Spiranes. IV. Alkyl, Cycloalkyl, Alkenyl, Aryl, Aralkyl, and Hydrazono Azaspirane Derivatives[1a]

CHARLES H. GROGAN,[1b] CHARLES F. GESCHICKTER, AND LEONARD M. RICE

Georgetown University Medical Center, Washington, D. C.

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Our previous investigation of dialkylaminoalkyl and heterocyclic-alkyl azaspirodiones and azaspiranes has been extended to include alkyl, alkenyl, alkoxyalkyl, cycloalkyl, aryl, aralkyl, and hydrazono N-substituents. Biological screening and pharmacological studies of these compounds have revealed a wide range of useful activity. Most notable were the effects produced on the peripheral and central nervous system. A number of compounds of these types exhibited, in varying degree, central nervous stimulant and depressant, local anesthetic, sedative, "tranquilizing," and hypnotic properties. Several of the azaspirodiones produced marked hypotension in the dog.

In our previous paper[2] we described the synthesis and chemical and pharmacological properties of a large number of dialkylaminoalkyl and heterocyclic-alkyl azaspiranes and azaspirodiones. This report also included the synthesis and properties of the necessary intermediate cyclic-*gem*-diacetic and *gem*-carboxyacetic acids and anhydrides as well as several new intermediate Guareschi imides and α-cycloalkylidene-α-cyanoacetic esters.

Further studies of the formation of azaspirodiones by the interaction of cyclic *gem*-diacetic and *gem*-carboxyacetic acid anhydrides with primary amines, followed by cyclization of the amic acids thus formed to the corresponding imides (azaspirodiones), have demonstrated that this is a method of wide versatility in the synthesis of spiro carbon heterocycles. In all cases studied the corresponding azaspirane base has been obtained readily by reduction of the azaspirodione with lithium aluminum hydride in ether, tetrahydrofuran or benzene. The choice of solvent for the reduction medium is largely governed by the solubility of the azaspirodione.

Ether is the preferred solvent for these reductions because of the relative convenience of manipulation during the process and the subsequent solvent removal. It was generally employed for the reduction of the alkyl, alkenyl, and hydrazine derivatives. However, the majority of the cycloalkyl, aryl, and aralkyl azaspirodiones were relatively insoluble in ether or tetrahydrofuran. While either of these solvents could be employed in a continuous extraction procedure, whereby the azaspirodione was extracted for several hours or days into the lithium aluminum hydride solution, the ready solubility of the cycloalkyl, aryl, and aralkyl azaspirodiones in benzene gave a considerable time factor advantage in favor of benzene as the solvent of choice for these types. Since the cycloalkyl, aryl, and aralkyl azaspiranes generally boiled quite high as compared to the alkyl, alkenyl, and hydrazine derivatives, the removal of the benzene reaction solvent posed no loss problem in these cases.

As experienced in the investigation of the synthesis of azaspirodiones from dialkylaminoalkyl and heterocyclic-alkylamines and cyclic-*gem*-diacetic and *gem*-carboxyacetic acid anhydrides, reaction of molar equivalents (or a slight excess of the amine) and the anhydride and heating to between 160–180° for 20 min. to 1 hr. was generally successful in the present studies in effecting the cyclization of the initially formed amic acid to the azaspirodione. However, in the cases of the cycloalkyl-, aryl-, and aralkylamines, cyclization was frequently found to be incomplete at this temperature range, unless protracted periods of heating (several hours) were employed. Frequently this led to excessive decomposition. The preferred procedure in forming the azaspirodiones from primary cycloalkyl-, aryl-, and aralkylamines was to heat the reaction mixture to 160–180° for 0.5 hr. and then raise the temperature of the oil bath to 220–240° over a period of 15–20 min. This procedure gave good yields of the desired product and lessened decomposition.

In the case of highly volatile amines where an excess of the saturated aqueous soution was not employed, such as propyl-, propargyl, and *unsym*-dimethylhydrazine, it was advantageous to first form the amic acid in a low boiling solvent such as ether, methylene chloride, or, in some instances, benzene, distil the solvent after a short reflux period, and complete the cyclization in the oil bath at 160–180°.

A wide variety of azaspirodiones and azaspiranes has been synthesized by this general procedure and their pharmacological properties have been investigated. These compounds are listed in the Tables I–VIII which show derivatives of the following spiro carbon ring systems: (Numbering of the illustrative graphic formulas corresponds to the numbering of the tables in which derivatives of these ring systems are listed.)

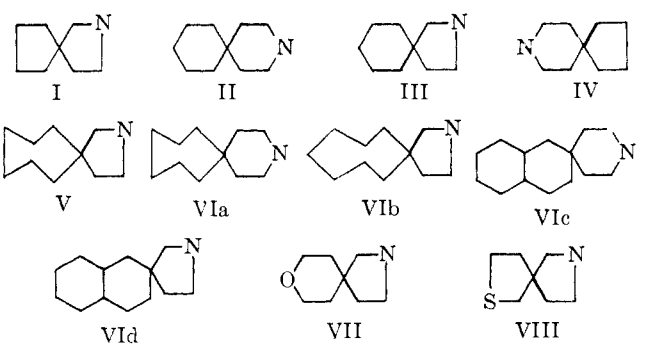


Table I, 2-azaspiro[4.4]nonane; Table II, 3-azaspiro[5.5]undecane; Table III, 2-azaspiro[4.5]decane; Table

(1) (a) Supported by the Geschickter Fund for Medical Research, Inc. (b) To whom inquiries should be addressed, National Institutes of Health, Bethesda, 14, Md.

(2) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.*, **6**, 388 (1963).

TABLE I: DERIVATIVES OF 2-AZASPIRO[4.4]NONANE

No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
					1,3-Diones						
1	H	Methyl	67–68 (0.02)	46–47	64.65	7.84	8.38	64.79	7.68	8.58	$C_9H_{13}NO_2$
2	H	Propyl	66–68 (0.1)		67.66	8.78	7.17	67.55	9.03	6.96	$C_{11}H_{17}NO_2$
3	H	Allyl	74–75 (0.25)		68.37	7.82	7.25	68.37	7.95	7.42	$C_{11}H_{15}NO_2$
4	H	Propargyl	80–83 (0.27)		69.09	6.85	7.33	68.87	6.69	7.44	$C_{11}H_{13}NO_2$
5	7-Methyl	Allyl	94–96 (0.4)		69.54	8.27	6.76	69.77	8.36	6.99	$C_{12}H_{17}NO_2$
6	7-Methyl	Methallyl	88–93 (0.05)		70.56	8.65	6.33	70.54	8.51	6.27	$C_{13}H_{19}NO_2$
7	H	Octadecyl	203–206 (0.18)	40–41	76.98	11.65	3.45	76.54	11.51	3.75	$C_{26}H_{47}NO_2$
8	H	Benzyl	130–138 (0.025)	59–60	74.05	7.04	5.76	74.26	7.16	5.98	$C_{15}H_{17}NO_2$
9	H	2,4-Dichlorobenzyl	155–160 (0.07)	71–72	57.71	4.84	22.71[a]	57.85	4.92	22.55[a]	$C_{15}H_{15}Cl_2NO_2$
10	H	Furfuryl	118–125 (0.05)	46–47	66.94	6.48	6.00	67.22	6.55	6.09	$C_{13}H_{15}NO_3$
11	H	3-Pyridylmethyl	130–145 (0.1)	57.5–58	68.83	6.60	11.47	69.17	6.65	11.49	$C_{14}H_{16}N_2O_2$[b]
12	H	2-Tetrahydropyranylmethyl	120–125 (0.03)	27–28	66.91	8.42	5.57	66.91	8.18	5.70	$C_{14}H_{23}NO_3$
13	H	Dimethylamino	89–91 (0.1)	55–56	61.20	8.22	14.28	61.48	8.24	14.62	$C_{10}H_{16}N_2O_2$
14	7-Methyl	Dimethylamino	88–90 (0.15)	45–46	62.83	8.63	13.32	63.11	8.94	13.22	$C_{11}H_{18}N_2O_2$
15	H	Dibutylamino	130–135 (0.18)				9.99			9.84	$C_{16}H_{28}N_2O_2$
16	7-Methyl	Dibutylamino	130–135 (0.2)		69.35	10.27	9.51	69.51	10.50	9.53	$C_{17}H_{30}N_2O_2$
17	H	Pyrrolidino		115–116	64.84	8.16	12.60	64.61	8.47	12.57	$C_{12}H_{18}N_2O_2$
18	H	Morpholino		151–152	60.48	7.61	11.76	60.80	7.60	11.92	$C_{12}H_{18}N_2O_3$
19	H	Piperidino		79–80	66.07	8.53	11.85	66.26	8.41	12.18	$C_{13}H_{20}N_2O_2$
					Bases						
20	H	Methyl	174–176 (atm.)		77.63	12.31	10.06	77.82	12.55	9.87	$C_9H_{17}N$[c]
21	H	Allyl	38–40 (0.4)		79.94	11.59	8.47	79.81	11.76	8.55	$C_{11}H_{19}N$[d]
22	H	Octadecyl	178–182 (0.17)		82.68	13.61	3.71	82.50	13.83	4.00	$C_{26}H_{51}N$[e]
23	H	Benzyl	78–80 (0.05)		83.66	9.83	6.51	83.58	9.73	6.37	$C_{15}H_{21}N$[f]
24	H	2,4-Dichlorobenzyl	100–103 (0.15)		63.39	6.74	4.93	63.64	6.78	5.21	$C_{15}H_{19}Cl_2N$[g]
25	H	Furfuryl	59–60 (0.07)		76.05	9.33	6.82	75.98	9.25	6.83	$C_{13}H_{19}NO$[h]
26	H	3-Pyridylmethyl	90–92 (0.1)		77.93	9.32	12.95	77.70	9.41	12.75	$C_{14}H_{20}N_2$[i]
27	H	2-Tetrahydropyranylmethyl	70–71 (0.08)		75.28	11.28	6.27	75.06	11.33	6.14	$C_{14}H_{25}NO$[j]

[a] Chlorine. [b] Imide hydrochloride, m.p. 182–183°. *Anal.* Calcd. for $C_{14}H_{25}ClN_2O_2$: Cl, 12.63. Found: Cl, 12.39. Imide methiodide, m.p. 149–150°. *Anal.* Calcd. for $C_{15}H_{27}IN_2O_2$: I, 32.86. Found: I, 33.14. [c] Hydrochloride, m.p. 135–136°. *Anal.* Calcd. for $C_9H_{18}ClN$: Cl, 20.18. Found: Cl, 20.06. Methiodide, m.p. 219–220°. *Anal.* Calcd. for $C_{10}H_{20}IN$: I, 45.14. Found: I, 44.98. Picrate, m.p. 198–199°. *Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: N, 15.21. Found: N, 15.34. [d] Hydrochloride, m.p. 133–134°. *Anal.* Calcd. for $C_{11}H_{20}ClN$: Cl, 17.57. Found: Cl, 17.39. [e] Hydrochloride, m.p. 198–200°. *Anal.* Calcd. for $C_{26}H_{52}ClN$: Cl, 8.56. Found: Cl, 8.38. Methiodide, m.p. 221–223°. *Anal.* Calcd. for $C_{27}H_{54}IN$: I, 24.42. Found: I, 24.61. [f] Hydrochloride, m.p. 200°. *Anal.* Calcd. for $C_{15}H_{22}ClN$: Cl, 14.08. Found: Cl, 14.00. Picrate, m.p. 114–115°. *Anal.* Calcd. for $C_{21}H_{24}N_4O_7$: N, 12.61. Found: N, 12.28. [g] Hydrochloride, m.p. 144–145° *Anal.* Calcd. for $C_{15}H_{20}Cl_3N$; Cl, 33.17. Found: Cl, 33.04. Methiodide, m.p. 163–164°. *Anal.* Calcd. for $C_{16}H_{22}Cl_2IN$: I, 29.78. Found: I, 30.14. [h] Hydrochloride, m.p. 91.5–93°. *Anal.* Calcd. for $C_{13}H_{20}ClNO$: Cl, 14.67. Found: Cl, 14.65. Methiodide, m.p. 160–161°. *Anal.* Calcd. for $C_{14}H_{22}INO$: I, 36.55. Found: I, 36.67. [i] Dihydrochloride, m.p. 238–240°. *Anal.* Calcd. for $C_{14}H_{22}Cl_2N_2$: Cl, 24.52. Found: Cl, 24.38. Dimethiodide, m.p. 180–182°. *Anal.* Calcd. for $C_{16}H_{26}I_2N_2$: I, 50.74. Found: I, 50.43. [j] Hydrochloride, m.p. 177–180°. *Anal.* Calcd. for $C_{14}H_{26}ClNO$: Cl, 13.65. Found: Cl, 13.86. Methiodide, m.p. 68–70°. *Anal.* Calcd. for $C_{15}H_{28}INO$: I, 34.74. Found: I, 34.42.

TABLE II

DERIVATIVES OF 3-AZASPIRO[5.5]UNDECANE

No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
					2,4-Diones						
1	H	Methyl	133–135 (1.5)	72–73[a]	67.66	8.78	7.17	67.96	8.80	7.13	$C_{11}H_{17}NO_2$
2	8-Methyl	Methyl	95–97 (0.08)	71–71.5	68.87	9.15	6.69	68.75	9.18	6.79	$C_{12}H_{19}NO_2$
3	9-Methyl	Methyl		102–103	68.87	9.15	6.69	69.17	9.39	6.78	$C_{12}H_{19}NO_2$
4	9-*t*-Butyl	Methyl		131–132	71.67	10.02	5.57	71.92	10.39	5.48	$C_{15}H_{25}NO_2$
5	H	Allyl	98–102 (0.2)		70.56	8.65	6.33	70.43	8.78	6.22	$C_{13}H_{19}NO_2$
6	H	Propyl	95–105 (0.05)		69.92	9.48		70.12	9.42		$C_{13}H_{21}NO_2$
7	H	Isopropyl	114 (0.25)	80–81	69.92	9.48		70.00	9.70		$C_{13}H_{21}NO_2$
8	H	Isobutyl	181–185 (12)	29–30	70.84	9.77	5.90	70.81	9.74	5.71	$C_{14}H_{23}NO_2$
9	H	3-Methoxypropyl	130–133 (0.2)		66.37	9.15	5.53	66.30	9.15	5.73	$C_{13}H_{23}NO_3$
10	H	Cyclopentyl	125–135 (0.05)	97–98	72.25	9.30	5.62	72.45	9.42	5.81	$C_{15}H_{23}NO_2$
11	H	Cyclohexyl	138–142 (0.05)	110–111	72.96	9.57	5.32	73.23	9.66	5.05	$C_{16}H_{25}NO_2$
12	H	2-Phenethyl	161–163 (0.2)	82–83	75.76	8.12	4.91	75.88	8.31	4.90	$C_{18}H_{23}NO_2$
13	H	p-α-Phenyliso-propyl	158–165 (0.025)	Glass	76.22	8.42	4.68	75.97	8.53	4.52	$C_{19}H_{25}NO_2$
14	H	Benzyl	150–155 (0.075)	62–63	75.20	7.80	5.16	75.18	7.84	4.93	$C_{17}H_{21}NO_2$
15	H	Homoveratryl	210–215 (0.25)	103–104	69.54	7.88	4.06	69.32	7.95	4.35	$C_{20}H_{27}NO_4$
16	H	2-Thiazolyl	195–205 (0.05)	142–143	59.06	6.10	10.60	59.37	6.10	10.64	$C_{12}H_{16}N_2O_2S$
17	H	Dimethylamino	117 (0.025)	118–120	64.25	8.99	12.49	64.16	9.01	12.34	$C_{12}H_{20}N_2O_2$
18	9-*t*-Butyl	Dimethylamino		118–119	68.52	10.06	9.99	68.61	10.13	10.18	$C_{16}H_{28}N_2O_2$
19	H	Piperidino		120–121	67.17	8.86	11.19	67.58	9.38	11.16	$C_{15}H_{24}N_2O_2$
20	H	Dibutylamino	150–160 (0.2)		70.09	10.46	9.08	70.68	10.66	9.02	$C_{18}H_{32}N_2O_2$
21	H	2,6-Dimethyl-morpholino		127–128	65.28	8.90	9.52	65.48	9.11	9.54	$C_{16}H_{26}N_2O_3$
22	H	Pyrrolidino		107–108	67.17	8.86	11.19	67.30	9.07	10.98	$C_{14}H_{22}N_2O_2$
					Bases						
23	H	Methyl	96–97 (10)		78.97	12.65	8.37	78.77	12.57	8.48	$C_{12}H_{23}N$[b]
24	8-Methyl	Methyl	73–74 (0.8)		79.49	12.79	7.72	79.77	12.97	7.75	$C_{13}H_{25}N$[c]
25	9-Methyl	Methyl	80–82 (1.2)		79.49	12.79	7.72	79.50	12.78	7.96	$C_{13}H_{25}N$[d]
26	H	Allyl	52–53 (0.2)		80.76	11.91	7.24	80.64	12.20	7.40	$C_{14}H_{25}N$[e]
27	H	3-Methoxypropyl	105–107 (0.4)		74.61	12.08	6.22	74.52	12.27	6.45	$C_{14}H_{27}NO$[f]
28	H	Cyclopentyl	175–176 (19)		81.38	12.29	6.33	81.26	12.07	6.18	$C_{15}H_{27}N$[g]
29	H	Cyclohexyl	188–190 (19)		81.63	12.42	5.95	81.75	12.37	6.17	$C_{16}H_{29}N$[h]
30	H	Benzyl	100–106 (0.05)		83.89	10.35	5.75	83.71	10.19	5.74	$C_{17}H_{25}N$[i]
31	9-*t*-Butyl	Methyl	66–68 (0.2)		80.65	13.08	6.27	80.88	13.24	6.13	$C_{15}H_{29}N$[c]
32	H	2-Phenethyl	119–125 (0.025)		83.99	10.57	5.44	84.20	10.77	5.44	$C_{18}H_{27}N$[k]
33	H	Homoveratryl	155–158 (0.12)	73–74	75.67	9.84	4.41	75.71	9.99	4.41	$C_{20}H_{31}NO_2$[l]

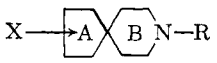
TABLE II (*Continued*)

No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
34	H	D-α-Phenylisopropyl	125–127 (0.27)		84.07	10.77	5.16	84.20	11.08	4.91	$C_{15}H_{23}N$[m]
35	H	Dimethylamino	73–75 (0.4)		73.41	12.32	14.27	73.26	12.11	14.09	$C_{12}H_{24}N$[n]

[a] A. J. Birch and R. Robinson, *J. Chem. Soc.*, 488 (1942), give b.p. 184° (15 mm.), m.p. 66°. [b] Hydrochloride, m.p. 251–252°. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.42. Found: Cl, 17.51. Methiodide, m.p. 284–285°. *Anal.* Calcd. for $C_{12}H_{24}IN$: I, 41.04. Found: I, 40.94. Picrate, m.p. 214–215°. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.14. Found: N, 14.26. [c] Hydrochloride, m.p. 236–237°. *Anal.* Calcd. for $C_{12}H_{24}ClN$: Cl, 16.28. Found: Cl, 16.01. Methiodide, m.p. 289–290°. *Anal.* Calcd. for $C_{13}H_{26}IN$: I, 39.26. Found: I, 39.29. Picrate, m.p. 160–161°. *Anal.* Calcd. for $C_{18}H_{26}N_4O_7$: N, 13.65. Found: N, 13.36. [d] Hydrochloride, m.p. 232–233°. *Anal.* Calcd. for $C_{12}H_{24}ClN$: Cl, 16.28. Found: Cl, 16.43. Methiodide, m.p. 308–309°. *Anal.* Calcd. for $C_{13}H_{26}IN$: I, 39.26. Found: I, 39.10. Methochloride, m.p. over 360°. *Anal.* Calcd. for $C_{13}H_{26}ClN$: Cl, 15.30. Found: Cl, 15.43. Ethiodide, m.p. 248–250°. *Anal.* Calcd. for $C_{14}H_{28}IN$: I, 37.63. Found: I, 37.45. Allyliodide, m.p. 193–194°. *Anal.* Calcd. for $C_{15}H_{28}IN$: I, 36.33. Found: I, 36.59. Dodeciodide, m.p. 249–250°. *Anal.* Calcd. for $C_{24}H_{48}IN$: I, 26.58. Found: I, 26.33. Picrate, m.p. 201–202°. *Anal.* Calcd. for $C_{18}H_{26}N_4O_7$: N, 13.65. Found: N, 13.45. [e] Hydrochloride, m.p. 221–222°. *Anal.* Calcd. for $C_{13}H_{24}ClN$: Cl, 15.43. Found: Cl, 15.38. [f] Hydrochloride, m.p. 247–249°. *Anal.* Calcd. for $C_{14}H_{28}ClNO$: Cl, 13.54. Found: Cl, 13.31. Methiodide, m.p. 148–149°. *Anal.* Calcd. for $C_{15}H_{30}INO$: I, 34.55. Found: I, 34.66. [g] Hydrochloride, m.p. 313–314°. *Anal.* Calcd. for $C_{15}H_{28}ClN$: Cl, 13.75. Found: Cl, 13.52. Methiodide, m.p. 263–264°. *Anal.* Calcd. for $C_{16}H_{30}IN$: I, 34.93. Found: I, 35.16. Picrate, m.p. 137–138°. *Anal.* Calcd. for $C_{21}H_{30}N_4O_7$: N, 12.43. Found: N, 12.32. [h] Hydrochloride, m.p. 328–329°. *Anal.* Calcd. for $C_{16}H_{30}ClN$: Cl, 13.04. Found: Cl, 12.83. Methiodide, m.p. 259–260°. *Anal.* Calcd. for $C_{17}H_{32}IN$: I, 33.63. Found: I, 33.57. Picrate, m.p. 134–135°. *Anal.* Calcd. for $C_{22}H_{32}N_4O_7$: N, 12.06. Found: N, 12.38. [i] Hydrochloride, m.p. 262–263°. *Anal.* Calcd. for $C_{17}H_{26}ClN$: Cl, 12.7. Found: Cl, 12.5. Methiodide, m.p. 242–244°. *Anal.* Calcd. for $C_{18}H_{28}IN$: I, 32.94. Found: I, 32.50. Picrate, m.p. 154–155°. *Anal.* Calcd. for $C_{20}H_{28}N_4O_7$: N, 11.85. Found: N, 11.85. [j] Hydrochloride, m.p. 295–296°. *Anal.* Calcd. for $C_{15}H_{30}ClN$: Cl, 13.64. Found: Cl, 13.35. Methiodide, m.p. 340–341°. *Anal.* Calcd. for $C_{16}H_{32}IN$: I, 34.74. Found: I, 35.00. Picrate, m.p. 245–246°. *Anal.* Calcd. for $C_{18}H_{32}N_4O_7$: N, 12.38. Found: N, 12.58. [k] Hydrochloride, m.p. 329–330°. *Anal.* Calcd. for $C_{18}H_{25}ClN$: Cl, 13.44. Found: Cl, 13.36. Methiodide, m.p. 218–219°. *Anal.* Calcd. for $C_{19}H_{30}IN$: I, 31.78. Found: I, 32.11. Picrate, m.p. 135–136°. *Anal.* Calcd. for $C_{21}H_{30}N_4O_7$: N, 11.52. Found: N, 11.43. [l] Hydrochloride, m.p. 262–263°. *Anal.* Calcd. for $C_{20}H_{32}ClNO_2$: Cl, 10.02. Found: Cl, 9.91. Methiodide, m.p. 235–236°. *Anal.* Calcd. for $C_{21}H_{34}INO_2$: I, 27.63. Found: I, 27.69. [m] Hydrochloride, m.p. 291–292°. *Anal.* Calcd. for $C_{19}H_{30}ClN$: Cl, 11.52. Found: Cl, 11.71. Methiodide, m.p. 222–223°. *Anal.* Calcd. for $C_{20}H_{32}IN$: I, 30.70. Found: I, 30.72. [n] Monohydrochloride, m.p. 210–211°. *Anal.* Calcd. for $C_{12}H_{24}ClN_2$: Cl, 15.23; N, 12.03. Found: Cl, 15.05; N, 12.20.

IV, 8-azaspiro[4.5]decane; Table V, 2-azaspiro[4.6]undecane; Table VI, 3-azaspiro[5.6]dodecane, 2-azaspiro[4.7]dodecane, spiro-*trans*-decalin-2,4′-piperidine and spiro-*trans*-decalin-2,3′-pyrrolidine; Table VII, 8-oxa-2-azaspiro[4.5]decane; and Table VIII, 7-thia-2-azaspiro[4.4]nonane.

In Table IX and in the discussion of the properties of these compounds the following general structural formula



is used for convenience of reference. In addition the numbers 55, 56, 65, 66, 75, etc., are used to designate the total number of atoms in rings A and B, respectively, when considered as separate rings (including the common spiro carbon atom, therefore, in the count for each ring for this purpose).

The azaspirodiones and azaspiranes, in the form of their acid addition and quaternary salts, were screened for pharmacological activity by rapid primary screening techniques.[3] When indicated by the primary screening data, further more definitive pharmacological evaluation was carried out and clinical effectiveness determined when indicated by the preliminary screening and pharmacological evaluation.

Pharmacology.—Concurrent with the toxicity range studies in the rat, careful gross observation of the animals was made at several dosage levels and signs of CNS stimulation (increased spontaneous motor activity; Straub tail; tremors; type, extent, and duration of convulsions; and hind-limb tonic extension) or depression (decreased spontaneous motor activity, body muscle tonus, and impairment of the righting reflex) were noted. Detection of sedative activity was made by observation of the exploratory nature of the rat[4] and further by the median motor relaxation dose technique of Durham, *et al.*[5] Where indicated additional evidence of "tranquilizing" activity was obtained by the potentiation (induction and duration of sleep) of a nonnarcotic dose of ethanol (5 ml./kg., p.o.).[6]

Local anesthetic activity was ascertained by the usual rabbit cornea method of Régnier[7] as compared to cocaine or procaine hydrochloride; or by intracutaneous administration (to rabbits or guinea pigs with or without epinephrine hydrochloride) and observation of the extent of the wheals produced and responses to probes applied within the wheal area.

The general type of pharmacological activity encountered in these compounds was predominantly evinced by their effects on the peripheral and central nervous system. Representative data are summarized in Table IX. From these data it can be seen that the azaspiranes were generally central nervous system stimulants as were a majority of the azaspirodiones with N-alkyl substituents. However, there was a small, well defined sedative, muscle relaxant, and "tranquilizing" activity range associated with the diones derived from the small spiro carbon rings bearing N-substituents having unsaturated linkages in the substituent. Derivatives of the 55 ring system were most definitive in this respect. This activity was present with allyl, methallyl, and propargyl substituents (Table I, **3–6**), was enhanced by alkyl substituents on the A ring, and was greatly decreased or absent with methyl or propyl N-substituents (Table I, **1**, **2**) (removal of the unsaturated linkages from the N-substituent). The incor-

(3) E. P. Rubacky, unpublished results.

(4) R. W. Ryall, *Nature*, **182**, 1606 (1958).

(5) N. W. Durham and T. S. Miya, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 208 (1957).

(6) F. Herr, J. Stewart, and M. P. Charest, *Arch. Intern. Pharmacodyn.*, **134**, 328 (1961).

(7) J. Régnier, *Compt. Rend.*, **177**, 558 (1923).

TABLE III

DERIVATIVES OF 2-AZASPIRO[4.5]DECANE

No.	X	R	B.p., °C. (mm.)	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Empirical formula
					1,3-Diones						
1	H	Methyl	105–106 (0.75)	76–77[a]	66.27	8.34	7.73	66.24	8.46	7.73	$C_{10}H_{15}NO_2$
2	7-Methyl	Methyl	80–83 (0.2)		67.66	8.78	7.17	68.00	8.68	7.47	$C_{11}H_{17}NO_2$
3	8-Methyl	Methyl	81–84 (0.2)		67.66	8.78	7.17	67.44	8.89	7.07	$C_{11}H_{17}NO_2$
4	H	Allyl	95–103 (0.05)	58–59	69.54	8.27	6.76	69.71	8.22	6.70	$C_{12}H_{17}NO_2$
5	H	Butyl	131–133 (1.3)		69.92	9.48	6.27	70.09	9.56	6.27	$C_{13}H_{21}NO_2$
6	H	Hexyl	107–116 (0.025)		71.76	10.03	5.57	71.99	10.09	5.36	$C_{15}H_{25}NO_2$
7	H	Dodecyl	168–173 (0.025)		75.17	11.12	4.18	75.44	10.88	4.11	$C_{22}H_{41}NO_2$
8	H	Dimethylamino		103–104	62.83	8.63	13.32	62.76	8.80	13.44	$C_{11}H_{18}N_2O_2$
9	H	2-Methyl-4-methoxyphenyl		168–169	71.06	7.37	4.87	71.40	7.51	5.22	$C_{17}H_{21}NO_3$
10	H	*o*-Chlorobenzyl		147–148	69.05	7.53	10.19[b]	69.24	7.58	10.18[b]	$C_{20}H_{26}ClNO_2$
11	7-Methyl	2,6-Dimethylmorpholino		74.5–75.5	64.26	8.63	9.99	64.62	8.53	9.87	$C_{15}H_{24}N_2O_3$
					Bases						
12	H	Methyl	64–68 (9)	56–58	78.36	12.50	9.14	78.69	12.67	8.91	$C_{10}H_{19}N$[c]
13	7-Methyl	Methyl	49–50 (0.6)		78.97	12.65	8.37	78.97	12.72	8.36	$C_{11}H_{21}N$[d]
14	8-Methyl	Methyl	60–61 (0.4)		78.97	12.65	8.37	78.62	12.65	8.35	$C_{11}H_{21}N$[e]
15	H	Butyl	110–111 (12)		79.93	12.90	7.17	79.95	12.95	7.42	$C_{13}H_{25}N$[f]
16	H	Hexyl	135–138 (10)		80.64	13.09	6.27	80.81	13.35	6.59	$C_{15}H_{29}N$[g]
17	H	Dodecyl	154–158 (0.45)		82.01	13.44	4.55	82.13	13.65	4.36	$C_{22}H_{43}N$[h]
18	H	2-Methyl-4-methoxyphenyl	120–125 (0.1)		78.72	9.71	5.40	78.64	9.64	5.48	$C_{17}H_{25}NO$[i]
19	8-*t*-Butyl	o-Chlorobenzyl	140–144 (0.4)		75.09	9.45	11.08[b]	75.17	9.61	11.20[b]	$C_{20}H_{30}ClN$[j]

[a] Melting point 79° given by S. Nakamura and M. Aimiya, Japanese Patent 7574 (October 19, 1955). [b] Chlorine. [c] Hydrochloride, m.p. 186–187°. *Anal.* Calcd. for $C_{16}H_{30}ClN$: Cl, 18.69. Found: Cl, 18.70. Methiodide, m.p. 241–242°. *Anal.* Calcd. for $C_{11}H_{22}IN$: I, 42.99. Found: I, 43.22. Picrate, m.p. 194–195°. *Anal.* Calcd. for $C_{19}H_{22}N_4O_7$: N, 14.65. Found: N, 14.49. Propane-1,3-bis-[2-methyl-2-azaspiro[4.5]decanyl]-diiodide, m.p. 264–265°. *Anal.* Calcd. for $C_{23}H_{44}I_2N_2$: I, 42.14. Found: I, 41.86. [d] Hydrochloride, m.p. 174–175°. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.40. Found: Cl, 17.20. Methiodide, m.p. 258–259°. *Anal.* Calcd. for $C_{12}H_{24}IN$: I, 41.04. Found: I, 41.31. Picrate, m.p. 121–122°. *Anal.* Calcd. for $C_{23}H_{31}N_4O_7$: N, 14.13. Found: 14.17. [e] Hydrochloride, m.p. 199–200°. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.40. Found: Cl, 17.21. Methiodide, m.p. 236–237°. *Anal.* Calcd. for $C_{12}H_{24}IN$: I, 41.04. Found: I, 41.31. Picrate, m.p. 162–163°. *Anal.* Calcd. for $C_{23}H_{31}N_4O_7$: N, 14.13. Found: N, 14.13. [f] Hydrochloride, m.p. 235–236°. *Anal.* Calcd. for $C_{13}H_{26}ClN$: Cl, 15.30. Found: Cl, 15.55. Methiodide, m.p. 114–115°. *Anal.* Calcd. for $C_{14}H_{28}IN$: I, 37.63. Found: I, 37.88. Picrate, m.p. 121–122°. *Anal.* Calcd. for $C_{25}H_{35}N_4O_7$: N, 13.20. Found: N, 12.90. [g] Hydrochloride, m.p. 235–236°. *Anal.* Calcd. for $C_{15}H_{30}ClN$: Cl, 13.64. Found: Cl, 13.53. Methiodide, m.p. 130–131°. *Anal.* Calcd. for $C_{16}H_{32}IN$: I, 34.74. Found: I, 34.89. Picrate, m.p. 93–94°. *Anal.* Calcd. for $C_{27}H_{39}N_4O_7$: N, 12.38. Found: N, 12.34. [h] Hydrochloride, m.p. 209–210°. *Anal.* Calcd. for $C_{21}H_{42}ClN$: Cl, 10.31. Found: Cl, 10.21. Methiodide, m.p. 198–199°. *Anal.* Calcd. for $C_{22}H_{44}IN$: I, 28.24. Found: I, 28.36. Picrate, oil. [i] Hydrochloride, m.p. 150–151°. *Anal.* Calcd. for $C_{17}H_{26}ClNO$: Cl, 11.98. Found: Cl, 11.63. Methiodide, m.p. 133–134°. *Anal.* Calcd. for $C_{18}H_{28}INO$: I, 31.62. Found: I, 31.45. [j] Hydrochloride, m.p. 196–198°. *Anal.* Calcd. for $C_{20}H_{31}Cl_2N$: ionic Cl, 9.95. Found: ionic Cl, 10.10. Methiodide, m.p. 196–197°. *Anal.* Calcd. for $C_{21}H_{33}ClIN$: I, 27.48. Found: I, 27.50.

poration of a sulfur atom in lieu of one of the carbon atoms in the A ring (Table VIII, **2**) did not appreciably affect the type of activity although it generally decreased its duration and increased toxicity. The inclusion of an oxygen atom (Table VII, **5**), with alkyl substituents (Table VII, **1**), in the A ring resulted in very potent compounds.

This sedative, muscle relaxant, and "tranquilizing" activity was diminished, abolished, or reversed (stimulant) if the size of either ring A or B, or both, was increased by the inclusion of additional carbon atoms. The N-allyl dione derivatives of the 56, 65, 66, and 75 rings (Table III, **4**; Table II, **5**; Table V, **2**) were stimulants. Aryl substituents, either on the nitrogen

TABLE IV

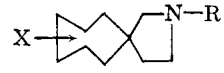
DERIVATIVES OF 8-AZASPIRO[4.5]DECANE

No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
					7,9-Diones						
1	H	Methyl	114–116 (0.9)	56–57	66.27	8.34	7.73	66.52	8.29	7.47	$C_{10}H_{15}NO_2$
2	2-Methyl	Methyl	86–89 (0.15)		67.66	8.78	7.17	67.83	8.81	7.10	$C_{11}H_{17}NO_2$
3	H	Dimethylamino		61–62	62.83	8.63	13.32	62.54	8.81	13.44	$C_{11}H_{18}N_2O_2$
4	H	*p*-Isopropylbenzyl	160–165 (0.2)	81–82	76.22	8.42	4.68	76.20	8.21	4.46	$C_{19}H_{25}NO_2$
					Bases						
5	H	Methyl	78–80 (11)		78.36	12.50	9.14	78.62	12.43	8.92	$C_{10}H_{19}N$[a]
6	2-Methyl	Methyl	57–59 (0.95)		78.97	12.65	8.37	78.63	12.58	8.20	$C_{11}H_{21}N$[b]
7	H	*p*-Isopropylbenzyl	118–123 (0.13)		84.07	10.77	5.16	84.34	11.00	5.21	$C_{19}H_{29}N$[c]

[a] Hydrochloride, m.p. 217–218°. *Anal.* Calcd. for $C_{10}H_{20}ClN$: Cl, 18.69. Found: Cl, 18.49. Methiodide, m.p. 272–273°. *Anal.* Calcd. for $C_{11}H_{22}IN$: I, 42.99. Found: I, 42.85. Picrate, m.p. 222–223°. *Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.65. Found: N, 14.97. [b] Hydrochloride, m.p. 221–222°. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.40. Found: Cl, 17.46. Methiodide, m.p. 283–284°. *Anal.* Calcd. for $C_{12}H_{24}IN$: I, 41.04. Found: I, 41.16. Picrate, m.p. 191–192°. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.14. Found: N, 14.08. [c] Hydrochloride, m.p. 243–244°. *Anal.* Calcd. for $C_{19}H_{30}ClN$: Cl, 11.52. Found: Cl, 10.96. Methiodide, m.p. 236–237°. *Anal.* Calcd. for $C_{20}H_{32}IN$: I, 30.70. Found: I, 30.82.

TABLE V

DERIVATIVES OF 2-AZASPIRO[4.6]UNDECANE



No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
					1,3-Diones						
1	H	Methyl	115–120 (0.2)	26–27	67.66	8.78	7.17	67.92	8.81	7.45	$C_{11}H_{17}NO_2$
2	H	Allyl	95–96 (0.08)		70.56	8.65	6.33	70.71	8.81	6.27	$C_{13}H_{19}NO_2$
3	H	Cyclooctyl	170–175 (0.025)	64–65	74.18	10.03	4.81	74.46	10.14	5.05	$C_{18}H_{29}NO_2$
4	H	Dimethylamino		89–90	64.26	8.99	12.49	64.62	9.10	12.70	$C_{12}H_{20}N_2O_2$
5	H	Piperidino		118–119			11.19			11.03	$C_{15}H_{24}N_2O_2$
6	H	2,6-Dimethyl-morpholino		109–110	65.28	8.90	9.52	65.55	9.17	9.56	$C_{14}H_{22}N_2O_3$
					Bases						
7	H	Methyl	88–90 (9)		78.97	12.65	8.37	78.80	12.70	8.36	$C_{11}H_{21}N$[a]
8	H	Allyl	69–70 (0.1)		80.76	11.99	7.25	80.72	11.94	7.41	$C_{13}H_{23}N$[b]
9	H	Cyclooctyl	111–114 (0.15)		82.06	12.63	5.32	81.95	12.76	5.49	$C_{18}H_{33}N$[c]

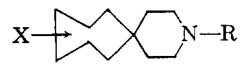
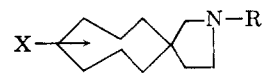
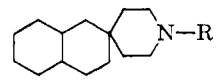
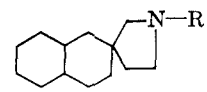
[a] Hydrochloride, m.p. 202–203°. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.42. Found: Cl, 17.47. Methiodide, m.p. 266–267°. *Anal.* Calcd. for $C_{12}H_{24}IN$: I, 41.04. Found: I, 41.12. Picrate, m.p. 187–188°. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.14. Found: N, 13.94. [b] Hydrochloride, m.p. 176–176.5°. *Anal.* Calcd. for $C_{13}H_{24}ClN$: Cl, 15.43. Found: Cl, 15.47. [c] Hydrochloride, m.p. 240–241°. *Anal.* Calcd. for $C_{18}H_{34}ClN$: Cl, 11.82. Found: Cl, 11.66. Methiodide, m.p. 256–257°. *Anal.* Calcd. for $C_{19}H_{36}IN$: I, 31.31. Found: I, 31.22. Deciodide, m.p. 59–61°. *Anal.* Calcd. for $C_{28}H_{54}IN$: I, 23.26. Found: I, 23.34.

atom of ring B or on ring A, also decreased the activity seen with the unsaturated aliphatic N-substituents (Table VII, **6** and several phenyl imides).

On passing to the hydrazine derivatives, the sedative and "tranquilizing" properties were still present in the imides and some of these compounds also produced rapid local anesthesia. The local anesthetic activity was most pronounced in the smaller ring systems, particularly the 55, thia55, and oxa65 rings (Table I, **13–19**; Table VII, **4**; Table VIII, **6**); while sedative, "tranquilizing", and hypnotic effects were generally encountered in varying degrees throughout the various ring systems.

Reduction of the hydrazine imides to azaspiranes again produced central nervous stimulants (Table II, **35**). Several of the azaspirodiones derived from hydrazines also produced a gradual prolonged lowering of blood pressure in dogs by an as yet undetermined

TABLE VI

No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
			DERIVATIVES OF 3-AZASPIRO[5.6]DODECANE								
											
1	H	Methyl	128–131 (0.6)	51–52	68.86	9.15	6.69	69.04	9.49	6.49	$C_{12}H_{19}NO_2$ 2,4-dione
2	H	Methyl	109–111 (10)		79.49	12.79	7.72	79.57	12.68	7.60	$C_{12}H_{23}N$ base[a]
			DERIVATIVES OF 2-AZASPIRO[4.7]DODECANE								
											
3	H	Dimethylamino	108–112 (0.15)		65.51	9.30	11.75	65.70	9.32	12.17	$C_{13}H_{22}N_2O_2$ 2,4-dione
			DERIVATIVES OF SPIRO-*trans*-DECALIN-2,4′-PIPERIDINE								
											
			2′,6′-Diones								
4		Methyl	140–144 (0.05)	93–94	72.25	9.30	5.62	72.26	9.65	5.77	$C_{15}H_{23}NO_2$
5		Dimethylamino		102–103	69.03	9.41	10.06	69.11	9.83	10.22	$C_{16}H_{26}N_2O_2$
6		*p*-Methylbenzyl	210–215 (0.2)		77.84	8.61	4.13	77.96	8.47	4.22	$C_{22}H_{29}NO_2$
			Bases								
7		Methyl	153–156 (10)		81.38	12.29	6.33	81.49	12.47	6.11	$C_{15}H_{27}N$[b]
8		*p*-Methylbenzyl	172–178 (0.1)		84.83	10.68	4.50	84.88	10.43	4.28	$C_{22}H_{33}N$[c]
			SPIRO-DECALIN-2,3′-PYRROLIDINE								
											
9		Methyl	125–130 (0.05)	[d]	71.45	9.00	5.95	71.28	8.89	5.78	$C_{14}H_{23}NO_2$ 2′,5′-dione
10		Methyl	73–75 (0.25)		81.09	12.15	6.76	80.96	12.25	7.07	$C_{14}H_{25}N$[e]

[a] Hydrochloride, m.p. 250–251°. *Anal.* Calcd. for $C_{12}H_{24}ClN$: Cl, 16.28. Found: Cl, 16.12. Methiodide, m.p. 300–301°. *Anal.* Calcd. for $C_{13}H_{26}IN$: I, 39.26. Found: I, 39.47. Picrate, m.p. 187–188°. *Anal.* Calcd. for $C_{18}H_{26}N_4O_7$: N, 13.65. Found: N, 13.44. [b] Hydrochloride, m.p. 252–253°. *Anal.* Calcd. for $C_{15}H_{28}ClN$: Cl, 13.75. Found: Cl, 13.61. Methiodide, m.p. 325–326°. *Anal.* Calcd. for $C_{16}H_{30}IN$: I, 34.93. Found: I, 34.86. Picrate, m.p. 182–183°. *Anal.* Calcd. for $C_{21}H_{30}N_4O_7$: N, 12.44. Found: N, 12.20. [c] Hydrochloride, m.p. 288–289°. *Anal.* Calcd. for $C_{22}H_{34}ClN$: Cl, 10.19. Found: Cl, 10.12. Methiodide, m.p. 220–221°. *Anal.* Calcd. for $C_{23}H_{36}IN$: I, 27.99. Found: I, 28.30. Butiodide, m.p. 190–192°. *Anal.* Calcd. for $C_{26}H_{42}IN$: I, 25.61. Found: I, 25.85. [d] Material partly liquid and partly solid, a mixture of isomers. The entire lot was reduced to the corresponding base without separation of the isomers. [e] Hydrochloride, m.p. 209–210°. *Anal.* Calcd. for $C_{14}H_{26}ClN$: Cl, 14.54. Found: Cl, 14.65. Methiodide, m.p. 265–266°. *Anal.* Calcd. for $C_{15}H_{28}IN$: I, 36.34. Found: I, 36.48. Picrate, oil.

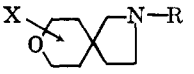
mechanism. The N-dimethylamino-66-dione (Table II, **17**) produced such effects in the dog.

The aralkyl N-substituents also produced central nervous system stimulants or depressants. The benzyl, substituted benzyl, phenethyl, and homoveratryl N-substituents (Table I, **23**, **24**; Table II, **30**, **32**, **33**; Table III, **19**; Table IV, **7**; Table VII, 8) produced behavioral changes in rats, and in addition showed varying degrees of antiinflammatory activity when assayed by the cotton pellet granuloma pouch and egg white inflammation methods.

The discussion of the properties of these compounds should not be concluded without mention of the remarkable solubility properties of the hydrazine imides. While these properties were noted throughout the range of ring sizes and hydrazines investigated, they were most remarkable with the small spiro carbon rings with N-hetero-or-N-lower dialkylamino substituents. The dimethylamino-55-dione was soluble in cold water and quite soluble in hot water; slightly soluble in cold petroleum ether, (30–60°) hexane, and ligroin; and quite soluble in these solvents when hot. Most of the hydrazine imides could be recrystallized from water or ligroin and in the case of the smaller molecules from water or petroleum ether (30–60°). In addition to being slightly to very soluble in alcohols, esters, ethers, ketones, benzene, and halocarbon solvents, the property of solubility in hydrophobic as well as hydrophilic solvents was thought to be quite remarkable.

TABLE VII

DERIVATIVES OF 8-OXA-2-AZASPIRO[4.5]DECANE

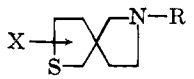


No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
				1,3-Diones							
1	7,9-Dimethyl	Allyl	87–89 (0.13)	55–56	65.80	8.07	5.90	65.69	7.81	6.15	$C_{13}H_{19}NO_3$
2	7,9-Dimethyl	Phenethyl	141–143 (0.01)		71.73	7.69	4.65	71.89	7.70	4.86	$C_{18}H_{23}NO_3$
3	7,9-Dimethyl	3-Methoxypropyl	118–122 (0.18)		62.43	8.61	5.20	62.58	8.83	5.01	$C_{14}H_{23}NO_4$
4	7,9-Dimethyl	Dimethylamino	125–130 (0.1)	121–122	59.98	8.39	11.66	60.32	8.57	11.89	$C_{12}H_{20}N_2O_3$
5	H	Allyl	97–99 (0.15)	57–58	63.14	7.23	6.69	63.27	7.39	6.68	$C_{11}H_{15}NO_3$
6	7-Methyl 9-Phenyl	Allyl	160–170 (0.2)	Glass	72.22	7.07	4.68	72.18	7.22	4.93	$C_{18}H_{21}NO_3$
				Bases							
7	7,9-Dimethyl	Allyl	41 (0.15)		74.59	11.08	6.69	74.69	11.22	6.90	$C_{13}H_{23}NO$[a]
8	7,9-Dimethyl	Phenethyl	116–118 (0.025)		79.07	9.95	5.12	79.34	9.95	5.12	$C_{18}H_{27}NO$[b]
9	7,9-Dimethyl	3-Methoxypropyl	70–72 (0.08)		69.66	11.28	5.80	69.89	11.51	5.68	$C_{14}H_{27}NO_2$[c]

[a] Hydrochloride, m.p. 187–188°. *Anal.* Calcd. for $C_{13}H_{24}ClNO$: Cl, 14.43. Found: Cl, 14.48. Butiodide, m.p. 180–181°. *Anal.* Calcd. for $C_{17}H_{32}INO$: I, 32.26. Found: I, 31.91. [b] Hydrochloride, m.p. 236–237°. *Anal.* Calcd. for $C_{18}H_{28}ClNO$: Cl, 11.44. Found: Cl, 11.28. Methiodide, m.p. 159–160°. *Anal.* Calcd. for $C_{19}H_{30}INO$: I, 30.56. Found: I, 30.61. Deciodide, m.p. 143–144°. *Anal.* Calcd. for $C_{30}H_{52}INO$: I, 22.28. Found: I, 22.53. [c] Hydrochloride, m.p. 190–191°. *Anal.* Calcd. for $C_{14}H_{28}ClNO_2$: Cl, 12.76. Found: Cl, 12.95. Methiodide, m.p. 131.5–132°. *Anal.* Calcd. for $C_{15}H_{30}INO_2$: I, 33.11. Found: I, 33.36.

TABLE VIII

DERIVATIVES OF 7-THIA-2-AZASPIRO[4.4]NONANE



No.	X	R	B.p., °C. (mm.)	M.p., °C.	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N	Empirical formula
1	H	Methyl		64–65	51.87	5.99	7.56	51.71	6.32	7.46	$C_8H_{11}NO_2S$ 1,3-dione
2	H	Allyl	107–110 (0.25)	50–51	56.85	6.20	6.63	56.93	6.30	6.87	$C_{10}H_{13}NO_2S$ 1,3-dione
3	H	Allyl	50–51 (0.2)		65.52	9.35	7.64	65.46	9.10	7.84	$C_{10}H_{17}NS$ base[a]
4	H	*p*-Methylbenzyl	165–175 (0.02)	69–70	65.43	6.22	5.09	65.61	6.35	4.90	$C_{15}H_{17}NO_2S$ 1,3-dione
5	H	*p*-Methylbenzyl	110–115 (0.05)		72.82	8.56	5.66	73.10	8.62	5.95	$C_{15}H_{21}NS$ base[b]
6	H	Dimethylamino		94–94.5	50.44	6.59	13.07	50.64	6.80	13.00	$C_9H_{14}N_2O_2S$ 1,3-dione

[a] Hydrochloride, m.p. 98–98.5°, very hygroscopic. *Anal.* Calcd. for $C_{10}H_{18}ClNS$: Cl, 16.13. Found: Cl, 15.80. [b] Hydrochloride, m.p. 204–205°. *Anal.* Calcd. for $C_{15}H_{22}ClNS$: Cl, 12.49. Found: Cl, 12.73.

Experimental

All melting points were obtained with a Fisher-Johns block type or Thomas-Hoover capillary type melting point apparatus and are corrected. Boiling points are obviously not corrected as the range observed during vacuum distillations is much larger than any correction. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

The necessary cyclic *gem*-diacetic and carboxy-acetic acids and anhydrides were obtained according to literature methods or modifications thereof as described in our previous paper.[2] The N,N-disubstituted hydrazines and N-aminoheterocycles were prepared by nitrosation of the corresponding secondary amines[8] or heterocyclic amines[9] and reduction of the N-nitroso derivatives with lithium aluminum hydride in ether. While the syntheses of the azaspirodiones and azaspiranes were accomplished by the general procedures outlined in the text, some of the useful vagaries employed to obtain specific members are illustrated in the detailed experimental examples that follow.

2-(3-Picolyl)-2-azaspiro[4.4]nonane-1,3-dione.—To 20 g. (0.13 mole) of cyclopentane-1-carboxy-1-acetic anhydride in a 50 ml. round-bottom flask was added 15 g. (0.138 mole) of 3-picolylamine and the mixture heated to 160–180° in an oil bath for 1 hr. On vacuum distillation there was obtained 30 g. (94%) of the title compound, b.p. 140–145° (0.1 mm.), as a viscous oil. On slurrying with absolute ether it solidified and melted at 54–56°. Recrystallization from acetone–ligroin gave analytical material, m.p. 57.5–58°.

(8) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 211.

(9) M. Rink and M. Mehta, *Naturwiss.*, **48**, 51 (1961).

TABLE IX

SUMMARY OF PHARMACOLOGICAL PROPERTIES OF SOME AZASPIRANES

X	R	AB[a]	Approx. LD_{50},[b] mg./kg.	Pharmacological effect[c]
		Diones		
H	Allyl	55	>500	Moderate sedation, tranquilization
7-Methyl	Allyl	55	>400	Moderate sedation, tranquilization
H	Methyl	55	>500	Slight sedation at toxic levels, respiratory irregularity, tremors
H	Propyl	55	~400	Very slight sedation at toxic levels, respiratory irregularity, tremors
H	Propargyl	55	~400	Deep sedation, tranquilization, hypnosis
7-Methyl	Methallyl	55	>300	Moderate sedation, tranquilization
H	Allyl	7-thia55	~250	Mild sedation lower doses, stimulation higher doses
H	Allyl	65	125	CNS stimulation
H	Allyl	66	250	CNS stimulation
H	Allyl	56	~250	CNS stimulation
H	Allyl	75	~300	CNS stimulation, nerve blocking
H	Allyl	8-oxa65	~300	Mild sedation, tranquilization
7,9-Dimethyl	Allyl	8-oxa65	>300	Deep sedation, tranquilization, hypnosis; potent
7,9-Dimethyl	3-Methoxypropyl	8-oxa65	>500	Mild sedation, tranquilization
7-Methyl-9-phenyl	Allyl	8-oxa65	~300	CNS stimulant, higher doses
H	Dimethylamino	55	>300	Local anesthesia, tranquilization
H	Morpholino	55	>200	Mild anesthesia, tranquilization
H	Dimethylamino	7-thia55	>200	Mild anesthesia
7,9-Dimethyl	Dimethylamino	8-oxa65	>300	Local anesthesia, sedation, tranquilization
9-*t*-Butyl	Dimethylamino	66	>200	Sedation, hypnosis
H	Dimethylamino	66	>300	Sedation, hypnosis, marked hypotension
H	Piperidino	75	>150	Mild sedation
H	Dimethylamino	10-6[d]	>150	Sedation, hypnosis
		Bases		
H	Methyl	66·HCl	>100	CNS stimulation
H	Methyl	66·MeI	>125	CNS stimulation, gangliophlegic
H	Methyl	10-6·HCl	>100	CNS stimulation
H	Methyl	10-6·MeI	200	CNS stimulation, gangliophlegic
H	Methyl	55·HCl	>125	CNS stimulation, epileptiform convulsions
9-Methyl	Methyl	66·HCl	>100	CNS stimulation
9-Methyl	Methyl	66·MeI	~125	CNS stimulation, gangliophlegic
H	Decyl	65·HCl	200	CNS stimulation
H	Decyl	65·MeI	25	CNS stimulation, gangliophlegic
H	Allyl	55·HCl	~75	CNS stimulation
H	Allyl	55·MeI	75	CNS stimulation
H	Dimethylamino	66·HCl	~150	CNS stimulation, higher doses loss of equilibrium

[a] The numbers in this column refer to the total number of atoms contained in rings A and B considered separately for convenience of designation. [b] Approximate LD_{50}/72 hr. were determined by administration of the compounds intraperitoneally to Wistar rats in the weight range 100–200 g. Both sexes were employed. [c] Those drugs which showed a sufficiently interesting activity profile in the preliminary screening procedures were studied in greater detail in the dog or the rabbit. Effects on the blood pressure, EKG, respiratory rate, and excursion were determined with a Sanborn Model 64, 4-channel, recording "Polyviso" apparatus. This apparatus provided high fidelity, rectilinear response, and permanent records by means of hot wire styli on a knife edge. Blood pressure was measured by means of a Statham, P-32, strain gage transducer pickup which supplied its signal to a strain gage amplifier. The EKG leads supplied a preamplifier that fed a d.c. amplifier which drove the recording styli. This setup permitted simultaneous obtention (measurement and recording) of arterial and venous pressures, EKG, heart rate, pneumogram, and pneumotachygram. It was used not only in determining the effects of new compounds on measurable cardiovascular parameters, respiratory rate, and excursion; but also in comparing with and ascertaining potentiation or antagonism of reference agents (epinephrine, norepinephrine, serotonin, acetylcholine, D-amphetamine, pentylenetetrazole), hexobarbital sodium, diphenylhydantoin, trimethadione, and histamine. These determinations were made by Dr. Eugene P. Rubacky and assistants. [d] 2-Decalin-4′-piperidine.

Hydrochloride was formed by bubbling gaseous hydrogen chloride through an ether solution of the base, m.p. 180–182°. Recrystallization from acetone–ether, m.p. 182–183°.

Methiodide was formed by refluxing the imide in acetone with a 10% excess of methyl iodide and adding ether, m.p. 149–150°, not changed on recrystallization from methylene chloride–ether.

2-(3-Picolyl)-2-azaspiro[4.4]nonane.—The dione (20 g., 0.082 mole) was dissolved in a large volume of ether (about 500 ml.) and added over 15 min. to a rapidly stirred solution of 15 g. of lithium aluminum hydride in 500 ml. of ether. The mixture was stirred for 4 hr., while protected from atmospheric moisture, and the complex then decomposed by the dropwise addition of water and stirred an additional 4 hr. The inorganic precipitate was filtered, the residue pressed tightly, and washed with ether. The ether filtrate and washings were dried overnight over anhydrous sodium sulfate, the ether evaporated, and the residue distilled to yield 16 g. (90%) of the title base, b.p. 90–92° (0.1 mm.).

A solution of 10 g. of the base in ether was saturated with gaseous hydrogen chloride to give the **dichloride,** m.p. 237–239°.

The melting point was raised to 238–240° on recrystallization from ethanol–ether.

Refluxing the base in ethyl acetate with a 10% excess of methyl iodide and cooling gave the partly-crystalline partly-tacky **dimethiodide,** m.p. 165–180°. Recrystallization from methylene chloride–ether raised the melting point to 180–182°.

2-(*o*-Chlorobenzyl)-8-*tert*-butyl-2-azaspiro[4.5]decane-1,3-dione.—Heating 13.5 g., (0.06 mole) of 4-*tert*-butylcyclohexane-1-carboxy-1-acetic anhydride with 10 g. (0.07 mole) of *o*-chlorobenzylamine for 0.5 hr. at 180° and then raising the temperature to 240° over a period of 20 min. gave a quantitative yield of the imide, m.p. 140–145°. Recrystallization from acetone–water gave m.p. 147–148°.

2-(*o*-Chlorobenzyl)-8-*tert*-butyl-2-azaspiro[4.5]decane.—The imide (20 g.) was dissolved in 50 ml. of benzene and added over a 15 min. period to a stirred solution of 15 g. of lithium aluminum hydride in 500 ml. of absolute ether, stirred 4 hr., decomposed with water, stirred 4 hr., filtered, and the residue washed with ether. The filtrate and washings were dried over anhydrous sodium sulfate. The ether and benzene were distilled and the residual oil was distilled *in vacuo* to give the title compound (18 g., 94%), b.p. 140–144° (0.04 mm.).

Ten grams of the base was dissolved in absolute ether and HCl gas bubbled in to give 10 g. of the **hydrochloride,** m.p. 192–198 , which on recrystallization from acetone–petroleum ether (30–60°) melted at 196–197°.

Refluxing 5 g. of the base with a 10% molar excess of methyl iodide in ethyl acetate for 30 min. and cooling gave the **methiodide,** m.p. 190–193°, which on recrystallization from acetone–ether melted at 196–197°.

2-Propyl-2-azaspiro[4.4]nonane-1,3-dione.—Cyclopentane-1-carboxy-1-acetic anhydride (15 g., 0.1 mole) was dissolved in 50 ml. of anhydrous methylene chloride and 0.2 mole of *n*-propylamine added. The mixture was refluxed for 15 min. and the solvent and excess propylamine distilled. The residue was heated in the oil bath at 160–180° for 1 hr. and then distilled to give the title compound (18.7 g., 91%), b.p. 66–68° (0.1 mm.).

2-Dimethylamino-2-azaspiro[4.7]dodecane-1,3-dione.—Cyclooctane-1-carboxy-1-acetic anhydride (12 g., 0.061 mole) was dissolved in 50 ml. of anhydrous methylene chloride and 0.12 mole of *unsym*-dimethylhydrazine added. The mixture was refluxed for 20 min., the solvent and excess *unsym*-dimethylhydrazine distilled, and the residue distilled *in vacuo* to give the product (14.3 g., 98%), b.p. 108–112° (0.15 mm.).

2-Morpholino-2-azaspiro[4.4]nonane-1,3-dione.—Cyclopentane-1-carboxy-1-acetic anhydride (4.9 g., 0.032 mole) and 3.3 g. (0.032 mole) of 4-aminomorpholine were heated in 10 ml. of benzene for 20 min. and then placed in an oil bath. As the temperature rose to 180° the benzene distilled and the residue was maintained at 160–190° for 0.5 hr. On cooling, the mass solidified to give a quantitative yield of the imide, m.p. 147–153°. Recrystallization from acetone–petroleum ether (30–60°) or water gave m.p. 151–152°. This derivative was less soluble than the corresponding dimethylamino compound of the same ring system. However, it was slightly soluble in cold water and in cold 30–60° petroleum ether.

2-Dibutylamino-7-methyl-2-azaspiro[4.4]nonane-1,3-dione.—3-Methylcyclopentane-1-carboxy-1-acetic anhydride, (8.1 g., 0.048 mole) was mixed with *unsym*-di-*n*-butylhydrazine (6.9 g., 0.048 mole) in 25 ml. of methylene chloride, refluxed 0.5 hr., and the methylene chloride distilled. The residue was heated to 160–180° for 1 hr. and then distilled to yield the title compound (12 g., 85%), b.p. 130–135° (0.2 mm.).

2-Dimethylamino-2-azaspiro[4.4]nonane-1,3-dione.—Cyclopentane-1-carboxy-1-acetic anhydride (15.4 g., 0.1 mole) was dissolved in 50 ml. of methylene chloride and 12 g. (0.12 mole) of *unsym*-dimethylhydrazine, dissolved in 25 ml. of methylene chloride, added. The mixture was refluxed for 15 min. and the methylene chloride distilled. The residue was heated in the oil bath for 40 min. at 180° and distilled *in vacuo*. The title compound, b.p. 89–91° (0.1 mm.) was obtained in 97% yield (19 g.). It solidified in the receiver and melted at 54–55°. The material was very soluble in acetone, ethanol, ethyl acetate, and methanol; soluble in water and ether. It crystallized in long needles from ligroin, m.p. 55–56°.

If a solution of 3 g. of the imide in ether was added to a saturated solution of HCl in ether, the immediate separation of the **hydrochloride** as a gummy precipitate resulted. The gummy material solidified and melted at 82–86°. On recrystallization from ethyl acetate, it melted at 84–87°.

Anal. Calcd. for $C_{10}H_{17}ClN_2O_2$: Cl, 15.24. Found: Cl, 14.63 (immediately after recrystallization and drying with ether and an air stream); Cl, 10.9 (after 48 hr. in a closed vessel).

On drying *in vacuo* the material rapidly disappeared from the bottom of the flask and sublimate appeared on the walls of the vessel. The sublimate contained no chlorine and melted at 55–56°, not depressed on admixture with the original imide. On drying in an air oven overnight at 80°, no chlorine was found in the remaining product, which proved to be the original imide. From these observations, it is concluded that the imide, 2-dimethylamino-2-azaspiro[4.4]nonane-1,3-dione, forms an unstable hydrochloride salt which gradually loses hydrogen chloride and reverts to the original imide.

3-Dimethylamino-3-azaspiro[5.5]undecane-2,4-dione.—Reaction of *unsym*-dimethylhydrazine with the anhydride of cyclohexane-1,1-diacetic acid, as described for the preceding 2-azaspiro[4.4]nonane derivative, gave the corresponding title compound, b.p. 123° (0.1 mm.) or 117° (0.075 mm.), m.p. 118–120°. Recrystallization from water gave analytical material, m.p. 118.5–119.5°. This imide likewise formed an unstable hydrochloride salt.

3-Dimethylamino-3-azaspiro[5.5]undecane.—Reduction of 20 g. of 3-dimethylamino-3-azaspiro[5.5]undecane-2,4-dione with 15 g. of lithium aluminum hydride in the usual manner gave the title base, b.p. 73–75° (0.4 mm.). When this base was dissolved in ether and gaseous HCl bubbled through the solution, the **hydrochloride** was obtained, m.p. 208–211°. Recrystallization from ethanol–ether gave analytical material, m.p. 210–211°.

Anal. Calcd. for $C_{12}H_{25}ClN_2$: Cl, 15.23; N, 12.03. Found: Cl, 15.05; N, 12.20.

3-Benzyl-3-azaspiro[5.5]undecane-2,4-dione.—Reaction of 0.1 molar quantities of cyclohexane-1,1-diacetic anhydride and benzylamine, cyclization at 180° for 1 hr., and heating to 240° for 15 min. gave the title imide in quantitative yield, m.p. 58–62°. Recrystallization from methanol–water gave analytically pure material, m.p. 62–63°. If the product is distilled *in vacuo*, one obtains a 96% yield of product, b.p. 150–155° (0.075 mm.).

3-Benzyl-3-azaspiro[5.5]undecane.—Reduction of the preceding imide with lithium aluminum hydride in the usual manner was accomplished by adding the imide, dissolved in benzene, to the metal hydride solution in ether. The product boiled at 100–106° (0.05 mm.). The **hydrochloride** was obtained by adding a slight excess of a saturated alcoholic–HCl solution to the base dissolved in ether. It melted at 261–263°, and at 262–263° on recrystallization from ethanol–ether.

3-Cyclohexylmethyl-3-azaspiro[5.5]undecane Hydrochloride.—When the preceding 3-benzyl-3-azaspiro[5.5]undecane hydrochloride was treated under catalytic hydrogenation conditions which might be expected to effect catalytic debenzylation, reduction of the phenyl ring took place instead. The hydrochloride (5 g.) was dissolved in 50% (v./v.) aqueous ethanol and 2 ml. of concentrated hydrochloric acid and 1 g. of platinum oxide catalyst were added. The mixture was hydrogenated in the low-pressure Parr hydrogenator overnight, filtered from catalyst, and the solvents removed in a rotary vacuum evaporator. The residue was dissolved in boiling ethanol, decolorized with Norit A, filtered, and cooled in the freezer. The white crystalline product obtained melted at 335° dec. (dependent on rate of heating and when put in the oil bath at 325°).

Anal. Calcd. for $C_{17}H_{32}ClN$: Cl, 12.40. Found: Cl, 12.28.

The infrared spectrum showed a complete lack of benzene unsaturation and any unsaturation whatever.