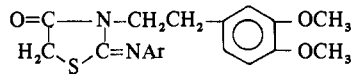
Table II. Substituted 4-Thiazolidones and Their Anticonvulsant Activity



No.	Ar	Mp,[a] °C	Yield, %	Molecular formula[b]	Protection, %	Mortality after 24 hr, %
1	C_6H_5	117	62	$C_{19}H_{20}N_2O_3S$	30	60
2	o-$CH_3C_6H_4$	126	55	$C_{20}H_{22}N_2O_3S$	70	20
3	m-$CH_3C_6H_4$	118	60	$C_{20}H_{22}N_2O_3S$	30	40
4	p-$CH_3C_6H_4$	160	64	$C_{20}H_{22}N_2O_3S$	40	50
5	3,4-$(CH_3)_2C_6H_3$	175	62	$C_{21}H_{24}N_2O_3S$	10	70
6	o-$OCH_3C_6H_4$	90	54	$C_{20}H_{22}N_2O_4S$	50	30
7	p-$OCH_3C_6H_4$	147	62	$C_{20}H_{22}N_2O_4S$	10	60
8	p-ClC_6H_4	150	60	$C_{19}H_{19}ClN_2O_3S$	60	50
9	p-BrC_6H_4	153	62	$C_{19}H_{19}BrN_2O_3S$	30	60
10	α-$C_{10}H_7$	128	58	$C_{23}H_{22}N_2O_3S$	50	40

[a,b] See footnotes to Table I.

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Synthesis of N′-Substituted Arylsulfonylpyrazoles, Their Anthelmintic Activity, and the Cytotoxicity of Some Hydrazides†

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Received September 10, 1971

Our continued interest in the synthesis of biological active heterocycles has led us to study the synthesis and anthelmintic activity of N′-substituted arylsulfonyl-3,5-dimethyl-4-arylazopyrazoles. These compounds displayed anthelmintic and cytotoxicity activities of different magnitudes. All are apparently nontoxic to mice at the dosages used.

Experimental Section

Melting points, taken with a Kofler hot-stage apparatus, are uncorr. Where analyses are indicated only by symbols of the elements, analytical result obtd for those elements were within ±0.4% of the calcd values.

2,3,4-Pentanetrione-3-arylhydrazons,[1] cinnamic acids, and hydrazides,[2] 3-nitro-4-methoxybenzenesulfonylhydrazide,[3] 3-chloro-4-methoxybenzenesylfonylhydrazide,[3] and 2,5-dichlorobenzenesulfonylhydrazide[4] were prepd by standard procedures.

2-Methoxy-3,5-dimethyl- and 2-Chloro-5-carboxybenzenesulfonyl Hydrazide. A soln of 2-methoxy-3,5-dimethyl- and 2-chloro-5-carboxybenzenesulfonyl chloride in EtOH was treated with NH_2NH_2–H_2O (98%) at 0°. It was left at room temp for several hr, when crystals of the hydrazide were obtd. Recrystn from EtOH gave a colorless product, mp 116–117°. 2-MeO-3,5-Me_2 deriv. *Anal.* ($C_9H_{14}N_2O_3S$) C, H, N. 2-Cl-5-CO_2H deriv, mp 87°. *Anal.* ($C_7H_7ClN_2O_4S$) C, H, N.

N′-Substituted Arylsulfonyl-3,5-dimethyl-4-arylazopyrazoles. A hot soln of arylsulfonylhydrazide (0.01 mole) in EtOH (30 ml)

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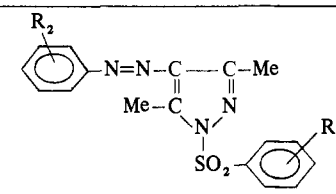
Table I. N^1-Arylsulfonyl-3,5-dimethyl-4-arylazopyrazoles



No.	R_1	R_2	Yield, %	Mp, °C	Color[a]	Formula[b]
1	3-NO_2-4-OMe	2-Cl	65	168–169	Ly	$C_{18}H_{16}ClN_5O_5S$
2	3-NO_2-4-OMe	4-OMe	95	194–195	y	$C_{19}H_{19}N_5O_6S$
3	3-NO_2-4-OMe	4-NO_2	80	167–168	O	$C_{18}H_{16}N_6O_7S$
4	3-Cl-4-OMe	2-Cl	65	150–151	Y	$C_{18}H_{16}Cl_2N_4O_3S$
5	3-Cl-4-OMe	2-NO_2	76	224–225	R	$C_{18}H_{16}ClN_5O_5S$
6	3-Cl-4-OMe	4-OMe	70	161–162	Y	$C_{19}H_{19}ClN_4O_4S$
7	2-OMe-5-Cl	2-NO_2	80	200–201	R	$C_{18}H_{16}ClN_5O_5S$
8	2,5-Cl	2-NO_2	90	190–191	DBn	$C_{17}H_{13}Cl_2N_5O_4S$
9	2-Cl-5-COOH	2-NO_2	96	220–221	BR	$C_{18}H_{14}ClN_5O_6S$
10	2-OMe-3,5-Me	4-OMe	96	154–155	Py	$C_{21}H_{24}N_4O_4S$

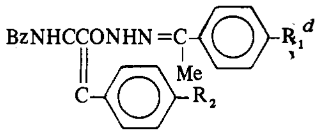
[a] B, brick; Bn, brown; D, dark; L, light; O, orange; P, pale; R, red; Y, yellow. [b] All compds were analyzed for C, H, N, S.

Table II. Biological Activities of N^1-Arylsulfonylpyrazoles

	% activity at highest tested dosage[b]							
	In Vivo				*In Vitro*			
	Mice				Manure			
No.[a]	Tg	N	C	O	R/Lv/Ad	Hc/Ts	F	Dose, ppm
1		0	0	60	75/0/0	100/100	0	100
2	0	0	0	0				400 mg/kg
3	0	0	0	0	50/0/0	100/100	0	100 mg/kg
4		0		0	0/0/0	60/90	0	100
5	0	0	0	0	0/0/0	0/50	0	100, 400 mg/kg
6	0	0	0	50				400 mg/kg
7	0				0/0/0	50/50	0	100
8	0				0/0/0	0/50	0	100
9	0	0	0	50				400 mg/kg
10	0	0	0	0				100

[a] Same as Table I. [b] Tg, *Toxoplasma gondii*–RH strain in mice prevention (of mortality); N, nematodes (*trichostrongyles* in mice); C, cestoses (tapeworms in mice); O, oxyurids (in mice); R, % repellency (of face fly oviposition); Lv, % contact activity on face fly larvae (prevention of pupation); Ad, % kill of adult face flies and/or pupae which fail to hatch; Hc, % inhibition of *Haemonchus contorus* larvae development; Ts, % inhibition of *Trichostorgylus spp.* larvae development; F, % inhibition of fungus growth.

Table III. Cytotoxicity of Hydrazide Derivatives against KB Strain of Human Carcinoma of the Nasopharynx



No.	R_1	R_2	Mp, °C	ED_{50}, μg/ml
1	2,4-$(OH)_2$[a]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	265	>10
2	2,4-$(OH)_2$-5-NO_2[b]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	160	22
3	2-$(OH)_4$-Me-5-Cl[c]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	187	18
4	3-Me-4-OH[c]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	278	84
5	2-OH-5-Cl[c]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	188	>100
6	4-OH[c]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	270	>100
7	2-OH-3-Me[c]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	280	>100
8	2-OH[c]	$3\text{-}NO_2\text{-}4\text{-}(OCH_3)$	260	>100
9	2-OH[b]	$3,4\text{-}(OCH_2O)$	173	93
10	4-OH[b]	$3,4\text{-}(OCH_2O)$	197	24
11	2-(OH)-3-Me[b]	$3,4\text{-}(OCH_2O)$	225	>100
12	3-Me-4-(OH)[b]	$3,4\text{-}(OCH_2O)$	192	23
13	2-(OH)-5-Cl[b]	$3,4\text{-}(OCH_2O)$	183	19
14	2,4-$(OH)_2$[b]	$3,4\text{-}(OCH_2O)$	215	23
15	2,4-$(OH)_2$-5-Br[b]	$3,4\text{-}(OCH_2O)$	240	47
16	2,4-$(OH)_2$-5-NO_2[b]	$3,4\text{-}(OCH_2O)$	225	24
17	2-(OH)-4-Me-5-Cl[b]	$3,4\text{-}(OCH_2O)$	200	59
18	2-(OH)-4,6-Me_2-5-Cl[b]	$3,4\text{-}(OCH_2O)$	221	59

[a]DMF. [b]Alkali diluted with saline. [c]Saline. [d]Supplied by R. P. Mahesh.

contg H_2SO_4 (2 ml) was added to 2,3,4-pentanetrione 3-arylhydrazone (0.01 mole) in a mixt of EtOH-AcOH on a steam bath for several hr. It was left overnight at room temp, when crystals sepd. This was recrystd from DMF-EtOH (Table I).

Acknowledgments. The authors thank Dr. H. B. Wood, H. W. Bond of Cancer Chemotherapy, NIH, Bethesda, Md., and Dr. W. C. McGuire of Phillips Roxane, Inc., for their cooperation and for the screening data.

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Preparation and Progestational Activity of 6-Cyano-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate and Related Compounds

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In recent years considerable attention has been given to the preparation of 6-substituted-6-dehydroprogestagens among which 6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**1**, chlormadinone acetate) and 6-methyl-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**2**, megestrol acetate) have found use in contraceptives. The progestational potentiating effect of the 16-methylene moiety has been demonstrated sometime ago.[1]

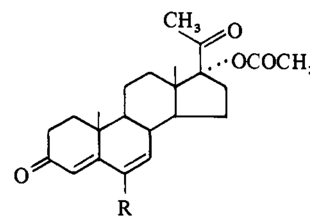
As an extension of our investigations[2] on the progestational activity of 6-dehydro-16-methylene-17α-acetoxyprogesterone derivatives in the present communcation, we wish to report the synthesis of 6-formyl-6-dehydro-16-methylene-17α-acetoxyprogesterone (**3**) and of 6-cyano-6-dehydro-16-methylene-17α-acetoxyprogesterone (**4**).

Table I. Progestational Activity[a,b]

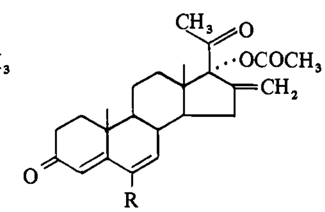
Compd	Activity
3	1[c]
4	5.8
7	0.45
8	2.1
11	1.8

[a]Progesterone = 1. [b]Progestational activity was detd in immature rabbits by the method of McPhail.[7] The compounds were dissolved in sesame oil for im administration. Progesterone in sesame oil was given im. The statistical analysis for the progestational assays utilized the randomized Bloch analysis of variance with Dunnett's and Duncan's multiple comparison procedure (see ref 8). [c]Approximate value.

The preparation of the 6-formyl **3** was carried out by converting the ethyl enol ether **5**[3] by the Vilsmeier reaction† to the 6-formyl enol ether **6**. On treatment with dichlorodicyanobenzoquinone (DDQ) in 95% aqueous acetone[5] **6** afforded the desired **3** in 45% yield.



1, R = Cl
2, R = CH_3

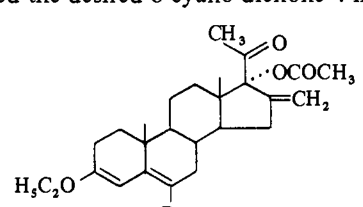


3, R = CHO
4, R = CN
9, R = CH=NOH
11, R = $CH=NOCH_3$

In order to prepare the 6-cyano derivative **4** the 6-formyl enol ether **6** was used as starting material. Reaction of **6** with NH_2OH gave the oximinomethyl compound **7** which when treated with NaOAc in refluxing Ac_2O afforded the 6-cyano enol ether **8**.‡

In contrast to the 6-formyl enol ether **6**, the 6-cyano enol ether **8** was completely inert toward DDQ. Even forcing conditions (large excess of DDQ in refluxing dioxane for 48 hr) failed to give any of the desired **4**. Only small amounts of the 6-cyano-$\Delta^{1,4,6}$-trienone and highly colored materials (probably DDQ adducts) could be isolated.

In order to overcome the difficulties in the dehydrogenation of **8**, the oximinomethyl enol ether **7** was treated with DDQ in 95% aqueous acetone. Rapid conversion to the corresponding dienone **9** occurred and the latter compound was isolated in 68% yield. Reaction of **9** with $POCl_3$ in pyridine afforded the desired 6-cyano dienone **4** in 70% yield.



5, R = H
6, R = CHO
7, R = CH=NOH
8, R = CN
10, R = $CH=NOCH_3$

†Burn, *et al.*,[4] described the prepn of the analogous 3-methoxy-$\Delta^{3,5}$-6-formyl compd from the corresponding 3-methyl enol ether.

‡A British patent[6] describes the preparation of the analogous 3-methoxy-$\Delta^{3,5}$-6-cyano compound.