M). A comparable potency relationship was observed *in vivo*.

In cold-stressed rats,[11] IVa and j and V did not decrease peripheral plasma corticosterone levels at oral doses which exceeded those used to induce a natriuretic response (100 mg/kg).[14] However, in rats, V caused adrenal hypertrophy, decreased male sex accessory organ weights, and decreased the rate of gain in body weight. These effects have not been observed with IVa and j.

Earlier studies[1,2] had established that VI possessed a highly desirable spectrum of activity in natriuretic and adrenal corticosteroid inhibition assays. It caused marked natriuresis in Na^+-depleted rats (a finding consistent with, but not proof of, aldosterone inhibition) at oral doses which did not suppress peripheral plasma corticosterone levels.[1] *In vitro* findings supported the *in vivo* observations.[1,2] Among the natriuretic agents tested in our laboratories, VI had been the most potent of those which appeared to act by selectively inhibiting aldosterone biosynthesis.[14] In the present series of compounds, both IVa and j had the same desirable biological selectivity as VI but were more active. In comparative studies, it was shown that VI was about two to three times as potent as VII. In turn, IVa was about twice as potent as VI, and IVj was about twice as potent as IVa (about four times as potent as VI and about eight to twelve times as potent as VII).[14] The biological activity of IVj will be described in greater detail elsewhere.

(11) W. A. Zuccarello and G. J. Frishmuth, unpublished observations.

Psychosedative Agents. N-(4-Phenyl-1-piperazinylalkyl)-Substituted Cyclic Imides

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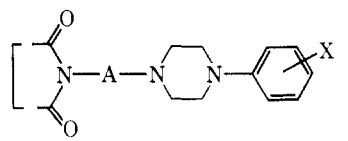
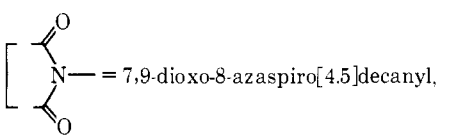
Fifty-two N-substituted cyclic imides bearing a 4-phenyl-1-piperazinylalkyl moiety were synthesized and screened as psychosedative agents. The results of two test methods, (a) antagonism of amphetamine–aggregation stress in mice and (b) suppression of the conditioned avoidance response in rats, indicate that these compounds possess in varying degrees psychotropic properties typical of major tranquilizers.

As part of an effort to develop nonphenothiazine psychosedative agents, we have prepared a series of N-(4-phenyl-1-piperazinylalkyl)-substituted cyclic imides of the following structure. The series is an extension of an earlier lead compound (**25**), which has been shown in preliminary screening to exert a selective depressant effect in mice.

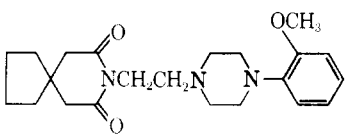




= 7,9-dioxo-8-azaspiro[4.5]decanyl,

2,4-dioxo-3-azaspiro[5.5]undecanyl, or glutarimido radicals

A = alkylene chain
X = various substituents



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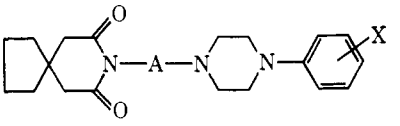
(12) To whom inquiries should be addressed.

Chemical Synthesis.—The compounds were generally synthesized either by condensing 1-(ω-aminoalkyl)-4-phenylpiperazine with the corresponding anhydride in pyridine, or by a nucleophilic substitution of an ω-chloroalkylimide with the appropriate phenylpiperazine (Scheme I). Other synthetic methods leading to special compounds are described in the Experimental Section. The physical constants of 52 N-(4-phenyl-1-piperazinylalkyl)-substituted cyclic imides are listed in Table I.

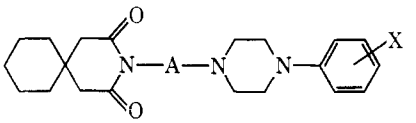
Biological Data.—The difference between "phenothiazine"-type psychosedative agents and other nonspecific sedative–hypnotic drugs on the behavior of test animals has been discussed by Domino.[2] Of special interest to us are the effects of the test compound on the conditioned avoidance response and on amphetamine toxicity. The effect of a compound on the conditioned avoidance response differentiates the compound as a tranquilizing drug from a nonspecific sedative–hypnotic drug. Its effect on amphetamine toxicity is to detect its possible value in treating stressful conditions in man. For the evaluation of the conditioned response the method generally used is that of Cook and Weidley.[3] A modified test[4] was developed in these laboratories which utilizes the environment of the test chamber itself as the conditioned stimulus. The ED_{50}'s for

(2) E. F. Domino in "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 341.
(3) L. Cook and E. Weidley, *Ann. N. Y. Acad. Sci.*, **66**, 740 (1957).
(4) J. R. Albert, *Pharmacologist*, **4**, 152 (1962).

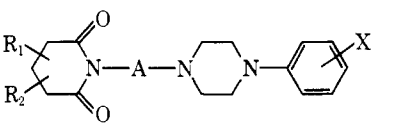
TABLE I



No.	R_1	R_2	X	A	Bp (mm) or mp, °C of free base	HCl mp, °C	Yield, %[c]	Method of prepn	Formula	Analyses
				A. 8-Azaspiro[4.5]decane-7,9-diones						
1			H		(167–168)		30	A	$C_{19}H_{25}N_3O_2$	C, H, N
2			H	CH_2	(135–137)		30	C	$C_{20}H_{27}N_3O_2$	C, H, N
3			H	$(CH_2)_2$	215–235 (0.45)	241.5–242.5	44	A	$C_{21}H_{29}N_3O_2 \cdot HCl$	C, H, N
4			H	$(CH_2)_3$	250–252 (0.5)	234.5–236.5	36	A	$C_{22}H_{31}N_3O_2 \cdot HCl$	C, H, N, Cl
5			H	$(CH_2)_4$	260–275 (0.1)	218.5–220.5	61	A	$C_{23}H_{33}N_3O_2 \cdot 2HCl$	C, H, N, Cl
6			H	$(CH_2)_5$	253–263 (0.2)	188.5–196.5	23	A	$C_{24}H_{35}N_3O_2 \cdot 2HCl$	C, H, N
7			H	$CH_2C{\equiv}CCH_2$	*a*	173–174	20	C	$C_{23}H_{29}N_3O_2 \cdot 2HCl$	C, H, N
8			H	$CH_2CH_2OCH_2CH_2$	190–260 (0.3)	155–157	20	B	$C_{23}H_{33}N_3O_3 \cdot HCl$	C, H, N, Cl
9			H	$CH_2CH_2CH(CH_3)CH_2$	235–250 (0.25)	207.5–212	50	A	$C_{24}H_{35}N_3O_2 \cdot 2HCl$	C, H, N, Cl
10			H	$CH(CH_3)CH_2$	230–240 (0.25)	255.5–257.5	52	A	$C_{22}H_{31}N_3O_2 \cdot 2HCl$	C, H, N, Cl
11			*o*-CH_3	$(CH_2)_2$	210 (0.3)	210.5–212.5	20	A	$C_{22}H_{31}N_3O_2 \cdot HCl$	C, H, N
12			*o*-CH_3	$(CH_2)_3$	230–250 (0.3)	254.5–255.5	18	A	$C_{23}H_{33}N_3O_2 \cdot HCl$	C, H, N
13			*o*-CH_3	$(CH_2)_4$	255 (0.01)	246–247.5	57	A	$C_{24}H_{35}N_3O_2 \cdot HCl$	C, H, N, Cl
14			*m*-CH_3	$(CH_2)_2$	225–235 (0.3)	205.5–207	15	A	$C_{22}H_{31}N_3O_2 \cdot HCl$	C, H, N, Cl
15			*m*-CH_3	$(CH_2)_3$	160–185 (0.1)	240.5–242.5	30	B	$C_{23}H_{33}N_3O_2 \cdot HCl$	C, H, N, Cl
16			*p*-CH_3	$(CH_2)_2$	165–200 (0.1)	236.5–238.5	36	A	$C_{22}H_{31}N_3O_2 \cdot 2HCl$	C, H, N
17			*p*-CH_3	$(CH_2)_3$	160–180 (0.1)	247–248	20	A	$C_{23}H_{33}N_3O_2 \cdot 2HCl$	C, H, N
18			*o*-Cl	$(CH_2)_2$	165–184 (0.1)	241–242.5	43	A	$C_{21}H_{28}ClN_3O_2 \cdot HCl$	C, H, N, Cl
19			*o*-Cl	$(CH_2)_3$	215–245 (0.1)	234.5–235.5	66	A	$C_{22}H_{30}ClN_3O_2 \cdot HCl$	C, H, N, Cl
20			*o*-Cl	$(CH_2)_4$	240–260 (0.2)	236–238	74	A	$C_{23}H_{32}ClN_3O_2 \cdot HCl$	C, H, N, Cl
21			*m*-Cl	$(CH_2)_2$	140–210 (0.1)	226.5–228.5	45	A	$C_{21}H_{28}ClN_3O_2 \cdot HCl$	C, H, N, Cl
22			*m*-Cl	$(CH_2)_3$	164–170 (0.1)	248–250.5	21	A	$C_{22}H_{30}ClN_3O_2 \cdot HCl$	C, H, N
23			*p*-Cl	$(CH_2)_2$	*a*	246.5–247.5	10	A	$C_{21}H_{28}ClN_3O_2 \cdot HCl$	C, H, N, Cl
24			*p*-Cl	$(CH_2)_3$	175–197 (0.1)	248–249	52	A	$C_{22}H_{30}ClN_3O_2 \cdot HCl$	C, H, N, Cl
25			*o*-OCH_3	$(CH_2)_2$	220–240 (0.35)	196.5–198.5	77	A, B	$C_{22}H_{31}N_3O_3 \cdot 2HCl$	C, H, N, Cl
26			*o*-OCH_3	$(CH_2)_3$	220–250 (0.1)	208.5–210.5	40	A	$C_{23}H_{33}N_3O_3 \cdot 2HCl$	C, H, N
27			*o*-OCH_3	$(CH_2)_4$	243–247 (0.2)	199.5–203	55	A	$C_{24}H_{35}N_3O_3 \cdot 2HCl$	C, H, N, Cl
28			*o*-OCH_3	$(CH_2)_5$	*a*	174.5–176.5	35	A	$C_{25}H_{37}N_3O_3 \cdot HCl$	C, H, N, Cl
29			*o*-OCH_3	$CH_2C{\equiv}CCH_2$	*a*	172–175	53	C	$C_{24}H_{31}N_3O_3 \cdot 2HCl$	C, H, N, Cl
30			*o*-OCH_3	$CH_2CH_2OCH_2CH_2$	240–260 (0.2)	206.5–208.5	50	B	$C_{24}H_{35}N_3O_4 \cdot 2HCl$	C, H, N, Cl
31			*m*-OCH_3	$(CH_2)_2$	185–210 (0.1)	211.5–213.5	45	A	$C_{22}H_{31}N_3O_3 \cdot HCl$	C, H, N
32			*m*-OCH_3	$(CH_2)_3$	220–260 (0.1)	235.5–237	42	A	$C_{23}H_{33}N_3O_3 \cdot HCl$	C, H, N, Cl
33			*p*-OCH_3	$(CH_2)_4$	240–266 (0.2–0.7)	205–207	32	A	$C_{22}H_{31}N_3O_3 \cdot HCl$	C, H, N, Cl
34			*p*-OCH_3	$(CH_2)_3$	220–245 (0.1)	225.5–226.5	17	B	$C_{23}H_{33}N_3O_3 \cdot HCl$	C, H, N, Cl
35			*o*-F	$(CH_2)_4$	*a*	193–194	40	B	$C_{23}H_{32}FN_3O_2 \cdot HCl$	C, H, N, Cl
36			*o*-CH_3SO_2NH	$(CH_2)_4$	*b*	263.5–264.5	48	B	$C_{24}H_{36}N_4O_4S \cdot HCl$	C, H, N, Cl, S
37			*o*-NO_2	$(CH_2)_4$	150–180 (0.1)	224–226	35	B	$C_{23}H_{32}N_4O_4 \cdot HCl$	C, H, N, Cl
				B. 3-Azaspiro[5.5]undecane-2,4-diones						



38			H	$(CH_2)_3$	263–276 (0.2)	254–255	46	A	$C_{23}H_{33}N_3O_2 \cdot HCl$	C, H, N, Cl
39			*o*-OCH_3	$(CH_2)_2$	230–260 (0.2)	211–212.5	35	A	$C_{23}H_{33}N_3O_3 \cdot HCl$	C, H, N, Cl
40			*o*-OCH_3	$(CH_2)_4$	230–270 (0.1)	202–203.5	37	A	$C_{25}H_{37}N_3O_3 \cdot HCl$	C, H, N, Cl
				C. Glutarimides						



41	H	H	H	$(CH_2)_2$		212–214.5	24	A	$C_{17}H_{23}N_3O_2 \cdot HCl$	C, H, N, Cl
42	H	H	H	$(CH_2)_3$	190–197 (0.07)	206.5–208	17	A	$C_{18}H_{25}N_3O_2 \cdot HCl$	C, H, N, Cl
43	3-CH_3	3-CH_3	H	$(CH_2)_3$	220–240 (0.2)	238.5–240.5	36	A	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	C, H, N, Cl
44	3-C_2H_5	3-C_2H_5	H	$(CH_2)_3$	236–250 (0.1)	233.5–235	43	A	$C_{22}H_{33}N_3O_2 \cdot HCl$	C, H, N, Cl
45	3-C_2H_5	3-CH_3	H	$(CH_2)_3$	226–246 (0.1)	231.5–232.5	27	A	$C_{21}H_{31}N_3O_2 \cdot HCl$	C, H, N, Cl
46	2-CH_3	2-CH_3	H	$(CH_2)_3$	200–230 (0.15)	223.5–229.5	25	B	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	C, H, N, Cl
47	2-CH_3	4-CH_3	H	$(CH_2)_3$	230–253 (0.2)	220.5–225	44	B	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	C, H, N, Cl
48	3-C_2H_5	3-C_2H_5	*o*-OCH_3	$(CH_2)_2$	230–260 (0.2)	230.5–232.5	40	A	$C_{22}H_{33}N_3O_3 \cdot HCl$	C, H, N, Cl
49	3-CH_3	3-CH_3	*o*-OCH_3	$(CH_2)_2$	216–230 (0.15)	201.5–204.5	36	A	$C_{20}H_{29}N_3O_3 \cdot 2HCl \cdot H_2O$	C, H, N, Cl
50	3-C_2H_5	3-CH_3	*o*-OCH_3	$(CH_2)_2$	230–255 (0.1)	190.5–196.5	18	A	$C_{21}H_{31}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, Cl
51	2-CH_3	4-CH_3	*o*-OCH_3	$(CH_2)_2$	210–235 (0.15)	114.5–116.5[d]	37	A	$C_{20}H_{29}N_3O_3$	C, H, N
52	2-CH_3	2-CH_3	*o*-OCH_3	$(CH_2)_2$	225–235 (0.15)	94–95.5[d]	34	A	$C_{20}H_{29}N_3O_3$	C, H, N

[a] Converted to HCl salt without distillation. [b] Purified by chromatography from PhH on 8 × 5 cm silica column; elution with PhH containing 5% EtOH. [c] Based on analytically pure sample. Many of these experiments were conducted only once and the optimal conditions were not established. [d] Melting point of free base.

suppression of the unconditioned escape response (UER) and the conditioned avoidance response (CAR) are determined. The ratio of these two ED_{50}'s is a measure of the drug's specificity as a psychosedative. The method of antagonism of amphetamine–aggregation stress developed by Burn and Hobbs[5] determines the ED_{50} of a drug that will antagonize the increased toxicity of amphetamine in mice produced by stress of

(5) J. H. Burn and R. Hobbs, *Arch. Int. Pharmacodyn. Ther.*, **113**, 290 (1958).

TABLE II
PSYCHOSEDATIVE ACTIVITY OF 1-PHENYL-4-PIPERAZINYL DERIVATIVES

Compounds	Antagonism of amphetamine-aggregation stress in mice ED_{50}, mg/kg sc	Suppression of CAR in rats ED_{50}, mg/kg ip		
		CER	CAR	CER/CAR
Chlorpromazine HCl	0.26	18.8	1.8	10.2
1	>40		Inactive	
2	14.7	13.9	12.2	1.1
3	31.8	>103	25.6	>4
4	2.4	79.0	38.6	1.9
5	3.3	>50	8.6	>5.9
6	9.1	29.1	20.6	1.1
7	>40	>50	>50	
8	>40	43.3	39.3	1.1
9	5.9	22.5	27.5	0.8
10	>40	>50	>50	
11	>20	>50	>50	
12	5.8	65.5	47.6	1.4
13	1.5	28.3	16.2	1.7
14	>20	>157	39.3	>4
15	10.6	>50	>50	
16	>80	>100	>100	
17	22.3	89.5	68.7	1.3
18	51.8	>100	95.4	>1
19	5.1	>140	35	>4
20	1.2	24.8	11.0	2.3
21	>40	>100	>100	
22	>20	>60	50	>1.2
23		>50	>50	
24	>40	184.4	75.1	2.5
25	9.5	>100	24.6	>4
26	5.1	38.2	12.5	3.1
27	0.39	2.8	2.4	1.2
28	0.92	17.7	16.7	1.1
29	20.0	>50	>50	
30	6.0	26.7	17.6	1.5
31	>40	>50	>50	
32	30.5	>50	41.1	>1.2
33	>40	>50	50	>1
34	40	42.3	26.6	1.6
35	0.87	17.5	8.5	2.1
36	31	>41.5	41.5	>1
37	9.5	35.9	12.4	2.9
38	4.5	>50	>50	
39	11.5	>117	38.7	>3
40	0.38	8.6	5.4	1.6
41	10.8	41.2	27.0	1.5
42	>40		>50	
43	29	82.1	43.9	1.9
44	33.5	79.7	45.3	1.8
45	30.5	>50	48.3	>1
46	>40	>50	>50	
47	36	>50	>50	
48	26	>50	45.7	>1
49	22	<127	42.7	<3
50	>40	>50	37.4	>1.3
51	>40	>50	>50	
52	28.5	>50	>50	

aggregation. These two testing methods provide us with the principal means of selecting compounds for further laboratory evaluation. The test results are listed in Table II.

The acute toxicities of several of the more important compounds of the series were determined (Table III). The compounds were administered intraperitoneally to Swiss-Webster strain mice. Determination of the LD_{50} was based on deaths occuring in the first 24 hr.

Structure–Activity Relationships.—The presence of 4-phenyl-1-piperazinylalkyl group in the total structure is essential for the biological effect as shown by closely related compounds[6] in the results of two testing methods (Table IV).

The glutarimides are less active than the corresponding 8-azaspiro[4.5]decane-7,9-diones (compare **43** with **4**, **49** with **25**), although the presence of 3,3-dimethyl groups in glutarimides is a desirable feature for activity (**43**, **49**).

(6) L. M. Rice, C. F. Goschickter, and C. H. Grogen, *J. Med. Chem.*, **6**, 388 (1963); **7**, 78 (1964).

SCHEME I

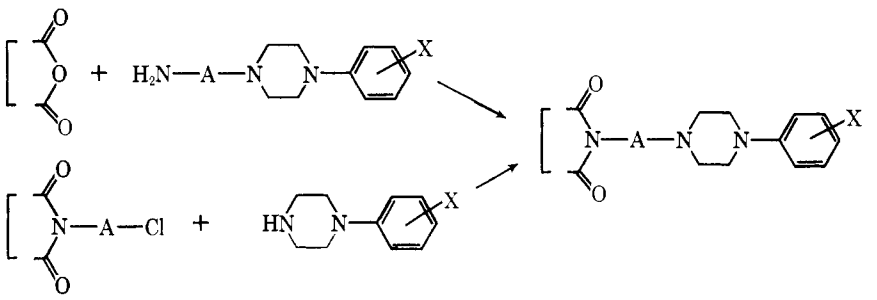
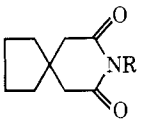
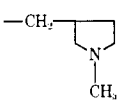
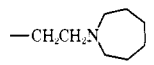
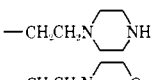
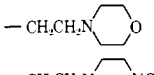
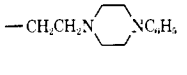


TABLE III

Compd	LD_{50} (95% confid limits), mg/kg ip
5	141.4
20	61.6
25	53.6
26	123.1
35	89.1
37	141.4
Chlorpromazine HCl	151 ± 24.2 (SE)

TABLE IV
BIOLOGICAL TESTING RESULTS ON SOME 8-SUBSTITUTED 8-AZASPIRO[4.5]DECANE-7,9-DIONES



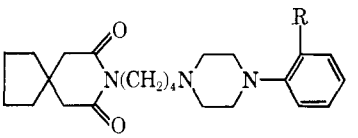
R	Antagonism of amphetamine–aggregation in mice ED_{50}, mg/kg sc	Suppression of CAR in rats ED_{50}, mg/kg ip UER	CAR	UER/CAR
	Inactive		Inactive	
	Inactive		Inactive	
	Inactive		Inactive	
	Inactive		Inactive	
	31.8	>103	25.6	>4

The biological activities change considerably with the length and types of the alkylene chain. Maximum potencies are observed with compounds with a four-carbon chain (**5**, **13**, **20**, **27**, **35–37**, **40**). Branching (compare **9** with **5**, **10** with **3**) and insertion of a hetero atom (compare 8 with **5**, **30** with **27**) or a triple bond (compare **7** with **5**, **29** with **27**) reduce the activity.

meta and *para* substitutions on the phenyl ring either abolish or reduce activities. However, the *ortho* substitution does enhance or retain the potency (**11–13**, **18–20**, **25–30**, **35–37**, **39**, **40**, **48–52**). In an *ortho* subseries, the ED_{50}'s for antagonism of amphetamine–aggregation stress in mice change inversely with Taft's E_s values[7] (Table V).

Based on the screening results reported in this paper and additional biological testing, such as gross behavior in monkeys, reduction of fighting behavior in mice, and antiemetic effect for antagonizing apomorphine-induced emesis in dogs, we have selected compounds **5**, **20**, **25**, **26**, **35**, and **37** for more extensive evaluation as potential psychosedative drugs. An advantage of this type of agent might be a departure from the phenothiazine structure and its serious undesirable symptomatic disturbances.[8]

TABLE V



Compd	R	Taft's E_s values	ED_{50}, mg/kg
27	CH_3O	0.99	0.39
35	F	0.49	0.87
20	Cl	0.18	1.2
13	CH_3	0.00	1.5
37	NO_2	−0.75	9.5
36	CH_3SO_2NH		31

Experimental Section

Conditioned Avoidance Response.—Rats were trained to climb over a barrier in a shuttle box within 30 sec of being placed in the box (CAR). Presentation of the animal to the test chamber comprises the conditioned stimulus (CS). After 30 sec, an electric shock is delivered for another 30 sec to the half of the box first occupied by the rat. This shock is the unconditioned stimulus (UCS). Upon receiving the shock, an untrained rat will escape to the other, or safe, side of the box. This is the unconditioned escape response (UER). Blockade of the CAR without effect on the UER is considered laboratory evidence of tranquilizing action.

Test compounds were administered intraperitoneally, and observations were begun 30 min later and continued throughout the next 30 min. An initial probe was made with four animals on a single dose. If the compound appeared only weakly active, four more animals were tested at that same dose, and, if still judged poorly active, the compound was discarded. If the compound appeared active, further doses were explored with four animals per dose level. The UER ED_{50} and CAR ED_{50} were then determined.

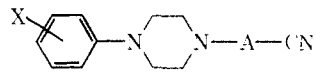
Amphetamine–Aggregation Stress.—Groups of 20 or more male mice, 18–20 g, were administered various dose levels of the test compound subcutaneously. The mice were then segregated in individual cages for 60 min, after which they were injected subcutaneously with 20 mg of *dl*-amphetamine sulfate/kg ($LD_{99.9}$) and aggregated into two cages (ten mice/cage). Twenty four hours later, deaths were recorded. The per cent protected from death at each dose was plotted on log-probit paper and the dose (ED_{50}) required for 50% protection and the 95% confidence limits were determined by the method of Litchfield and Wilcoxon.

1-Phenylpiperazines were either obtained from commercial sources or synthesized by known methods as shown in the following example for 1-*o*-methanesulfonamidophenylpiperazine.

(7) J. E. Leffler and E. Grunwald, "Rates and Equilibrium of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 228.

(8) E. F. Domino, ref 2, p 346.

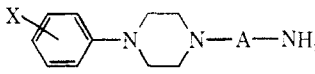
TABLE VI



X	A	% yield	Mp, °C	Formula	Analyses
m-CH_3	CH_2	87	65–67	$C_{13}H_{17}N_3$	C, H, N
o-OCH_3	$(CH_2)_4$	80	167–180 (0.1)[a]	$C_{16}H_{23}N_3O$	C, H, N
o-OCH_3	$(CH_2)_6$	80	86–87	$C_{18}H_{27}N_3O$	C, H, N
m-OCH_3	$(CH_2)_2$	83	103–105	$C_{14}H_{19}N_3O$	C, H, N
p-OCH_3	CH_2	80	118–119.5	$C_{13}H_{17}N_3O$	C, H, N
m-Cl	CH_2	91	120–122	$C_{12}H_{14}ClN_3$	C, H
H	$CH_2CH(CH_3)CH_2$	65	81–83	$C_{15}H_{21}N_3$	C, H, N

[a] Boiling point, °C (mm).

TABLE VII



X	A	% yield	Bp, °C (mm)	$n^{25}D$	Formula	Analyses
o-CH_3	$(CH_2)_3$	69	90–120 (0.03)	1.5511	$C_{14}H_{23}N_3$	C, H
m-CH_3	$(CH_2)_2$	86	117–134 (0.3)	1.5638	$C_{13}H_{21}N_3$	C, H
m-CH_3	$(CH_2)_3$	48	120 (0.18)	1.5656	$C_{14}H_{23}N_3$	C, H
m-Cl	$(CH_2)_2$	62	108–140 (0.15)	1.5827	$C_{12}H_{18}ClN_3$	C, H
o-OCH_3	$(CH_2)_3$	85	140–155 (0.15)	1.5621	$C_{14}H_{23}N_3O$	C, H
o-OCH_3	$(CH_2)_4$	80	150–160 (0.25)	1.5496	$C_{15}H_{25}N_3O$	C, H
o-OCH_3	$(CH_2)_5$	58	163–172 (0.2)	1.5444	$C_{16}H_{27}N_3O$	C, H
m-OCH_3	$(CH_2)_3$	69	155–165 (0.15)	1.5561	$C_{14}H_{23}N_3O$	C, H
p-OCH_3	$(CH_2)_2$	87	145–147 (0.1) (mp 64–66)		$C_{13}H_{21}N_3O$	C, H
H	$CH_2CH(CH_3)(CH_2)_2$	82	138–155 (0.17)	1.5485	$C_{15}H_{25}N_3$	C, H

Ethyl 4-*o*-Methanesulfonamidophenylpiperazine-1-carboxylate.—A solution of ethyl 4-*o*-aminophenylpiperazine-1-carboxylate[9] (8.3 g, 0.033 mole) in 50 ml of pyridine was treated dropwise over 30 min with an equimolar amount (3.8 g) of $MeSO_2Cl$. The mixture was heated at 100° for 1 hr and concentrated. The solid residue was recrystallized from absolute EtOH; mp 114–116°, yield 8.6 g (79%). *Anal.* ($C_{14}H_{21}N_3O_4S$) C, H, N.

1-*o*-Methanesulfonylphenylpiperazine.—A solution of 4-*o*-methanesulfonamidophenylpiperazine-1-carboxylate (3.3 g, 0.01 mole) in ethanolic KOH (12 g of KOH in 100 ml of EtOH) was refluxed for 4 hr. The reaction mixture was neutralized with concentrated HCl and filtered. The filtrate was concentrated to an oily residue (crude yield, theoretical). The compound decomposed on distillation. The HCl salt was prepared in 57%, mp 251–252°. *Anal.* ($C_{11}H_{17}N_3O_2S \cdot HCl$) C, H, N.

1-(ω-Cyanoalkyl)-4-phenylpiperazines were obtained by condensing equimolar amounts of ω-chloroalkylnitriles and appropriate 1-phenylpiperazines with excess anhydrous Na_2CO_3 in C_6H_6.[10–13] The physical constants of new compounds are tabulated in Table VI.

1-(ω-Aminoalkyl)-4-phenylpiperazines were prepared from the corresponding ω-cyanoalkyl derivatives either by a LAH reduction or a catalytic hydrogenation at room temperature under 84 kg/cm² pressure of H_2 with W-6 Raney Ni as the catalyst.[11,12] The physical properties of new compounds are tabulated in Table VII.

1-Nitroso-4-phenylpiperazine.—A solution of 1-phenylpiperazine (32.4 g, 0.2 mole) in 250 ml of H_2O was treated with concentrated HCl to congo red at 0°, followed by 50 ml of 2 *N* aqueous $NaNO_2$. After being stirred for 3 hr at 0°, the mixture was filtered to yield 29.8 g (78%) of light yellow solid, mp 69–70° (MeOH). *Anal.* ($C_{10}H_{13}N_3O$) C, H, N.

1-Amino-4-phenylpiperazine.—1-Nitroso-4-phenylpiperazine (28.8 g, 0.15 mole) was reduced with LAH (8.5 g, 0.23 mole) in THF. The reaction complex was decomposed carefully with H_2O (12.4 ml, 0.69 mole). The organic solution was concentrated and distilled giving 20.3 g of crude product, bp 88–110° (0.1 mm). The distillate was crystallized from 60 ml of cyclohexane to furnish 16.8 g (63%) of pure material, mp 59–61°. *Anal.* ($C_{10}H_{15}N_3$) C, H, N.

3-(4-Phenyl-1-piperazinyl)-2-butanone.—Anhydrous Na_2CO_3 (13.2 g, 0.13 mole), 1-phenylpiperazine (16.2 g, 0.1 mole), and 3-bromo-2-butanone (15.1 g, 0.1 mole) were refluxed in 100 ml of *n*-BuOH for 15 hr. The mixture was filtered. The filtrate was concentrated and distilled under reduced pressure giving 18.7 g (80.6%) of a yellow liquid, bp 135–150° (0.17 mm), $n^{25}D$ 1.5506. *Anal.* ($C_{14}H_{20}N_2O$) C, H, N.

1-(4-Phenyl-1-piperazinyl)propanone was prepared similarly in 80.6% yield, bp 143–150° (0.32 mm), $n^{25}D$ 1.5576. *Anal.* ($C_{13}H_{18}N_2O$) N.

3-(4-Phenyl-1-piperazinyl)-2-butanone oxime was prepared in 46% yield, mp 124–126°. *Anal.* ($C_{14}H_{21}N_3O$) C, H.

1-(4-Phenyl-1-piperazinyl)propanone oxime was prepared in 94% yield, mp 163–166°. *Anal.* Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21. Found: C, 66.16; H, 7.92.

1-(2-Amino-3-butyl-4-phenylpiperazine.—LAH reduction of 3-(4-phenyl-1-piperazinyl)-2-butanone oxime in THF afforded this compound in 65% yield, bp 140–153° (0.22 mm), $n^{25}D$ 1.5616. *Anal.* ($C_{14}H_{23}N_3$) C, H.

1-(2-Aminopropyl)-4-phenylpiperazine was also prepared by a LAH reduction of the corresponding oxime in 76.8% yield, bp 136–148° (0.15 mm), mp 67–68°. *Anal.* Calcd for $C_{13}H_{21}N_3$: C, 71.19; H, 9.65. Found: C, 70.47; H, 8.99.

8-(2-Hydroxyethyl)-8-azaspiro[4.5]decane-7,9-dione.—A mixture of 3,3-tetramethyleneglutaric anhydride (16.8 g, 0.1 mole), 2-aminoethanol (12.2 g, 0.2 mole), and 200 ml of dry pyridine was refluxed for 3 hr. The mixture was concentrated and distilled giving 16.9 g (80%) of the product, bp 125–140° (0.23 mm), $n^{25}D$ 1.5138. *Anal.* ($C_{11}H_{17}NO_3$) C, H, O.

8-(3-Hydroxypropyl)-8-azaspiro[4.5]decane-7,9-dione was prepared similarly in 62% yield, bp 155–170° (0.1–0.15 mm), $n^{25}D$ 1.5010. *Anal.* ($C_{12}H_{19}NO_3$) C, H, N.

8-[2-(2-Hydroxyethoxy)ethyl]-8-azaspiro[4.5]decane-7,9-dione was prepared similarly in 81% yield, bp 191–204° (0.08–0.18 mm), $n^{25}D$ 1.5008. *Anal.* ($C_{13}H_{21}NO_4$) C, H.

8-(2-Chloroethyl)-8-azaspiro[4.5]decane-7,9-dione.—A mixture of 8-(2-hydroxyethyl)-8-azaspiro[4.5]decane-7,9-dione (6.0 g, 0.028 mole), dry pyridine (2.4 g, 0.03 mole), and 100 ml of dry C_6H_6 was cooled to 10° and treated dropwise with 3.6 g (0.03 mole) of $SOCl_2$. The reaction mixture, after being heated at

(9) V. Prelog and Z. Blazek, *Collection Czech. Chem. Commun.*, **6**, 211 (1934).

(10) C. B. Pollard and L. J. Hughes, *J. Am. Chem. Soc.*, **77**, 40 (1955).

(11) S. Hayao and R. N. Sheet, *J. Org. Chem.*, **26**, 3415 (1961).

(12) R. H. Mull, R. B. Mizzoni, M. R. Dapero, and M. R. Egbert, *J. Med. Chem.*, **5**, 944 (1962).

(13) C. B. Pollard, E. G. Ritz, and R. Robbins, *J. Am. Chem. Soc.*, **75**, 2989 (1953).

60–65° for 1 hr, was filtered to remove pyridine hydrochloride. The filtrate was washed with 20 ml of H_2O, dried ($MgSO_4$), concentrated, and distilled giving 4.5 g (69%) of the product, bp 120–122° (0.05 mm), $n^{25}D$ 1.5143. *Anal.* ($C_{11}H_{16}ClNO_2$) C, H, Cl.

8-(3-Chloropropyl)-8-azaspiro[4.5]decane-7,9-dione was prepared similarly in 73% yield, bp 155–162° (0.06 mm), $n^{25}D$ 1.5114. *Anal.* ($C_{12}H_{18}ClNO_2$) C, H, N.

8-[2-(2-Chloroethoxy)ethyl]-8-azaspiro[4.5]decane-7,9-dione was obtained similarly in 50% yield, bp 155–165° (0.25 mm), $n^{25}D$ 1.5069. *Anal.* ($C_{13}H_{20}ClNO_3$) C, H.

8-(2-Propargyl)-8-azaspiro[4.5]decane-7,9-dione.—A solution of 3,3-tetramethyleneglutaric anhydride (15.2 g, 0.09 mole) and propargylamine (5.0 g, 0.09 mole) in 200 ml of pyridine was refluxed for 15 hr. The reaction mixture was concentrated and distilled giving 14.1 g (76%) of product, bp 129–145° (0.15 mm). *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

N-[ω-(4-Phenyl-1-piperazinyl)alkyl]Cyclic Imides. Method A.—An equimolar mixture of cyclic acid anhydride and 1-(ω-aminoalkyl)-4-phenylpiperazine in dry pyridine (0.1 mole/400 ml) was refluxed for 15 hr. The mixture was concentrated; if the ir spectrum showed typical imide bands (1700 and 1710 cm^{-1}), the residue was purified by either distillation or crystallization. If the spectrum showed amide acid bands (1680, 1760, 330 cm^{-1}) instead, the residue was refluxed with ten times its weight of Ac_2O for 15 hr. The residue obtained by removal of Ac_2O was purified either by distillation or recrystallization.

Method B.—A mixture of 8-(ω-chloroalkyl)-8-azaspiro[4.5]-decane-7,9-dione (0.1 mole), 1-phenylpiperazine (0.1 mole), anhydrous Na_2CO_3 (0.3 mole), and dry C_6H_6 was refluxed for 15 hr. The reaction mixture was filtered. The filtrate was concentrated and distilled to give the product.

Method C. 8-(4-Phenyl-1-piperazinyl)-8-azaspiro[4.5]decane-7,9-dione.—A mixture of 3,3-tetramethyleneglutarimide (3.3 g, 0.02 mole), 37% formalin (1.8 ml, 0.022 mole), 1-phenylpiperazine (3.2 g, 0.02 mole), and 20 ml of EtOH was heated at 100° for 30 min. Dilution of the reaction mixture with 30 ml of H_2O separated 2.0 g of the white crystalline product, mp 135–137°.

8-[4-(4-Phenyl-1-piperazinyl)-2-butynyl]-8-azaspiro[4.5]decane-7,9-dione Dihydrochloride.—A mixture of 8-(2-propargyl)-8-azaspiro[4.5]decane-7,9-dione (6.0 g, 0.03 mole), 37% formalin (2.4 g, 0.03 mole), Cu_2Cl_2 (73 mg), AcOH (1.8 g, 0.03 mole), H_2O (2.9 ml), and 1-phenylpiperazine (4.8 g, 0.03 mole) was heated at 40° under N_2 for 7 hr. The mixture was extracted with three 75-ml portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was treated with a calculated amount of EtOH–HCl giving the product in 20% yield as dihydrochloride salt, mp 173–174°.

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Mammalian Antifertility Agents. VI. A Novel Sequence for the Preparation of 1,2-Disubstituted 3,4-Dihydronaphthalenes[1]

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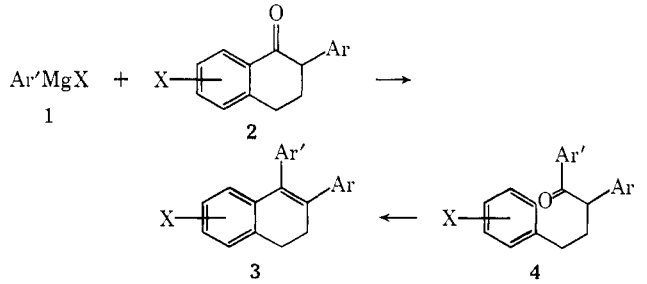
Condensation of the formyl derivatives of substituted acetophenones with the ylide from *m*-methoxybenzyltriphenylphosphonium chloride afforded an intermediate which was elaborated to 1,2-disubstituted dihydronaphthalenes. A series of basic and glyceryl ethers of the *cis*-tetrahydronaphthalenes was prepared. The same intermediate was converted by a different route to the *trans*-tetrahydronaphthalene. Several of the compounds are potent estrogen antagonists.

The 1,2-diaryl-3,4-dihydronaphthalenes constitute a group of compounds with potent antigonadotrophic and uterotrophic activities.[1-3] The nucleus of this system has usually been prepared by condensation of the appropriate 2-aryl-1-tetralone with the Grignard reagent of the aryl group which is to appear at the 1 position. Yields in this reaction have tended to be poor due to extensive enolization of the ketone by the Grignard reagent; large amounts of unreacted ketone are characteristically recovered. Preparation of the nucleus by cyclization of a ketone such as **4** would circumvent the Grignard reaction.



The recently reported condensation of phosphoranes with hydroxymethylene derivatives of ketones at the potential aldehyde[4] promised ready access to the desired intermediates (**11–13**) (Scheme I). The substituted acetophenones were formylated with ethyl formate and NaOEt in EtOH.[5] Reaction of **8** with the preformed ylide from *m*-methoxybenzyltriphenylphosphonium chloride led to a complex mixture. We then found, however, that simply refluxing the sodium enolate of **8** with the phosphonium salt in THF led cleanly to condensation products whose ir absorption (1700, 1660 cm^{-1}) and nmr spectra (integral ratio Ar*H*:O*CH*$_3$, 8:3) suggested a mixture of the α,β and β,γ unsaturated ketones. Catalytic hydrogenation of the total mixture gave the oily **11**. Treatment of this with *p*-toluenesulfonic acid in refluxing C_6H_6 gave the dihydronaphthalene **14** identical in all respects with an authentic sample.[6]

Desoxyanisoin (**6**) and *p*-methoxy-α-cyclopentylacetophenone (**7**) gave the corresponding substituted bu-

(1) Previous paper in this series: D. Lednicer, D. E. Emmert, G. W. Duncan, and S. C. Lyster, *J. Med. Chem.*, **10**, 1051 (1967).

(2) W. L. Bencze, L. I. Barsky, R. W. J. Carney, A. A. Renzi, and G. deStevens, *ibid.*, **10**, 138 (1967).

(3) For a recent review see I. Scheer, *Ann. Rept. Med. Chem.*, **3**, 200 (1967).

(4) P. F. Beal III, J. C. Babcock, and F. H. Lincoln, *J. Am. Chem. Soc.*, **88**, 3131 (1966).

(5) W. Wislicenus and A. Ruthing, *Ann.*, **379**, 229 (1911); attempts to carry out this reaction under the more usual conditions (Et_2O and EtOH-free NaOEt) gave only traces of product.

(6) D. Lednicer, S. C. Lyster, B. D. Aspergren, and G. W. Duncan, *J. Med. Chem.*, **9**, 172 (1966).