crystallized from EtOH to yield 1.8 g of phenyl *N*-furfuryl-4-phenoxy-5-(dimethylsulfamoyl)orthanilate, mp 165–166 °C. This compound was hydrogenated in the presence of Pd/C as described above for 21a, yielding, after recrystallizing from EtOH and drying at 100 °C in vacuo, 0.6 g of 21b, mp 201 °C dec. Anal. (C_{19}-$H_{19}KN_2O_7O_2$) C, H, N.

   Potassium *N*-Furfuryl-4-(*N*-methylanilino)-5-(methylsulfamoyl)orthanilate (21c) and Potassium *N*-Furfuryl-4-(*N*-methylanilino)-5-(dimethylsulfamoyl)orthanilate (21d). Compound 16 (10.3 g, 20 mmol) was allowed to react with dimethyl sulfate (5.7 mL) and the reaction mixture was fractionated by column chromatography as described in the next to the last example for compound 12, to give 2.5 g of phenyl *N*-furfuryl-4-(*N*-methylanilino)-5-(methylsulfamoyl)orthanilate, R_f 0.26, mp 142–143 °C, and 2.4 g of phenyl *N*-furfuryl-4-(*N*-methylanilino)-5-(dimethylsulfamoyl)orthanilate, R_f 0.49, mp 173–174 °C, both identified by NMR. Hydrogenation of these compounds by means of Pd/C and precipitation of the resulting sulfonic acids in the form of the potassium salts from aqueous solution, as described for 21a above, yielded, after drying at 100 °C, 1.5 g of 21c, mp 180 °C dec, as a dihydrate [Anal. ($C_{19}H_{24}KN_3O_8S_2$) C, H, N] and 1.6 g 21d, mp 168 °C dec, as a monohydrate [Anal. ($C_{20}H_{24}KN_3O_7S_2$) C, H, N].

Notes

A New Class of Nonhormonal Pregnancy-Terminating Agents. Synthesis and Contragestational Activity of 3,5-Diaryl-*s*-triazoles[1]

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A series of 3,5-diaryl-*s*-triazoles were synthesized and evaluated as postimplantation contragestational agents. The introduction of various substituents (e.g., an *o*-alkyl chain on one phenyl and a *m*-alkoxy group on the other) was found to increase the potency. Several compounds with very high pregnancy-terminating activity in both hamsters and rats were obtained. One of these, 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-*s*-triazole, DL 111 (36), was selected for detailed evaluation in various animal species. A synthetic scheme for the preparation of these compounds and preliminary structure–activity relationships are presented.

   In a search for new nonhormonal compounds with antifertility activity, we found a new class, i.e., 2-aryltriazolo[5,1-*a*]isoindoles and the corresponding 5,6-dihydroisoquinolines, with pronounced activity in our primary screening tests as postcoital pregnancy-terminating agents. Our interest in this class was increased by the promising results obtained with selected compounds in various animal species, including monkeys and baboons.[2–8]

   In an attempt to enhance potency, we synthesized some series of tricyclic analogues, in which the triazole ring was replaced by differently fused pyrazoles[9] and imidazoles.[10] As a result of this effort, the 2-aryltriazolo[5,1-*a*]isoquinoline class yielded potent compounds, but their very sustained pharmacokinetic profiles and/or their low solubility, even in oily vehicles, hindered their use in clinical studies.[11,12]

   Since it was apparent that the bridge linking the benzo ring to the triazole moiety strongly affects both the potency

(1) Presented in part at the 10th World Congress of Fertility and Sterility, July 5–11, 1980, Madrid, abstract 347.

(2) L. J. Lerner, G. Galliani, M. C. Mosca, and A. Omodei-Salé, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 34, 338 (1975).

(3) L. J. Lerner, G. Galliani, P. Carminati, and M. C. Mosca, *Nature (London)*, 256, 130 (1975).

(4) G. Galliani and L. J. Lerner, *Am. J. Vet. Res.*, 37, 263 (1976).

(5) G. Galliani, L. Gallico, C. Cattaneo, and L. J. Lerner, *Acta Endocrinol. (Copenhagen)*, Suppl., 212, 126 (1977).

(6) L. J. Lerner, A. Omodei-Salé, G. Galliani, R. Heywood, J. M. Hall, and A. M. Grant, *Fertil. Steril.*, 28, 290 (1977).

(7) G. Galliani, L. Gallico, C. Cattaneo, and A. Assandri, *Arzneim.-Forsch.*, 30, 972 (1980).

(8) G. Galliani, L. J. Lerner, C. Caramel, R. Maraschin, S. Nani, and A. Nava, *Arzneim.-Forsch.*, 32, 123 (1982).

(9) (a) E. Toja, A. Omodei-Salé, C. Cattaneo, and G. Galliani, *Eur. J. Med. Chem.*, 17, 223 (1982). (b) A. Omodei-Salé, E. Toja, G. Galliani, and L. J. Lerner, U.S. Patent 4075342 (1978).

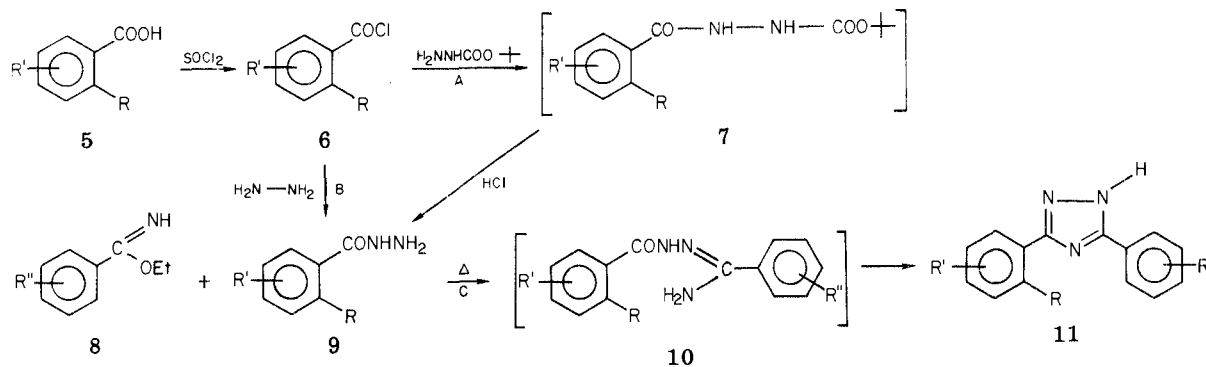†Present address: Pierrel Research Laboratories, Via degli Artigianelli 10, 20159 Milano, Italy.

Scheme I

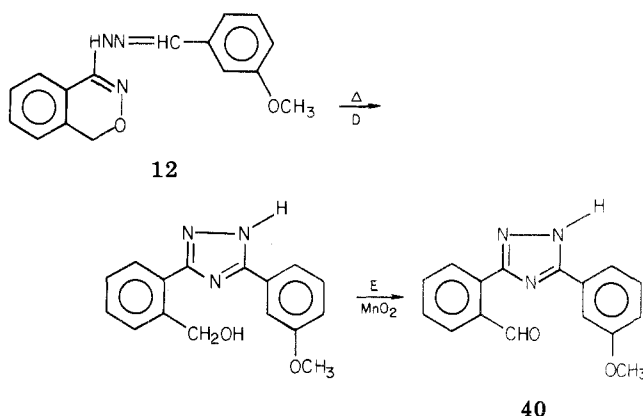Table I. Pregnancy-Terminating Activity and Solubility of the Four Parent Triazole Derivatives

no.	structure	ED_{50}, (mg/kg)/day sc[a] hamster	ED_{50}, (mg/kg)/day sc[a] rat	solu-bility,[b] mg/mL
1		3.5	1.8	~30
2		1	16	~100
3		0.25	2.5	~10
4		0.3	2	>100

[a] Test compounds, dissolved in sesame oil containing 20% benzyl benzoate, were administered to groups of 5-30 animals, at three to six dose levels. Animals were treated daily for 5 consecutive days, from day 4 to day 8 in hamsters, and from day 6 to day 10 in rats. The ED_{50} is the dose required to terminate pregnancy in 50% of the animals. [b] In sesame oil containing 20% of benzyl benzoate.

and the solubility of compounds 1-3 (Table I), we decided to synthesize the analogue 4, in which an *o*-methyl group on one phenyl ring replaces the methylene chain. This modification produced a compound with contragestational activity comparable to that of the related tricyclic derivatives and, as expected, with markedly increased solubility in oily vehicles. We report here the synthesis of a series of 3,5-diaryl-*s*-triazoles and discuss their structure-activity relationships.

Chemistry. The 3,5-diaryl-*s*-triazoles listed in Table III were readily prepared by heating together equimolar amounts of substituted benzhydrazides 9 and ethyl benzimidates 8[13] (Scheme I, method C). The reaction proceeds

(10) (a) E. Toja, A. Omodei-Salé, D. Favara, C. Cattaneo, L. Gallico, and G. Galliani, *Arzneim.-Forsch.*, accepted for publication. (b) G. Winters, G. Odasso, G. Galliani, and L. J. Lerner, U.S. Patent 4 024 149 (1977).

(11) (a) G. Galliani, T. Cristina, U. Guzzi, A. Omodei-Salé, and A. Assandri, *J. Pharmacobio-Dyn.*, 5, 55 (1982). (b) Unpublished results from these laboratories.

(12) G. Galliani and A. Omodei-Salé, *J. Small Anim. Pract.*, 23, 295 (1982).

Scheme II

via ring closure of the initially formed benzoylamidrazones 10.

The intermediate benzhydrazides 9 (Table II) were prepared from the substituted benzoic acids 5 by treatment with thionyl chloride, followed by reaction with *tert*-butyl carbazate in the presence of triethylamine. Subsequent cleavage of 7 with hydrochloric acid in a biphasic system yielded the desired hydrazides (method A), avoiding 1,2-disubstitution. Alternatively, the 2-methyl and 2-ethyl benzhydrazides (13 and 16) were prepared by the careful addition of the corresponding benzoyl chlorides to an excess of hydrazine hydrate (method B).
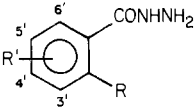
The 2-hydroxymethyl derivative 39 was synthesized by the rearrangement of 4-[(3-methoxybenzylidene)-hydrazino]-1*H*-2,3-benzoxazine (12) in refluxing xylene[14] (method D) as shown in Scheme II. Oxidation of 39 with manganese dioxide gave the aldehyde 40 (method E).

Structure-Activity Relationships. The pregnancy-terminating activities in the primary screening test in hamsters of the 3,5-diaryl-*s*-triazoles 26-75 after subcutaneous administration are shown in Table III. Although the parent 3,5-diphenyl-*s*-triazole (26) shows some degree of activity, a suitable function, such as methyl (27 and 30), ethyl (33 and 36), hydroxymethyl (39), or formyl (40), at the ortho position of a phenyl ring (formally that in position 3 of the *s*-triazole) is an important structural feature for contragestational activity. The potency is maximal with the ethyl substituent and strongly declines when the alkyl chain is branched (34 and 37) or elongated (35 and 38). Moving the methyl group from the ortho position (27 and 30) to the para (29 and 32) or meta position (28 and 31) greatly decreases the potency. The results suggest that the steric hindrance (cf. 26 with 33 and

(13) I. Y. Postovskii and N. N. Vereshchagina, *Zh. Obshch. Khim.*, 29, 2139 (1959); *Chem. Abstr.*, 54, 9898c (1960).

(14) G. Pifferi and P. Consonni, *J. Heterocycl. Chem.*, 9, 581 (1972).

Table II. Intermediate Substituted Benzoic Acid Hydrazides 9

$$\text{R'} \begin{array}{c} 6' \\ 5' \\ 4' \quad 3' \end{array} \text{—CONHNH}_2 \quad \text{R}$$

no.	R	R'	mp, °C	yield, %	crystn solvent	method	formula	anal.[a]
13	CH_3	H	123–125[b]	63	CH_2Cl_2-i-Pr_2O	B	$C_8H_{10}N_2O$	
14	H	3'-CH_3	88–90[c]	98	hexane[d]	A	$C_8H_{10}N_2O$	
15	H	4'-CH_3	112–114[e]	92	hexane[d]	A	$C_8H_{10}N_2O$	
16	C_2H_5	H	107–110	90	petroleum ether[d]	A	$C_9H_{12}N_2O$	C, H, N
			108–111	91		B		
17	$CH(CH_3)_2$	H	88–89	72	i-Pr_2O-pet. ether	A	$C_{10}H_{14}N_2O$	C, H, N
18	$(CH_2)_3CH_3$	H	79–80	71	i-Pr_2O	A	$C_{11}H_{16}N_2O$	C, H, N
19	CH_3	4'-Cl	151–152	79	CH_2Cl_2-i-Pr_2O	A	$C_8H_9ClN_2O$	C, H, N, Cl
20	CH_3	4'-CH_3	120–122	82	CH_2Cl_2	A	$C_9H_{12}N_2O$	H, N, C[g]
21	CH_3	4'-CH_3O	133–135	83	CH_2Cl_2-i-Pr_2O	A	$C_9H_{12}N_2O_2$	C, H, N
22	CH_3	5'-Cl	166–168	86	CH_2Cl_2	A	$C_9H_9ClN_2O$	C, H, N
23	CH_3	5'-CH_3	159–161	81	CH_2Cl_2	A	$C_9H_{12}N_2O$	C, H, N
24	CH_3	5'-CH_3O	111–112	57	CH_2Cl_2-i-Pr_2O	A	$C_9H_{12}N_2O_2$	C, H, N
25	H	3'-CH_3O	79–80[f]	61	CH_2Cl_2-i-Pr_2O	A	$C_8H_{10}N_2O_2$	

[a] New compounds were analyzed for C, H, and N; analytical results were within ±0.4% of theoretical values unless otherwise stated. [b] Literature[29] mp 125–127 °C. [c] Literature[30] mp 97 °C. [d] Crude product was triturated and filtered from the solvent listed. [e] Literature[31] mp 116–117 °C. [f] Literature[32] mp 90 °C. [g] C: calcd, 65.83; found, 65.15.

34) in the neighborhood of the triazole ring greatly affects the contragestational activity.

The effect upon contragestational activity of a second substitution R', in addition to the *o*-methyl group, is illustrated by the following examples. The introduction of chloro (**41** and **44**) or methyl (**42** and **45**) substituents in position 4' led to a twofold increase in potency, whereas 4'-methoxy (**43** and **46**), 5'-chloro (**47** and **50**), 5'-methyl (**48** and **51**), or 5'-methoxy (**49** and **52**) derivatives were considerably less active.

The effect on the activity of a substituent R'' on the phenyl ring at position 5 of the triazole while retaining the activity-enhancing *o*-methyl or *o*-ethyl substitution on the other phenyl ring was studied. Among all the monosubstitutions, only *m*-alkoxy substituents, such as methoxy (**30** and **36**), ethoxy (**54** and **66**), and allyloxy (**55** and **67**), increase the potency above that of the unsubstituted derivatives (**27** and **33**). Although the 4''-methoxy analogue (**68**) was less than one-third as potent as **36**, activity comparable to those of the most potent compounds of this series was obtained with the 3'',4''-dimethoxy (**73**) or 3'',4''-methylenedioxy (**74**) derivatives. Other dimethoxy (**72** and **75**) and dimethyl (**71**) analogues were considerably less potent than **36**. A few triazoles were also tested orally in the hamster (Table III), but by this route even the most potent compounds displayed weak activity, no more than $^1/_{30}$th the activity after subcutaneous administration. Consideration of all the compounds of Table III led to the selection of **36**, **44**, **45**, **66**, and **74** [ED_{50} = 0.03–0.04 (mg/kg)/day, sc] for further evaluations. These derivatives and the parent compound **27** were tested subcutaneously in the rat, a species which has been found to be less sensitive than the hamster to the ring-closed analogue 2-(3-ethoxyphenyl)-5,6-dihydro-*s*-triazolo[5,1-*a*]isoquinoline.[5,7] The data in Table IV show a high pregnancy-terminating activity [ED_{50} = 0.3–0.6 (mg/kg)/day, sc] in this species also. Furthermore, in agreement with the results obtained in the hamster, these compounds also had weak oral activity in the rat. We suggest that, as in the case of tricyclic triazole derivatives, the decreased oral activity can be attributed to metabolic factors.[11,15]

In conclusion, synthetic changes in a series of 3,5-diaryl-*s*-triazoles produced compounds with high pregnancy-terminating activity plus good liposolubility. The most potent compounds were those with *o*-methyl or *o*-ethyl substituents on one phenyl ring and *m*-alkoxy or 3,4-dimethoxy substitution patterns on the other. From these, 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-*s*-triazole, DL 111 (**36**), was selected for studies on the mechanism of action and for detailed evaluation in several animal species.[16–18] Like fused triazoles,[3,5] this compound and its analogues were found to be devoid of hormonal activity.[16]

Experimental Section

Capital letters designate the step in the synthetic procedure, as given in Schemes I and II and in Tables II and III.

Substituted Benzoic Acids (5). When not commercially available, the substituted benzoic acid starting materials were prepared by methods similar to those described in the literature: 2-ethylbenzoic acid by hydrogenation of 2-acetylbenzoic acid;[19] 2-isopropylbenzoic acid[20] by reaction of diethyl phthalate with methylmagnesium bromide, to give 3,3-dimethylphthalide, followed by hydrogenation; 2-*n*-butylbenzoic acid[21] by reaction of *n*-propylcadmium with phthalic anhydride,[22] followed by hydrogenation; 4-chloro-2-methylbenzoic acid and 5-chloro-2-methylbenzoic acid by hydrolysis with dilute H_2SO_4 of the cor-

(15) A. Assandri, A. Perazzi, E. Martinelli, P. Ferrari, A. Ripamonti, G. Tuan, and G. Galliani, *Arzneim.-Forsch.*, **31**, 2104 (1981).

(16) G. Galliani, A. Assandri, L. Gallico, F. Luzzani, C. Oldani, A. Omodei-Salé, A. Soffientini, and G. Lancini, *Contraception*, **23**, 163 (1981).

(17) A. Assandri, A. Perazzi, A. Omodei-Salé, and G. Galliani, *Eur. J. Drug Metab. Pharmacokinet.*, **8**, 9 (1983).

(18) F. Luzzani and G. Galliani, *Contraception*, **23**, 325 (1981).

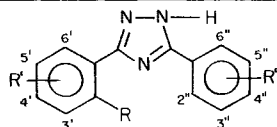(19) J. Kallonitsch, H. E. Mertel, and V. C. Verdi, *J. Org. Chem.*, **27**, 3362 (1962).

(20) B. B. Elsner, H. E. Strauss, and E. J. Forbes, *J. Chem. Soc.*, 578 (1957).

(21) C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron*, **18**, 617 (1962).

(22) P. L. de Benneville, *J. Org. Chem.*, **6**, 462 (1941).

Table III. 3,5-Diaryl-s-triazoles and Pregnancy-Terminating Activity in Hamsters

no.	R	R'	R''	mp, °C	yield, %	crystn solvent	method	formula	anal.[a]	sc	po[c]
26	H	H	H	191-192[b]	40	hexane	C	$C_{14}H_{11}N_3$	C, H, N	6	(10)
27	CH_3	H	H	112-114	70	i-Pr$_2$O-hexane	C	$C_{15}H_{13}N_3$	C, N, H	0.3	10
28	H	3'-CH_3	H	171-173[d]	25	AcOEt	C	$C_{15}H_{13}N_3$	C, H, N	>20	
29	H	4'-CH_3	H	180-183[e]	40	i-Pr$_2$O	C	$C_{15}H_{13}N_3$	C, H, N	>20	
30	CH_3	H	3''-CH_3O	100-102	60	i-Pr$_2$O-hexane	C	$C_{16}H_{15}N_3O$	C, H, N	0.08	5
31	H	3'-CH_3	3''-CH_3O	144-146	53	70% EtOH	C	$C_{16}H_{15}N_3O$	C, H, N	15	
32	H	4'-CH_3	3''-CH_3O	155-157	72	70% EtOH	C	$C_{16}H_{15}N_3O$	H, N, C[f]	7	
33	C_2H_5	H	H	124-126	34	i-Pr$_2$O-hexane	C	$C_{16}H_{15}N_3$	C, H, N	0.15	5
34	$CH(CH_3)_2$	H	H	165-167	75	i-Pr$_2$O-hexane	C	$C_{17}H_{17}N_3$	C, H, N	10	
35	$(CH_2)_3CH_3$	H	H	121-122	78	i-Pr$_2$O-hexane	C	$C_{18}H_{19}N_3$	H, N, C[g]	17	
36	C_2H_5	H	3''-CH_3O	72-75	64	i-Pr$_2$O-hexane	C	$C_{17}H_{17}N_3O$	C, H, N	0.04	4
37	$CH(CH_3)_2$	H	3''-CH_3O	125-126	78	i-Pr$_2$O-hexane	C	$C_{18}H_{19}N_3O$	C, H, N	4	(10)
38	$(CH_2)_3CH_3$	H	3''-CH_3O	101-102	64	i-Pr$_2$O-hexane	C	$C_{19}H_{21}N_3O$	C, H, N	12	(10)
39	CH_2OH	H	3''-CH_3O	157-159	92	EtOH	D	$C_{16}H_{15}N_3O_2$	C, H, N	0.08	15
40	CHO	H	3''-CH_3O	164-166	60	CH_2Cl_2-i-Pr$_2$O	E	$C_{16}H_{13}N_3O_2$	C, H, N	0.1	10
41	CH_3	4'-Cl	H	135-136	52	CH_2Cl_2-i-Pr$_2$O	C	$C_{15}H_{12}ClN_3$	C, H, N, Cl	0.14	4
42	CH_3	4'-CH_3	H	139-141	35	i-Pr$_2$O	C	$C_{16}H_{15}N_3$	C, H, N	0.2	>5
43	CH_3	4'-CH_3O	H	152-153	80	i-Pr$_2$O	C	$C_{16}H_{15}N_3O$	C, H, N	>10	
44	CH_3	4'-Cl	3''-CH_3O	137-139	71	CH_2Cl_2-i-Pr$_2$O	C	$C_{16}H_{14}ClN_3O$	C, H, N, Cl	0.04	5
45	CH_3	4'-CH_3	3''-CH_3O	106-108	45	i-Pr$_2$O-hexane	C	$C_{17}H_{17}N_3O$	C, H, N	0.04	10
46	CH_3	4'-CH_3O	3''-CH_3O	121-122	68	i-Pr$_2$O	C	$C_{17}H_{17}N_3O_2$	C, H, N	0.2	>5
47	CH_3	5'-Cl	H	170-172	58	i-Pr$_2$O	C	$C_{15}H_{12}ClN_3$	C, H, N, Cl	1.2	
48	CH_3	5'-CH_3	H	147-149	34	i-Pr$_2$O	C	$C_{16}H_{15}N_3$	C, H, N	>10	
49	CH_3	5'-CH_3O	H	144-145	73	CH_2Cl_2-i-Pr$_2$O	C	$C_{16}H_{15}N_3O$	C, H, N	>10	
50	CH_3	5'-Cl	3''-CH_3O	169-171	65	i-Pr$_2$O	C	$C_{16}H_{14}ClN_3O$	C, H, N	0.35	
51	CH_3	5'-CH_3	3''-CH_3O	127-130	52	i-Pr$_2$O	C	$C_{17}H_{17}N_3O$	H; C[h]	2.5	
52	CH_3	5'-CH_3O	3''-CH_3O	112-114	76	i-Pr$_2$O	C	$C_{17}H_{17}N_3O_2$	C, H, N	1	
53	CH_3	H	2''-CH_3O	160-161	15	i-Pr$_2$O	C	$C_{16}H_{15}N_3O$	C, H, N	0.5	>5
54	CH_3	H	3''-C_2H_5O	84-86	55	i-Pr$_2$O-hexane	C	$C_{17}H_{17}N_3O$	C, H, N	0.06	5
55	CH_3	H	3''-CH_2=$CHCH_2O$	72-75	65	i-Pr$_2$O-hexane	C	$C_{18}H_{17}N_3O$	C, H, N	0.15	5
56	CH_3	H	2''-CH_3	125-126	30	i-Pr$_2$O	C	$C_{16}H_{15}N_3$	C, H, N	0.7	>10
57	CH_3	H	3''-CH_3	87-90	35	cyclohexane	C	$C_{16}H_{15}N_3$	C, H, N	4	
58	CH_3	H	4''-CH_3	124-125	55	i-Pr$_2$O	C	$C_{16}H_{15}N_3$	C, H, N	20	
59	CH_3	H	2''-Cl	109-111	61	CH_2Cl_2-hexane	C	$C_{15}H_{12}ClN_3$	C, H, N, Cl	15	
60	CH_3	H	3''-Cl	147-148	52	C_6H_6-cyclohexane	C	$C_{15}H_{12}ClN_3$	C, H, N, Cl	0.6	>20
61	CH_3	H	4''-Cl	150-151	31	C_6H_6-cyclohexane	C	$C_{15}H_{12}ClN_3$	C, H, N, Cl	4	
62	CH_3	H	3''-CF_3	158-159	50	C_6H_6-cyclohexane	C	$C_{16}H_{12}F_3N_3$	C, H, N	0.6	>20
63	CH_3	H	4''-F	119-121	35	C_6H_6-cyclohexane	C	$C_{15}H_{12}FN_3$	C, H, N	3.5	
64	CH_3	H	4''-$N(CH_3)_2$	173-175	65	i-Pr$_2$O	C	$C_{17}H_{18}N_4$	C, H, N	(10)	
65	CH_3	H	4''-C_6H_5	165-167	72	CH_2Cl_2-i-Pr$_2$O	C	$C_{21}H_{17}N_3$	C, H, N	(10)	
66	C_2H_5	H	3''-C_2H_5O	84-86	68	i-Pr$_2$O-hexane	C	$C_{18}H_{19}N_3O$	C, H, N	0.04	4
67	C_2H_5	H	3''-CH_2=$CHCH_2O$	oil	88		C	$C_{19}H_{19}N_3O$	C, H, N[i]	0.12	5
68	C_2H_5	H	4''-CH_3O	128-129	71	Et$_2$O-hexane	C	$C_{17}H_{17}N_3O$	C, H, N	0.15	5
69	C_2H_5	H	3''-F	112-114	33	Et$_2$O-hexane	C	$C_{16}H_{14}FN_3$	C, H, N	0.4	>5
70	C_2H_5	H	3''-C_6H_5	161-162	60	Et$_2$O-hexane	C	$C_{22}H_{19}N_3$	C, H, N	(10)	(10)

Table IV. Pregnancy-Terminating Activity of the Selected Compounds in Rats

no.	ED$_{50}$, (mg/kg)/day	
	sc	po
27	2	50
36	0.6	25
44	0.5	>10
45	0.6	>10
66	0.3	>10
74	0.6	~20

responding nitriles;[23] 4-methoxy-2-methylbenzoic acid[24] and 5-methoxy-2-methylbenzoic acid[25] by catalytic hydrogenation of the corresponding 5-methoxy- and 6-methoxyphthalides. All the catalytic hydrogenations were carried out in alkaline solution at 80 °C (10 atm) in the presence of 10% Pd/C.

Ethyl-substituted Benzimidates (8). Imidate salts were prepared from the appropriate benzonitriles by the Pinner method,[26] except for those of the ortho-substituted derivatives, which were synthesized by reaction of the corresponding amides with triethyloxonium tetrafluoroborate.[27] The free imidates (8) were obtained by treating the salts with dilute K$_2$CO$_3$ and immediately extracting with Et$_2$O or CH$_2$Cl$_2$.

Method A. 4-Methoxy-2-methylbenzoic Acid Hydrazide (21). A mixture of 4-methoxy-2-methylbenzoic acid (8.33 g, 0.05 mol) and SOCl$_2$ (7.25 mL, 0.1 mol) was refluxed for 2 h. The reaction mixture was concentrated under vacuum; the residue was dissolved in C$_6$H$_6$ and evaporated under reduced pressure to give 9.3 g of the corresponding benzoyl chloride 6, which was then used without further purification.

A solution of the above acid chloride (9.3 g) in 25 mL of CH$_2$Cl$_2$ was added slowly, at 20 °C, to a mixture of *tert*-butyl carbazate (6.6 g, 0.05 mol) and triethylamine (10.56 mL, 0.075 mol) in 45 mL of CH$_2$Cl$_2$. After 2 h of stirring, the reaction was complete [TLC (C$_6$H$_6$/AcOEt, 7:3)], and 37% HCl (44 mL) was added dropwise over 15 min. The mixture was stirred for 30 min and then adjusted to pH 8 with 30% NaOH. The organic phase was separated and the aqueous layer was reextracted with CH$_2$Cl$_2$. The combined extract was washed with H$_2$O, dried (MgSO$_4$), and concentrated to about 100 mL, and then *i*-Pr$_2$O (200 mL) was added. After the solution was cooled overnight, the resulting precipitate was filtered, and the filtrate was washed with *i*-Pr$_2$O and dried to give 7.45 g (82.7%) of 21: mp 133–135 °C; IR (Nujol) 3325, 1650, 1615, 1580, 1535 cm^{-1}; NMR (Me$_2$SO-d_6) δ 2.35 (s, 3 H), 3.80 (s, 3 H), 4.43 (br s, 2 H), 6.7–7.5 (m, 3 H), 9.43 (br s, 1 H).

Method B. 2-Ethylbenzoic Acid Hydrazide (16). To a suspension of 2-ethylbenzoic acid (245 g, 1.62 mol) in 1,2-dichloroethane (500 mL) was added SOCl$_2$ (168 mL, 2.3 mol), and the mixture was stirred at 30 °C for 2 h and refluxed for an additional 2 h. The solvent was removed by evaporation; the residue was dissolved in 100 mL of C$_6$H$_6$ and concentrated under vacuum to yield crude 2-ethylbenzoyl chloride. This intermediate was dissolved in CH$_2$Cl$_2$ (1.3 L) and added dropwise over 2 h, at 0–5 °C, to a mechanically stirred solution of hydrazine hydrate (324 mL, 6.7 mol) in EtOH (1.3 L). The mixture was stirred at room temperature for 3 h; the upper layer was separated, and the

(23) H. de Diesbach and P. Dobbelmann, *Helv. Chim. Acta*, 14, 369 (1931).
(24) M. V. Sargent, P. Vogel, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1986 (1975).
(25) M. S. Gibson and J. M. Walthew, *J. Chem. Soc.*, 4603 (1963).
(26) A. Pinner and F. Klein, *Chem. Ber.*, 10, 1889 (1877).
(27) L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.*, 33, 1679 (1968).
(28) H. Eilingsfeld, *Chem. Ber.*, 98, 1308 (1965).
(29) H. L. Yale and K. Losee, *J. Med. Chem.*, 9, 478 (1966).
(30) D. H. Hey and D. H. Kohn, *J. Chem. Soc.*, 3177 (1949).
(31) J. P. Horwitz and V. A. Grakanskas, *J. Org. Chem.*, 19, 194 (1954).
(32) K. Hutton *J. Org. Chem.*, 20, 855 (1955).
(33) K. T. Potts, *J. Chem. Soc.*, 3461 (1954).
(34) H. Weidinger and J. Kranz, *Chem. Ber.*, 96, 1064 (1963).

71	C$_2$H$_5$	H	2'',3''-(CH$_3$)$_2$	154–155	44	*i*-Pr$_2$O	C	C$_{18}$H$_{19}$N$_3$O$_2$	C, H, N	2 (10)
72	C$_2$H$_5$	H	2'',3''-(CH$_3$O)$_2$	139–141	72	CH$_2$Cl$_2$-*i*-Pr$_2$O	C	C$_{18}$H$_{19}$N$_3$O$_2$	C, H, N	0.05 (10)
73	C$_2$H$_5$	H	3'',4''-(CH$_3$O)$_2$	57–60	58	*i*-Pr$_2$O–hexane	C	C$_{18}$H$_{19}$N$_3$O$_2$	C,[k]	>5
74	C$_2$H$_5$	H	3'',4''-(OCH$_3$O)	108–110	72	*i*-Pr$_2$O–hexane	C	C$_{17}$H$_{15}$N$_3$O$_2$	H, N[l]	0.03 (10)
75	C$_2$H$_5$	H	3'',5''-(CH$_3$O)$_2$	133–135	72	*i*-Pr$_2$O–hexane	C	C$_{18}$H$_{19}$N$_3$O$_2$	C, H, N	3

^{a} See corresponding footnote in Table II. ^{b} Literature[33] mp 189–190 °C. ^{c} Numbers in parentheses indicate highest dose at which the compound was tested and found inactive. ^{d} Literature[34] mp 160–163 °C. ^{e} Literature[33] mp 189 °C. ^{f} C: calcd, 72.43; found, 71.99. ^{g} C: calcd, 72.43; found, 77.94; found, 77.42. ^{h} C: calcd, 73.09; found, 72.63. N: calcd, 73.09; found, 72.63. ^{i} Analyzed as the hydrochloride, mp 130–132 °C. ^{k} H: calcd, 6.19; found, 6.68. ^{l} C: calcd, 12.54. ^{l} C: calcd, 69.61; found, 70.14. calcd, 15.04; found, 14.54.

lower layer was extracted with CH_2Cl_2 (200 mL). The combined extract was washed with three 300-mL portions of saturated sodium chloride solution and dried (Na_2SO_4). Removal of solvent yielded crystalline 16 (241 g, 90.6%): mp 108–111 °C; IR (Nujol) 3400, 1660 (sh), 1615, 1600, 1520, 960 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H), 2.80 (q, 2 H), 4.10 (br s, 2 H), 6.5–7.3 (br, 1 H), 7.30 (s, 4 H).

Method C. One-Pot Procedure. 3-(4-Chloro-2-methylphenyl)-5-phenyl-*s*-triazole (41). A solution of the hydrazide 19 (1.48 g, 8 mmol) and ethyl benzimidate (1.32 g, 8.8 mmol) in CH_3CN (5 mL) was refluxed for 1 h. The solvent was distilled and the residue was kept at 110 °C for 2 h. The solid that formed [intermediate amidrazone, TLC ($CHCl_3$/MeOH, 9:1)] was heated at 200 °C for 10 min. The cooled reaction mixture was taken up in CH_2Cl_2 (50 mL), decolorized with activated charcoal, and crystallized by the addition of *i*-Pr_2O to yield 1.1 g (51.2%) of product: mp 135–136 °C; IR (Nujol) 3150, 1610, 1565, 1395, 871 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (s, 3 H), 6.8–8.2 (m, 8 H), 12.95 (br s, 1 H).

Two-Step Procedure. 5-(2-Ethylphenyl)-3-(3-methoxyphenyl)-*s*-triazole (36). The following procedure was adopted for the preparation of molar amounts of 36. Cyclization of the benzoylamidrazone 10, isolated in the first step under basic conditions, avoids the formation of small amounts of the corresponding 1,3,4-oxadiazole.[28]

In a round-bottom flask equipped with a mechanical stirrer, reflux condenser, and Dean–Stark apparatus, a slurry of 2-ethylbenzoic acid hydrazide (16; 348 g, 2.12 mol) and ethyl 3-methoxybenzimidate (380.5 g, 2.12 mol) in 2.6 L of 1,2-dichloroethane was refluxed for 5 h, while EtOH was azeotropically removed. The mixture was cooled, the product was filtered, and the filtrate was washed with cold 1,2-dichloroethane, and dried in vacuo to yield 555 g (87.2%) of 10 (R = Et; R' = H, R'' = 3-MeO), mp 185–187 °C.

This acylamidrazone (297.4 g, 1 mol) was dissolved in 1.6 L of warm 2-ethoxyethanol, K_2CO_3 (138.2 g, 1 mol) was added, and the mixture was refluxed for 3 h, H_2O being azeotropically distilled off. The slurry was concentrated, then poured into water (1 L), neutralized with 5 N HCl, and extracted with CH_2Cl_2 (3 × 400 mL). The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated, and the residue was crystallized from *i*-Pr_2O/ hexane to give 198 g (70.9%) of 36, mp 72–75 °C. Alternatively, the crude product was purified via mesylate prepared in AcOEt, from which the pure triazole 36 was recovered after neutralization of an aqueous suspension with dilute NaOH.

Method D. 3-[2-(Hydroxymethyl)phenyl]-5-(3-methoxyphenyl)-*s*-triazole (39). To a warm solution of 4-hydrazino-1*H*-2,3-benzoxazine (15.4 g, 95 mmol) in EtOH (220 mL) was added 3-methoxybenzaldehyde (11.48 mL, 95 mmol), and the mixture was allowed to stand at room temperature overnight. The precipitate was filtered and dried to give 11.41 g of 12, mp 143 °C dec. A second crop of product (4.88 g) separated on standing (61.3% total yield). An analytical sample from EtOH had mp 137–139 °C dec; NMR ($CDCl_3$) δ 3.83 (s, 3 H), 5.03 (s, 2 H), 6.7–8.2 (m, 8 H), 8.35 (s, 1 H), 8.1–10.0 (br, 1 H).

A mixture of the above hydrazone 12 (16 g, 57 mmol) and 160 mL of xylene was refluxed for 45 min and cooled in a ice bath. The resulting precipitate was filtered and recrystallized from EtOH to yield 14.7 g (92%) of 39: mp 157–159 °C; NMR (C-D_3COCD_3) δ 3.87 (s, 3 H), 4.75 (s, 2 H), 5.0–6.4 (br, 1 H), 6.9–8.3 (m, 8 H), 12.7–14.5 (br, 1 H).

Method E. 2-[3-(3-Methoxyphenyl)-*s*-triazol-5-yl]benzaldehyde (40). A slurry of 39 (5 g, 18 mmol) and activated MnO_2 (25 g) in dry C_6H_6 (200 mL) was stirred at room temperature for 6 h. Then, four 5-g portions of MnO_2 were added over a period of 4 h until oxidation was complete, as monitored by TLC (C_6H_6/AcOEt, 6:4). The solvent was evaporated, and the residue was taken up in H_2O, adjusted to pH 10 with 10% NaOH, and filtered. The filtrate was made acid to pH 5 with 8% HCl, and the precipitate that formed was filtered off, washed with H_2O, and dried. Recrystallization from *i*-Pr_2O/CH_2Cl_2 yielded 3 g (60%) of 40: mp 164–166 °C; IR (Nujol) 3250 (sh), 3200, 1670, 1650, 1600, 1550, 1240 cm^{-1}; NMR ($CDCl_3$) δ 3.85 (s, 3 H), 6.8–8.4 (m, 8 H), 10.75 (s, 1 H), 8.3–14.7 (br, 1 H).

Biological Methods. Complete experimental details for the pregnancy-terminating activity determination can be found in ref 9a and 16. A synopsis of the methods is given in footnote *a* of Table I.