C, 50.1 H, 2.7 N, 19.4 S, 9.3	C, 49.8 H, 2.5 N, 18.9 S, 9.1

(Continued)

Table II—(*Continued*)

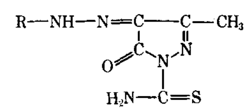
Sample No.	R′	Yield, %	M.p., °C.	Color	Formula	Anal., % Calcd.	Anal., % Found
20	2,6-Cl_2-4-NO_2Ph	70	234–235	Deep-red needles	$C_{15}H_9Cl_2N_5O_2S$	C, 45.9 H, 2.2 N, 17.7 S, 8.1	C, 45.6 H, 2.0 N, 17.4 S, 8.0
21	2,4-$(NO_2)_2$Ph	65	278–279	Violet needles	$C_{15}H_{10}N_6O_4S$	C, 48.6 H, 2.7 N, 22.7 S, 8.6	C, 48.2 H, 2.8 N, 22.3 S, 8.4

Table III—*N*-Phenyl-*N*′-2(4-phenyl-5-arylazothiazolyl)thiocarbamides



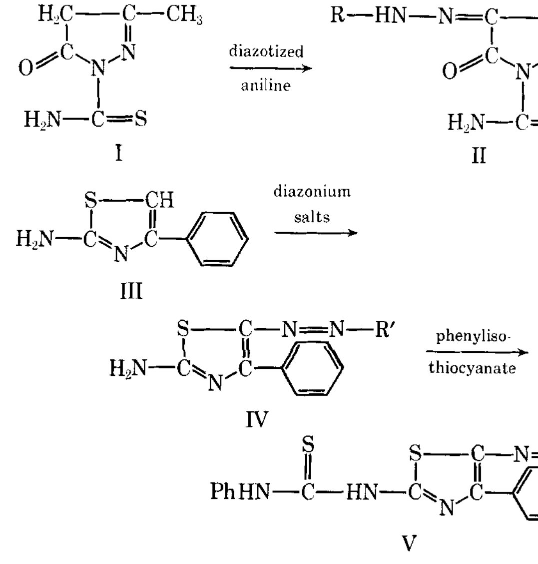
Sample No.	R′	Yield, %	M.p., °C.	Color	Formula	Anal., % Calcd.	Anal., % Found
1	2,5-MeO_2Ph	65	141–142	Orange-red needles	$C_{24}H_{21}N_5O_2S_2$	C, 60.6 H, 4.4 N, 14.7 S, 13.4	C, 60.2 H, 4.0 N, 14.4 S, 13.0
2	2-MePh	69	254–255	Red needles	$C_{23}H_{19}N_5S_2$	C, 64.3 H, 4.4 N, 16.3 S, 14.9	C, 64.0 H, 4.2 N, 16.0 S, 14.5
3	2,5-Cl_2Ph	72	256–257	Deep-red plates	$C_{22}H_{15}Cl_2N_5S$	C, 54.5 H, 3.1 N, 14.4 S, 13.2	C, 54.4 H, 2.7 N, 14.6 S, 13.0
4	3-NO_2Ph	58	262–263	Yellow-orange needles	$C_{22}H_{16}N_6O_2S_2$	C, 57.4 H, 3.5 N, 18.2 S, 13.9	C, 57.6 H, 3.4 N, 17.9 S, 13.3
5	4-EtOPh	65	242–243	Red needles	$C_{24}H_{21}N_5O_2S$	C, 62.7 H, 4.6 N, 15.2 S, 13.9	C, 62.5 H, 4.3 N, 14.7 S, 13.5
6	2,6-Me_2Ph	75	185–186	Orange-red needles	$C_{24}H_{21}N_5S_2$	C, 65.0 H, 4.7 N, 15.8 S, 14.4	C, 65.3 H, 4.5 N, 15.5 S, 14.1
7	4-ClPh	60	255–256	Red plates	$C_{22}H_{16}ClN_5S_2$	C, 58.7 H, 3.5 N, 15.5 S, 14.2	C, 58.2 H, 3.2 N, 15.2 S, 13.8
8	4-MeOPh	74	239–240	Orange needles	$C_{23}H_{19}N_5OS_2$	C, 62.0 H, 4.2 N, 15.7 S, 14.3	C, 61.6 H, 4.6 N, 15.6 S, 14.0
9	2,4-Me_2Ph	71	258–259	Orange needles	$C_{24}H_{21}N_5S_2$	C, 65.0 H, 4.7 N, 15.8 S, 14.4	C, 64.7 H, 4.3 N, 15.2 S, 14.1
10	2-Cl-4-NO_2Ph	55	280–281	Violet needles	$C_{22}H_{15}ClN_6O_2S_2$	C, 53.4 H, 3.3 N, 16.9 S, 12.9	C, 53.1 H, 3.0 N, 16.4 S, 12.5
11	3-MeOPh	76	235–236	Orange plates	$C_{23}H_{19}N_5OS_2$	C, 62.0 H, 4.2 N, 15.7 S, 14.3	C, 62.4 H, 3.8 N, 15.5 S, 13.9
12	2-MeOPh	75	227–228	Orange needles	$C_{23}H_{19}N_5OS_2$	C, 62.0 H, 4.2 N, 15.7 S, 14.3	C, 62.2 H, 3.0 N, 15.2 S, 13.8
13	2-NO_2Ph	70	164–165	Brown needles	$C_{22}H_{16}N_6O_2S_2$	C, 57.4 H, 3.5 N, 18.2 S, 13.9	C, 57.5 H, 3.2 N, 18.4 S, 13.6
14	2,5-Me_2Ph	68	260–261	Orange needles	$C_{24}H_{21}N_5S_2$	C, 65.0 H, 4.7 N, 15.8 S, 14.4	C, 65.2 H, 4.5 N, 15.4 S, 14.1
15	2,4-$(NO_2)_2$Ph	56	287–288	Reddish-brown needles	$C_{22}H_{15}N_5O_4S_2$	C, 52.2 H, 2.9 N, 19.4 S, 12.6	C, 52.0 H, 2.7 N, 19.0 S, 12.2

Table IV—Spectral Properties of 1-Thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones[a]



Sample No.	R	C=O Cyclic	C=C—NH—N=	C=N	>C=S	NH, NH$_2$ Associated	Substituted Phenyl Ring
1	2-MeOPh	1665	1550	1615	1430	3365	750
2	3-ClPh	1680	1552	1595	1410	3360	745
3	2-NO$_2$Ph	1675	1550	1600	1420	3370	748
4	4-NO$_2$Ph	1680	1550	1600	1410	3365	755
5	4-SO$_2$NH$_2$Ph	1675	1550	1595	1410	3365	755
6	2-MePh	1670	1550	1610	1430	3370	758
7	2,5-Cl$_2$Ph	1675	1550	1612	1410	3375	820
8	2,5-Me$_2$Ph	1670	1552	1605	1435	3375	815
9	3-MeOPh	1670	1550	1600	1420	3380	745
10	2,6-Me$_2$Ph	1675	1552	1598	1435	3375	780
11	2-Cl-4-NO$_2$Ph	1680	1550	1590	1435	3370	785
12	4-EtOPh	1680	1550	1595	1425	3385	760
13	2-Cl-6-MePh	1670	1550	1605	1430	3360	755
14	4-MePh	1670	1552	1600	1410	3365	750
15	4-ClPh	1675	1550	1600	1415	3370	755

[a] IR (cm.$^{-1}$) $\nu_{max.}$ (KBr disc).



Scheme I

EXPERIMENTAL[3]

1-Thiocarbamoyl-3-methyl-2-pyrazolin-5-one—Thiosemicarbazide hydrochloride (12.7 g., 0.1 mole) was dissolved in water (30 ml.) and mixed with acetoacetic ester (13 ml., 0.1 mole). Ethyl 3-oxobutyrate-β-thiosemiarbazone separated after 15 min. and recrystallized from ethanol as colorless needles, yield 19.09 g., 90%; m.p. 92–93° (from ethanol) [lit. (12) m.p. 93°].

The latter (50 g.) was suspended in liquid ammonia (25 ml.) and thoroughly stirred until it gradually dissolved. The mixture was then made acidic with concentrated HCl. 1-Thiocarbamoyl-3-methyl-2-pyrazolin-5-one precipitated and was recrystallized as colorless needles, yield 2.9 g., 76%; m.p. 181–182° (from DMF–ethanol) [lit. (12) m.p. 180°].

1-Thiocarbamoyl-3-methyl-4-(2-methoxyphenylhydrazono)-2-pyrazolin-5-one—*o*-Anisidine (2.5 ml., 0.02 mole) was dissolved in 3 *N* HCl (2.5 ml.) and cooled to 0°. Sodium nitrite (1.4 g., 0.02 mole) dissolved in water (20 ml.) was gradually added. The diazonium salt solution was filtered into a well-cooled, stirred mixture of sodium acetate (5 g.) and 1-thiocarbamoyl-3-methyl-2-pyrazolin-5-one (3.14 g., 0.02 mole) in acetic acid (50 ml.). 1-Thiocarbamoyl-3-methyl-4-(2-methoxyphenylhydrazono)-2-pyrazolin-5-one started precipitating almost immediately. After standing for 2 hr., the precipitate was filtered, washed with water, and recrystallized as orange needles, yield 4.3 g., 82%; m.p. 210–211° (DMF–ethanol).

Anal.—Calcd. for $C_{12}H_{13}N_5O_2S$: C, 49.4; H, 4.4; N, 24.0; S, 11.0. Found: C, 49.0; H, 4.6; N, 23.6; S, 10.7.

By adopting a similar procedure as above, several 1-thiocarbamoyl-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones, described in Table I, were obtained.

2-Amino-4-phenylthiazole—A mixture of acetophenone (24.0 ml., 0.2 mole), thiourea (30.4 g., 0.4 mole), and iodine (50.8 g., 0.2 mole) was heated overnight on a steam bath. This was cooled and extracted with ether (2 × 25 ml.) to remove unreacted acetophenone and iodine. The residue was then dissolved in hot water and filtered to remove sulfur and other impurities. The solution was cooled somewhat (about 20°) and made alkaline with concentrated ammonia. The 2-amino-4-phenylthiazole thus precipitated was recrystallized as long colorless needles, yield 38.7 g., 65%; m.p. 145° (from H_2O–ethanol) [lit. (13) m.p. 147°].

2-Amino-4-phenyl-5-phenylazothiazole—Aniline (1.85 g., 0.02 mole) was dissolved in 3 *N* HCl (2.5 ml.) and cooled to 0°. Sodium nitrite (1.4 g., 0.02 mole) dissolved in water (25 ml.) was added. The diazonium solution was filtered to a well-cooled suspension of 2-amino-4-phenylthiazole (3.52 g., 0.02 mole) and sodium acetate (5 g.) in ethanol (50 ml.). After 2 hr., 2-amino-4-phenyl-5-phenylazothiazole was filtered and washed well with water. It was recrystallized as red needles, yield 4.5 g., 80%; m.p. 191–192° (from DMF–ethanol) [lit. (18) m.p. 195°].

Anal.—Calcd. for $C_{15}H_{12}N_4S$: C, 64.2; H, 4.2; N, 20.0; S, 11.4. Found: C, 63.7; H, 4.4; N, 19.6; S, 11.2.

Similarly prepared 2-amino-4-phenyl-5-arylazothiazoles are summarized in Table II.

***N*-Phenyl-*N*′-2(4-phenyl-5-phenylazothiazolyl)thiocarbamide**—A mixture of phenylisothiocyanate (1.35 g., 0.01 mole) and 2-amino-4-phenyl-5-phenylazothiazole (2.80 g., 0.01 mole) in benzene (15 ml.) was refluxed for 6–8 hr. on a steam bath. The solvent was removed and the residue was repeatedly triturated with petroleum ether (b.p. 40–60°) and then with ether. The crystalline thiocarbamide thus obtained was recrystallized from DMF–ethanol as deep red needles, yield 3.1 g., 75%; m.p. 241–242°.

Anal.—Calcd. for $C_{22}H_{17}N_5S_2$: C, 63.6; H, 4.1; N, 16.8; S, 15.4. Found: C, 63.2; H, 4.5; N, 16.6; S, 15.1.

Similarly a number of *N*-phenyl-*N*′-2(4-phenyl-5-arylazothiazolyl)-thiocarbamides were prepared which are summarized in Table III.

REFERENCES

(1) R. W. Brockman, J. R. Thomson, M. J. Bell, and H. E. Skipper, *Cancer Res.*, **16**, 167(1956).

(2) F. A. French and B. L. Freedlander, *ibid.*, **18**, 1920(1958).

(3) *Ibid.*, **20**, 505(1960).

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[3] Melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were measured with a Beckman IR4 spectrophotometer.

(4) F. A. French and E. J. Blanz, Jr., *Cancer Res.*, **23,** 9(1963).

(5) F. A. French and E. J. Blanz, Jr., *J. Med. Chem.*, **9,** 585 (1966).

(6) E. J. Modest, H. N. Schlein, and G. E. Foley, *J. Pharm. Pharmacol.*, **9,** 68(1957).

(7) R. E. Harmon, F. E. Dutton, and H. D. Warren, *J. Med. Chem.*, **11,** 627(1968).

(8) S. S. Sabnis and K. D. Kulrami, *Indian J. Chem.*, **1,** 447 (1963).

(9) F. D. Popp and W. Kirsch, *J. Org. Chem.*, **26,** 3858(1961).

(10) M. G. Dhapalapur, S. S. Sabnis, and C. V. Deliwala, *J. Med. Chem.*, **11,** 154(1968).

(11) H. G. Garg and R. A. Sharma, *J. Med. Chem.*, **12,** 1122 (1969).

(12) S. C. De and D. N. Dutt, *J. Indian Chem. Soc.*, **7,** 473(1930).

(13) R. M. Dodson and L. C. King, *J. Amer. Chem. Soc.*, **67,** 2242(1945).

(14) F. B. Dains, R. Q. Brewster, and C. P. Olander, *Org. Synth. Coll.*, **1,** 447.

(15) H. G. Garg, Ph.D. thesis, Agra University, Agra, India, 1959.

(16) H. Yasuda, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)*, **56,** 267(1962).

(17) H. Yasuda and H. Midorikawa, *J. Org. Chem.*, **31,** 1722 (1966).

(18) H. Beyer and G. Walter, *Chem. Ber.*, **85,** 1077(1952).

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Release of Medroxyprogesterone Acetate from a Silicone Polymer

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Abstract ☐ The *in vitro* release of medroxyprogesterone acetate from a silicone rubber matrix was studied. A nonlinear dependence of release rate upon medroxyprogesterone acetate concentration within the matrix was found. Based upon a model system, equations were derived to explain this behavior and to include other parameters which may influence the release rate. Since the model, in part, is dependent upon a receding medroxyprogesterone acetate layer within the matrix, a photograph depicting depletion zones as a function of time is presented. In contrast to the T. Higuchi model for drug release, this model includes the boundary diffusion layer. Comparison of the two models suggested that when the boundary layer was considered, a better fit of experimental data to theory was found. The applicability of the model to an *in vivo* system is discussed. This study has suggested that the partition coefficient, diffusion coefficients, medroxyprogesterone acetate concentration within the polymer, and agitation conditions play important roles in the release process.

Keyphrases ☐ Medroxyprogesterone acetate release rate, *in vitro*—physicochemical factors ☐ Silicone rubber matrix—medroxyprogesterone acetate release ☐ Matrix boundary diffusion layer model—equations derived ☐ Partition coefficient—silicone, medroxyprogesterone acetate ☐ Vapor phase chromatography—determination

The use of a rubber material as a delivery system for various chemicals has been a subject of considerable interest. The B. F. Goodrich Co. (1) has recently incorporated toxic substances into a rubber matrix and observed effective antifouling activity for prolonged periods. Some therapeutic implications of silicone rubber as a drug delivery system have been described previously (2).

The advantage of silicone rubber as a dosage form for medroxyprogesterone acetate has been discussed by Mishell *et al.* (3). It was shown that medroxyprogesterone acetate was readily absorbed from a vaginal device in sufficient quantity to inhibit ovulation. This drug delivery system promises to be a unique approach in the field of contraception.

Although other investigators (4, 5) have studied the diffusion of drugs across silicone membranes, an *in vitro* study on the release of a drug embedded in a silicone matrix has not been presented. Therefore, the present study was designed to investigate the physicochemical factors involved in the release of medroxyprogesterone acetate from a silicone matrix system. The interdependence of various parameters can be described by mathematical relationships based upon a physical model which is an extension of concepts set forth by Higuchi (6).

EXPERIMENTAL

Medroxyprogesterone acetate[1]-silicone[2] cylinders, 4 cm. by 0.5 cm., were prepared by levigating the required amount of drug into the elastomer and polymerizing with catalyst. The mixture was then forced into prewashed vinyl tubing and allowed to cure. After the cylinders were removed from the tubing and weighed, 24 were mounted between two circular disks and secured in a 3-l. jacketed beaker. Figure 1 is a schematic diagram of the *in vitro* dissolution apparatus. Distilled water from eight 5-gal. carboys was pumped at a rate of about 60 l./day through a 37° water bath, which preheated the water, into the beaker. The effluent was discarded into a drain. This constant flow of water approximates a "perfect sink" condition, *i.e.*, there is no significant concentration build-up in the dissolution media. The same water bath provided 37° water which was continuously circulated through the walls of the beaker,

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[1] The Upjohn Co.'s trademark for medroxyprogesterone acetate is Provera.

[2] Silastic Elastomer, Dow Corning Corp., Midland, Mich.