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Bicyclic Bases. IV.[1] Aryl Substituted Bridged Hydroisoindolines

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Maleimide has been condensed with 6,6-diphenylfulvene and several related arylfulvenes. The resulting adducts were alkylated on the imide nitrogen atom and then reduced with lithium aluminum hydride to give a series of aryl bridged hydroisoindolines. Although interesting central anticholinergic and antiedema activities were found for these compounds, a peculiar toxicity developed upon chronic administration in animals.

As part of a search for compounds that might possess antiinflammatory and central anticholinergic activity, we have prepared stereoisomers of 8-diphenylmethylene-2-methyl-tetrahydro-4,7-methanoisoindoline (IX and X) and a series of related compounds. The *exo*-form of this bridged hydroisoindoline is analogous in many respects to the antispasmodic orphenadrine which is reported[2] to have a pharmacological action resembling the central effects of atropine by producing an inhibitory action on cerebral motor areas.

Our first goal was to prepare the *endo*- and *exo*-isomers IX and X and to evaluate them pharmacologically.

Alder, Chambers and Trimborn[3] have reported on the diene condensation of diphenylfulvene (I) with maleic anhydride, acrylic acid, acrylonitrile and methyl vinyl ketone. These workers found that

(1) Part III, *J. Org. Chem.*, **26**, 4898 (1961).
(2) New and Nonofficial Drugs, 1961, J. B. Lippincott Co., Phila., Pa., p. 313; see also G. Cronheim, *J. Pharmacol. Exptl. Therap.*, **122**, 16A (1958).
(3) K. Alder, F. W. Chambers, and W. Trimborn, *Ann. Chem.*, **566**, 27 (1950).

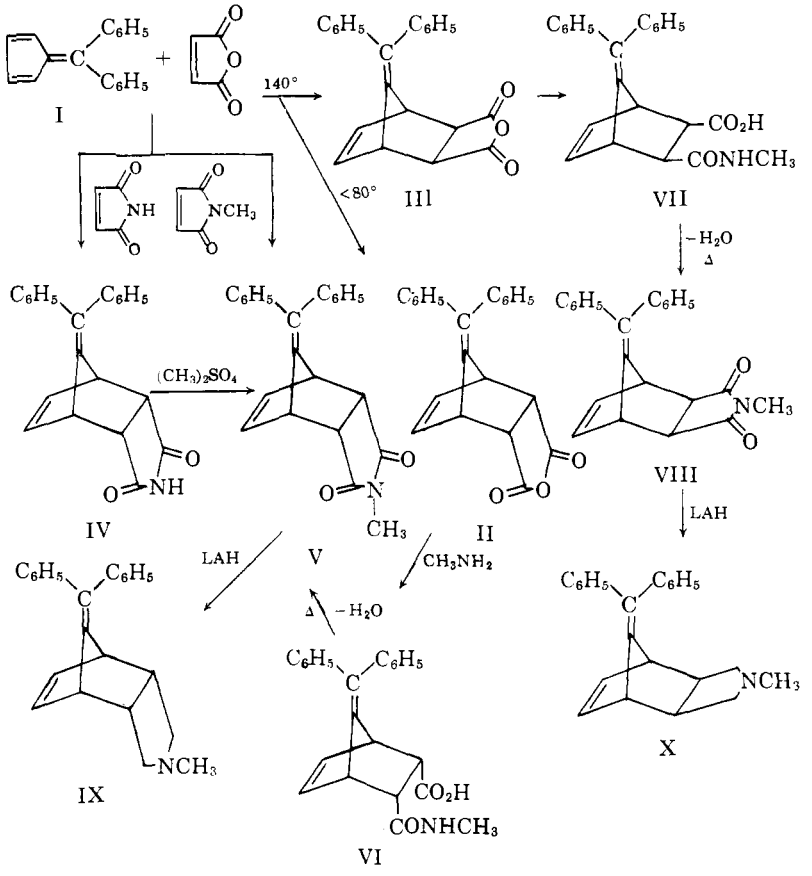
diphenylfulvene and maleic anhydride condensed at temperatures up to 80° to give predominantly the *endo*-adduct II while at higher temperature (refluxing xylene), a mixture of *endo*- and *exo*-products was obtained with the latter isomer (III) predominating. The structures were established by a series of reactions involving the double bonds and lactone formation of the diacids derived from the anhydrides.

We have condensed diphenylfulvene with maleimide and N-methylmaleimide. Only one stereoisomer was found in each case when the condensation was carried out at temperatures up to 80°. These adducts IV and V were inter-related by methylation of the maleimide adduct IV. The stereochemistry was proven by reaction of the known *endo*-anhydride II[3] with methylamine to give the amide acid VI with subsequent thermal cyclic dehydration to V. The best yields of V from thermal dehydration of VI were in the range of 40–50% when the reaction was carried out in refluxing toluene. The low yields apparently were due to a partial reversal of the Diels–Alder reaction at the temperatures necessary to effect ring closure. Attempts to dehydrate amide acid VI by chemical methods, *e.g.*, acetic anhydride or thionyl chloride in pyridine, were largely unsuccessful.

Entry into the *exo* series was obtained *via* the *exo*-maleic anhydride adduct III reported by Alder.[3] Rather than completely separate the mixture of adducts II and III obtained from the condensation of diphenylfulvene and maleic anhydride, we used a mixture, consisting largely of the *exo*-adduct III, and converted it to a mixture of amide acids VI and VII in which VII predominated. Thermal dehydration of this mixture in refluxing benzene selectively dehydrated the *exo*-amide acid VII to the *exo*-imide VIII. Proof for the homogeneity of imides V and VIII was obtained by paper strip chromatography.

Attempts to obtain the *exo*-N-methylimide VIII by the condensation of diphenylfulvene with N-methylmaleimide at 140° or by heating the *endo*-N-methylimide V at 140° were unsuccessful. Paper strip chromatographic analysis showed that a mixture of the *endo*- and *exo*-imides was obtained in both cases. However, alumina chromatography of the condensation product obtained at 140° led only to the isolation of a 40% yield of *endo*-adduct V. Apparently in the diene condensation of diphenylfulvene with N-methylmaleimide at an elevated temperature, considerably less of the *exo*-adduct is formed than with maleic anhydride under similar conditions.

The desired amines IX and X were readily obtained by lithium aluminum hydride reduction of the corresponding imides V and VIII. Bridged hydroisoindoline IX in pharmacological testing[4] was found



to be relatively more effective than atropine in inhibiting the tremor produced by Tremorine[5] (mice, I.P., ED_{50} 25 mg./kg.; 95% confidence limits 17–38 mg./kg.), compared to its ability to antagonize the action of acetylcholine on the rabbit ileum[6] (ED_{50} 570γ/100 ml.) The comparable figures for atropine are: anti-Tremorine, mice, I.P., ED_{50} 1.5 mg./kg. (0.83–27); anticholinergic ED_{50} 1.36 γ/100 ml. The ratio for anti-Tremorine/peripheral anticholinergic activity for compound IX is 417 while that for atropine is 16.7. This 25-fold difference in ratios suggests that the anticholinergic activity of compound IX is largely central in nature. Also, compound IX was

(4) We are indebted to our Department of Biological Research and in particular to Drs. A. P. Roszkowski and J. F. Gardocki and their co-workers for these pharmacological results.

(5) S. Y. P'an, R. Carioto, E. Timmens, and J. F. Gardocki, *Arch. inter. pharmacodynamie*, **120**, 222 (1959).

(6) L. C. Miller, T. J. Becker, and M. L. Tainter, *J. Pharmacol. Exptl. Therap.*, **92**, 260 (1948).

effective in an oral dose of 30 mg./kg. in causing a 30% inhibition of serotonin-induced rat paw edema[7] suggesting antiinflammatory activity. The *exo*-stereoisomer X was qualitatively similar to IX in these tests, but somewhat weaker in its actions.

These biological results encouraged us to expand the series. Variations of the tetrahydro-4,7-methanoisoindolines are presented in Table III. All of these compounds were prepared by lithium aluminum hydride reduction of the corresponding imides. The yields in this reduction were very good in most cases. The intermediate imides are listed in Table II. Imides without a substituent on the nitrogen atom were obtained by condensation of maleimide with the appropriate fulvene. These imides were then alkylated with either methyl sulfate, ethylene chlorohydrin or phenethyl bromide in the presence of alkali. The phenethylimide XXVII was also obtained by reaction of anhydride II with phenethylamine followed by dehydration of the resulting amide acid. However, the yield of XXVII by alkylation of imide IV with phenethyl bromide was far superior.

For the preparation of the requisite fulvenes, the Thiele method[8] was found to be most satisfactory. In the case of diphenylfulvene, a modification of the procedure of Wagner and Hunt[9] using a 75% excess of cyclopentadiene consistently gave 80% yields of pure crystalline fulvene from benzophenone. The other two known fulvenes 6,6-dimethyl[10] and 6-methyl-6-phenylfulvene[8] were prepared satisfactorily by the known methods. From *p*-chlorobenzophenone and cyclopentadiene, a good yield (70%) of crystalline fulvene XI was obtained. However, *m*-trifluoromethylbenzophenone failed to give a crystalline fulvene and so the crude reaction product was condensed with maleimide. With *o*-methylbenzophenone, the Wagner and Hunt procedure using sodium ethoxide failed. The use of potassium *t*-butoxide under reflux for several days led to a modest yield (40% as judged by ultraviolet absorption) of crude, non-crystalline 6-phenyl-6-*o*-tolylfulvene (XIII). With cyclopentadiene and sodium ethoxide, 2-benzoylpyridine gave a mixture which after reaction with maleimide led to a modest yield of the desired imide XXX.[11] A summary of the fulvene preparations is given in Table I.

Hydrogenation of the imide V was carried out in tetrahydrofuran

(7) L. O. Randall, J. J. Selitto, and J. Valdes, *Arch. inter. pharmacodynamie*, **113**, 233 (1957); see also E. P. Benditt and D. A. Rowley, *Science*, **123**, 24 (1954).

(8) J. Thiele, *Ber.*, **33**, 666 (1900); see J. H. Day, *Chem. Rev.*, **53**, 167 (1953).

(9) E. C. Wagner and W. C. Hunt, *J. Chem. Educ.*, **28**, 309 (1951).

(10) D. Craig, J. J. Shipman, J. Kiehl, F. Widmer, R. Fowler, and A. Hawthorne, *J. Am. Chem. Soc.*, **76**, 4573 (1954).

(11) The nature of the other products from this reaction is the subject of a separate investigation and will be reported elsewhere.

over palladium catalyst to reduce the ring double bond selectively. In ethanol solution with the same catalyst, both double bonds were reduced. Both the dihydro- and tetrahydroimides (XLII and XLIV, respectively) were reduced to the corresponding amines (XLIII and XLV) with lithium aluminum hydride. These compounds are listed in Table IV along with other miscellaneous compounds such as the lithium aluminum hydride reduction product XLVI of amide acid VI and the methiodide XLVII of amine IX.

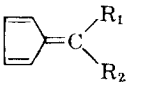
Very recently, two reports have appeared[12] on the investigation of compounds resulting from the Diels–Alder reaction of various fulvenes and maleimides as possible pyrethrum synergists. Several points of overlapping work are noted in Tables II and III. The Czech workers report[12b] no evidence for the formation of *exo*-isomers in the condensation of diphenylfulvene with various maleimides even at elevated temperatures. These results are in contrast to our findings. Also, Furdik and Sutoris[12b] were unable to form *exo*-imides by cyclodehydration of *exo*-amide acids. Since we were able to dehydrate *exo*-amide acid VII to *exo*-imide VIII without difficulty, we cannot agree with their statement that "the production of *exo*-isomers by diene synthesis, starting with diphenylfulvene and an N-substituted maleimide, is impossible due to factors of steric hindrance."

Further pharmacological testing[4] showed that many of the compounds of Table III possessed both peripheral and central anticholinergic activity. Compound XXXV was particularly noteworthy for its anti-Tremorine activity,[5] showing an ED_{50} of 13.5 mg./kg. (mice, I.P., 95% confidence limits 9.2–19.8 mg./kg.). Also, about half of the hydroisoindolines were able to block serotonin induced edema in the rat paw, although none was more active than compound IX.

Subacute toxicity tests in rats and dogs in preparation for trial in man revealed that a peculiar gastrointestinal hemorrhage was produced by compounds IX and XXXV. The effect was dose dependent and could be detected in dogs at doses as low as 10 mg./kg./day orally after several weeks. Autopsy revealed echymotic hemorrhage in the stomach and longitudinal hemorrhagic streaks along the mucosa of the remainder of the gastrointestinal tract. All other physiology was normal including that of the blood.

Acknowledgment.—We are indebted to Mrs. Mary C. Christie for many of the analyses and spectra and to the United States Rubber Co. for a generous gift of maleimide.

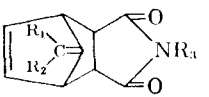
(12a) M. Furdik and V. Sutoris, *Chem. Zvesti*, **14**, 564 (1960); (b) **15**, 173 (1961).

TABLE I: 6,6-DISUBSTITUTED FULVENES 

Cpd.	R_1	R_2	M.p., °C. or B.p., °C.	(Mm.)	Ultraviolet spectrum[a] MeOH λ_{max} mμ	(ε)	Yield, %	Description
I	C_6H_5	C_6H_5	78–81		323	20,200	90	Red crystals
XI	C_6H_5	*p*-ClC_6H_4	73–74		324	18,400	72	Red crystals[b]
XII	C_6H_5	*m*-$CF_3C_6H_4$	[c]		319	14,000	76[d]	Red oil
XIII	C_6H_5	*o*-$CH_3C_6H_4$	[c]		313	11,670	40[d]	Red oil
XIV	C_6H_5	CH_3	90–108	2.5[e]	287	16,640	62	Red oil
XV	CH_3	CH_3	52–55	15[f]	265	14,700	49	Yellow oil n_D^{23} 1.5421
XVI	C_6H_5	2-C_5H_4N	[c]		324	12,200	25[g]	Red oil

[a] A maximum at 237–245 mμ (ε 13–14,000) is also present in compounds I, XI, XII and XIII. [b] Calcd. for $C_{18}H_{13}Cl$: C, 81.65; H, 4.95. Found: C, 81.87; H, 4.81. [c] Not isolated in pure state. [d] Yield is based on ultraviolet absorption of isolated crude product. [e] Lit. b.p. 130.5° (10.5 mm.).[8] [f] Lit. b.p. 76.8° (50 mm.); n_D^{25} 1.5441.[10] [g] Based on the yield of reaction product with maleimide.

TABLE II

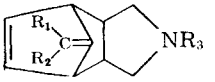
7-R_1,R_2-METHYLENE-N-R_3-5-NORBORNENE-2,3-DICARBOXIMIDES[a] 

Cpd.	R_1	R_2	R_3	M.p., °C.	λ_{max}^{MeOH} mμ	(ε)	Yield, %	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
IV	C_6H_5	C_6H_5	H	208–210[b]	247	17,200	80	$C_{22}H_{17}NO_2$	80.71	5.23	4.28	80.90	5.30	4.05
V	C_6H_5	C_6H_5	CH_3	176–177.5[c]	245	17,670	78	$C_{23}H_{19}NO_2$	80.91	5.61	4.10	80.81	5.79	4.31
VII	C_6H_5	C_6H_5	CH_3	152–160[d]	243	15,100	32.5	$C_{23}H_{19}NO_2$	80.91	5.61	4.10	80.53	5.67	4.02
XVII[e,f]	C_6H_5	C_6H_5	C_2H_5	118–121[g,h]	246	16,600	73.5	$C_{24}H_{21}NO_2$	81.10	5.96	3.91	80.97	6.01	3.35
XVIII[f]	C_6H_5	*p*-ClC_6H_4	H	208–211[i]	249	18,600	80	$C_{22}H_{16}ClNO_2$	73.02	4.46	3.87	73.15	4.47	3.80
XIX	C_6H_5	*p*-ClC_6H_4	CH_3	132–136[j]	248	18,900	94.6	$C_{23}H_{18}ClNO_2$	—	—	3.73	—	—	3.62
XX[f]	C_6H_5	*o*-$CH_3C_6H_4$	H	185–188.5[j]	244	15,400	55	$C_{23}H_{19}NO_2$	80.91	5.61	4.10	81.05	5.78	4.38
XXI	C_6H_5	*o*-$CH_3C_6H_4$	CH_3	161–162[k]	242	16,490	74	$C_{24}H_{21}NO_2$	—	—	3.94	—	—	3.82

XXII[f]	C_6H_6	*m*-$CF_3C_6H_4$	H	180–183[j]	244	17,700[l]	67.8	$C_{23}H_{16}F_3NO_2$	69.85	4.08	3.54	69.86	4.27	3.30
XXIII	C_6H_6	*m*-$CF_3C_6H_4$	CH_3	135–137[g]	245	17,900[m]	18.4	$C_{24}H_{18}F_3NO_2$	—	—	3.42	—	—	3.30
XXIV[f]	C_6H_5	CH_3	H	159–160[n]	238	11,200	71	$C_{17}H_{15}NO_2$	—	—	5.28	—	—	5.07
XXV	C_6H_5	CH_3	CH_3	170–172°	237	11,400	95	$C_{18}H_{17}NO_2$	77.39	6.13	5.01	77.23	6.31	4.72
XXVI	C_6H_5	C_6H_5	CH_2CH_2OH	171–172[p]	245	18,400	76	$C_{24}H_{21}NO_3$	77.60	5.70	3.77	77.72	5.75	3.50
XXVII	C_6H_5	C_6H_5	$CH_2CH_2C_6H_5$	174–176[q]	246	18,920	51.5	$C_{30}H_{25}NO_2$	83.50	5.84	3.25	83.37	6.04	3.54
XXVIII[r]	CH_3	CH_3	H	178–182[p], 195–200[q]	—	—	83	$C_{12}H_{13}NO_2$	70.91	6.45	6.89	70.91	6.49	6.71
XXIX	CH_3	CH_3	CH_3	142–143[s]	—	—	41	$C_{13}H_{15}NO_2$	—	—	6.45	—	—	6.33
XXX[f,t]	C_6H_5	2-C_5H_4N	H	224–226[u]	243	15,900	25	$(C_{21}H_{16}N_2O_2)_2 \cdot H_2O$	74.76[t]	5.08	8.30	74.90	4.82	8.22
XXXI	C_6H_5	2-C_5H_4N	CH_3	169–170[k]	245	18,100	69.5	$C_{22}H_{18}N_2O_2$	—	—	8.18	—	—	8.05

[a] Stereochemistry of all the compounds is *endo*, except for VII, which has the *exo*-configuration. [b] From ethyl acetate. [c] From diethyl ether: reported[12b] m.p. 1 83°. [d] From acetone–petroleum ether (30-60°). [e] From diphenylfulvene and N-ethylmaleimide. [f] Stereochemistry assigned by analogy. [g] From diethyl ether–petroleum ether. [h] Reported[12b] m.p. 118°. [i] From methylene chloride–ethyl acetate. [j] From methylene chloride–diethyl ether–petroleum ether. [k] From ethanol–water. [l] Also, λ_{max}^{MeOH} 227 mμ (ε 17,850). [m] Also, λ_{max}^{MeOH} 227 mμ (ε 18,400). [n] From benzene. [o] From benzene–hexene. [p] From methylene chloride–ether. [q] From MeOH [r] Stereocbemistry assigned from ref. 12a. [s] From isopropyl alcohol; reported ref. 12b, m.p. 145°. [t] Hemihydrate. [u] From $CHCl_3$.

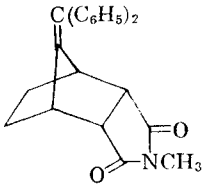
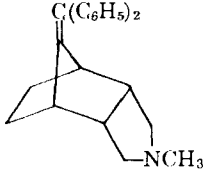
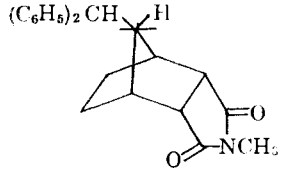
TABLE III: 8-R_1,R_2-METHYLENE-2-R_3-3a,4,7,7a-TETRAHYDRO-4,7-METHANOISOINDOLINES[a]

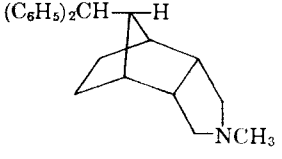
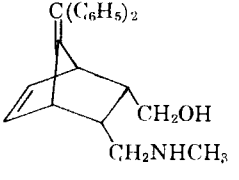
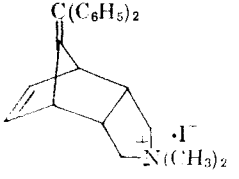


					λMeOH		Yield,		Calcd.			Found		
Cpd.	R_1	R_2	R_3	M.p., °C.	mμ	(ε)	%	Formula	C	H	N	C	H	N
XXXII[b]	C_6H_6	C_6H_6	H	186.5–190[c]	245	20,400	48	$C_{22}H_{21}N \cdot C_4H_4O_4$	75.16	6.07	3.37	74.95	6.02	3.34
IX	C_6H_6	C_6H_5	CH_3	74–77[d,e]	247	18,000	—	$C_{23}H_{23}N$	88.13	7.40	4.47	88.13	7.77	4.28
IX[f]	C_6H_6	C_6H_6	CH_3	203.5–205.5[g]	245	19,200	90.5	$C_{23}H_{23}N \cdot C_4H_4O_4$	75.50	6.34	3.26	75.35	6.16	3.33
X[f]	C_6H_5	C_6H_5	CH_3	176–178[g]	243	14,600	91.5	$C_{23}H_{23}N \cdot C_4H_4O_4$	75.50	6.34	3.26	75.47	6.36	2.96
XXXIII	C_6H_5	C_6H_5	C_2H_5	90.5–92.5[e,h]	245	18,150	72	$C_{24}H_{25}N$	75.82	6.59	4.28	75.52	6.54	4.26
XXXIV[b]	C_6H_5	*p*-ClC_6H_4	CH_3	160–161[i]	248	18,990	85	$C_{23}H_{22}ClN \cdot C_4H_4O_4$	69.89	5.67	3.02	70.08	5.69	3.01
XXXV[b]	C_6H_5	*o*-$CH_3C_6H_4$	CH_3	140.5–142[i]	242	17,280	69.5	$C_{24}H_{25}N \cdot C_4H_4O_4$	75.82	6.59	3.16	75.59	6.61	3.12
XXXVI[b]	C_6H_6	*m*-$CF_3C_6H_4$	CH_3	143–146[j]	247	15,900	58	$C_{24}H_{22}F_3N \cdot C_4H_4O_4$	67.59	5.27	2.82	67.88	5.26	2.67
XXXVII[f]	C_6H_6	CH_3	CH_3	164–165[j]	233	15,400	62	$C_{18}H_{21}N \cdot C_4H_4O_4$	71.91	6.86	3.81	71.62	7.00	3.76
XXXVIII[k]	C_6H_5	C_6H_5	CH_2CH_2OH	176–179[l]	247	19,700	60.5	$(C_{24}H_{25}NO)_2 \cdot C_4H_4O_4$	77.78	6.78	3.49	77.68	6.64	3.38
XXXIX[b]	C_6H_6	C_6H_6	$CH_2CH_2C_6H_6$	178–179[m]	247	19,200	48	$C_{30}H_{29}N \cdot C_4H_4O_4$	78.59	6.40	2.70	78.32	6.46	2.60
XL[b]	CH_3	CH_3	CH_3	144–149[i,n]	—	—	78	$C_{13}H_{19}N \cdot C_4H_4O_4$	66.86	7.59	4.59	66.87	7.65	4.50
XLI[f]	C_6H_6	2-C_5H_4N	CH_3	175–176[j]	240	18,700	46.5	$C_{22}H_{22}N_2 \cdot C_4H_4O_4$	72.54	6.09	6.51	72.44	6.17	6.47

[a] Stereochemistry of all the compounds is *endo*, except for X which has the *exo* configuration. [b] As hydrogen maleate. [c] From ethanol. [d] Reported, ref. 12b, $n^{20}D$ 1.6010. [e] From petroleum ether. [f] As hydrogen fumarate. [g] From methanol–ether. [h] Reported ref. 12b, m.p. 75°. [i] From acetone–ether. [j] From isopropyl alcohol–ether. [k] As fumarate salt. [l] From ethanol–ether. [m] From *n*-butyl alcohol. [n] Reported ref. 12a m.p. 38° for free base.

TABLE IV: MISCELLANEOUS COMPOUNDS

Compound no. →	XLII	XLIII[b]	XLIV
Structure			
M.p. °C	140–140.5[a]	191–192[c]	206.5–209[d]
λ_{max}^{MeOH}, mμ and ε	245 17,500	245 20,000	—
Yield, %	92	82	45
Formula	$C_{23}H_{21}NO_2$	$C_{23}H_{25}N \cdot C_4H_4O_4$	$C_{23}H_{23}NO_2$
Analyses, % C, Calcd., found	80.44 80.40	75.15 74.91	79.97 80.05
Analyses, % H, Calcd., found	6.16 6.23	6.77 6.80	6.71 6.74
Analyses, % N, Calcd., found	4.08 4.06	3.25 3.32	4.06 4.15

Compound no.	XLV[b]	XLVI[e]	XLVII
Structure			
M.p., °C.	238–239[c]	212–214[f]	261.5–262.5[c]
λ_{max}^{MeOH}, mμ and ε	—	247 16,750	245 16,700
Yield, %	93.5	26	86
Formula	$C_{23}H_{27}N \cdot C_4H_4O_4$	$(C_{23}H_{25}NO)_2 \cdot C_4H_4O_4$	$C_{24}H_{26}IN$
Analyses, % C, Calcd., found	74.80 74.70	77.09 77.17	63.30 63.29
Analyses, % H, Calcd., found	7.21 7.23	6.99 7.12	5.76 5.87
Analyses, % N, Calcd., found	3.23 3.06	3.90 3.80	3.07 3.10

[a] From ether–petr. ether. [b] As hydrogen fumarate. [c] From MeOH–ether. [d] From CH_2Cl_2–ether. [e] As fumarate. [f] From MeOH.

Experimental[13]

6-*p*-Chlorophenyl-6-phenylfulvene (XI).—To a sodium ethoxide solution, prepared by dissolving 2.3 g. (0.1 g.-atom) of sodium in 100 ml. of absolute ethanol, was added 21.67 g. (0.1 mole) of *p*-chlorobenzophenone and 50 ml. of absolute ethanol. The suspension was stirred in a warm water bath until the ketone was almost dissolved. A solution of 11.6 g. (0.175 mole) of freshly distilled cyclopentadiene was added rapidly under nitrogen, and the mixture was stirred at room temperature for 2 hr. Scratching the sides of the flask induced crystallization. After cooling the mixture in an ice-bath for 0.5 hr., the crystals were collected by filtration and air-dried to give 19.03 g. (72%) of product, m.p., 73–74°; λ_{max}^{KBr} 2.85, 3.24, 3.35-3.38, 6.25, 6.65, 6.86 μ.

Essentially this procedure was used to prepare fulvenes I, XII, XIV and XVI of Table I.

6-Phenyl-6-*o*-tolylfulvene (XIII).—Under nitrogen, 1.17 g. (0.03 g.-atom) of potassium was added to 120 ml. of dried *t*-butyl alcohol and dissolved by heating under reflux for 1 hr. A solution of 5.90 g. (0.03 mole) of *o*-methylbenzophenone in 10 ml. of *t*-butyl alcohol was added rapidly, then 4.45 ml. (0.054 mole) of freshly distilled cyclopentadiene. A white solid precipitated. The mixture was brought into solution by refluxing and was stirred under nitrogen at reflux for 66 hr. The dark brown solution was diluted with water and extracted twice with ether. The ether extracts were washed with water and dried over magnesium sulfate. Concentration gave 5.89 g. of crude material; λ_{max}^{neat} 3.20, 3.24, 3.30, 5.95, 6.20, 6.30, 6.66, 6.75, 6.86 μ; $\lambda_{max}^{CH_3OH}$ 237 mμ (ϵ 10,660), 313 mμ (ϵ 11,670).

***endo*-7-Diphenylmethylene-5-norbornene-2,3-dicarboximide (IV).**—The condensation of 48 g. (0.208 mole) of diphenylfulvene (I) and 20 g. (0.208 mole) of maleimide was carried out at reflux in 500 ml. of benzene. The solution, red at the onset, turned golden after refluxing for 1.5 hr. Crystals were obtained after cooling, scratching, and diluting with petroleum ether. The product was filtered and air-dried, affording 54.6 g. (80%) of IV, m.p. 202–212° dec. An analytical sample was prepared by recrystallization first from acetone and then from ethyl acetate, m.p. 208–210°; λ_{max}^{KBr} 3.15, 3.25, 5.64, 5.86, 6.24, 6.69, 6.91, 7.39 μ.

Imides XVIII, XX, XXII, XXIV, XXVIII and XXX of Table II were prepared by this procedure.

***endo*-7-Diphenylmethylene-N-methyl-5-norbornene-2,3-dicarboximide (V).**—To a solution of 5.2 g. of 85% potassium hydroxide in 150 ml. of water and 250 ml. of 95% ethanol was added 23.6 g. (0.072 mole) of IV. To the resultant clear solution was added dropwise with stirring 9.95 g. (0.079 mole) of dimethyl sulfate. Crystallization began within 2 min. The thick mixture was stirred for 2 hr. at room temperature and then heated under reflux for 2 hr. with the addition of about 200 ml. of ethanol to afford solution.

The ethanol was removed *in vacuo*. The mixture was cooled and the solid filtered, washed with water, and dried in the steam oven. There was obtained 24.5 g. of V, m.p. 166–171° dec. This sample was recrystallized from ether, affording 19.7 g. (78%) of material, m.p. 176–177.5° dec.; λ_{max}^{KBr} 3.29, 3.38, 5.60, 5.85, 6.24, 6.33, 6.68, 6.73, 6.89, 6.96, 7.23 μ.[14]

(13) Melting points are corrected. Infrared spectra were determined with a Perkin Elmer Model 21 and ultraviolet spectra in methanol solution with a Cary Model 14 spectrometer.

(14) Paper chromatography of the *endo*-imide V and the *exo*-imide VIII showed R_f values of 0.8 and 0.67, respectively. The compounds were spotted on Whatman no. 1 paper which was then wet with formamide. The chromatograms were run in heptane saturated with formamide by the descending technique for 3 to 6 hr.

The methylated imides XIX, XXI, XXIII, XXV, XXIX and XXXI of Table II were prepared by this method.

***endo*-7-Diphenylmethylene-5-norbornene-2,3-dicarboxylic Anhydride (II).**[3]—Diphenylfulvene (I) (2.30 g., 0.01 mole) was combined with 0.98 g. (0.01 mole) of maleic anhydride in 10 ml. of benzene and allowed to stand for 3.5 days at room temperature. The thick slurry of crystals then was filtered, washed with benzene and ether and air-dried, affording 2.54 g. (79.5%) of II, m.p. 163–167°. A sample was recrystallized twice, once from ethyl acetate and once from methylene chloride-ether, affording crystals melting at 165–168°. The literature[3] melting point for the compound is 174°.

7-Diphenylmethylene-*endo*-2-methylcarbamoyl-5-norbornene-*endo*-3-carboxylic acid (VI).—Condensed methylamine (5 ml., 0.11 mole) in 50 ml. of chilled methanol was added to 300 ml. of methanol chilled in a Dry-Ice-acetone bath. Then 31 g. (0.096 mole) of II was added in small portions. The mixture, which turned creamy white, was allowed to come to room temperature. The product was removed by filtration, washed with ether and dried, giving 18.5 g. (56%) of VI, m.p. 157–159°. After one recrystallization from methanol-ethyl acetate, the product melted at 157.5–158.5°; λ_{max}^{KBr} 2.97, 3.3, 5.83, 6.1, 6.25, 6.37, 6.68, 6.90 μ; $\lambda_{max}^{CH_3OH}$ 247 mμ (ϵ 17,800).

Anal. Calcd. for $C_{23}H_{25}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.68; H, 6.04; N, 3.86.

Thermal Ring Closure of 7-Diphenylmethylene-*endo*-2-methylcarbamoyl-5-norbornene-*endo*-3-carboxylic Acid (VI) to Give *endo*-Diphenylmethylene-N-methyl-5-norbornene-2,3-dicarboximide (V).—A suspension of approximately 120 g. of crude VI in 2 l. of toluene was brought into solution by adding 800 ml. of isopropyl alcohol. The alcohol was removed by azeotropic distillation and then most of the toluene was removed slowly by distillation at atmospheric pressure for 4.5 hr. The solution was concentrated to dryness *in vacuo*, diluted with methylene chloride and the product was crystallized by dilution with ether–petroleum ether. A yield of 91.8 g. of crude crystalline product was obtained. Recrystallization from methylene chloride–ether gave 55.1 g. (48.6% yield based on anhydride (II) of V, m.p. 173–175.5°; λ_{max}^{KBr} 2.91, 3.31, 3.40, 5.61, 5.90, 6.25, 6.35, 6.69, 6.75, 6.91, 6.98, 7.24 μ.

***exo*-7-Diphenylmethylene-5-norbornene-2,3-dicarboxylic Anhydride (III).**[3]—To a refluxing solution of 19.6 g. (0.2 mole) of maleic anhydride in 300 ml. of dry xylene was added a solution of 46.0 g. (0.2 mole) of diphenylfulvene in 360 ml. of xylene. The solution was refluxed for 5 hr. and then concentrated to dryness *in vacuo*. The product was crystallized from methylene chloride–ether, filtered and air-dried, affording a mixture of II and III, m.p. 137–150°. By repeated fractional crystallization from methylene chloride–ether, the mixture was separated into two batches: 17.7 g. (23.4%) enriched in *endo*-adduct II, m.p. 143–150°, and 31.4 g. (41.5%) enriched in *exo*-adduct III, m.p. 139–143°. The literature[3] melting point for the *exo*-anhydride is 147–148°.

7-Diphenylmethylene-*exo*-2-methylcarbamoyl-5-norbornene-*exo*-3-carboxylic Acid (VII) and *exo*-7-Diphenylmethylene-N-methyl-5-norbornene-2,3-dicarboximide (VIII).—To a solution of 4.7 ml. (0.1056 mole) of methylamine in 350 ml. of methanol, chilled in a Dry-Ice-acetone bath, was added with stirring 31.4 g. (0.096 mole) of *exo*-enriched anhydride III. After the addition was complete, the bath was removed and the mixture was allowed to come to room temperature. The solution was concentrated to dryness *in vacuo*. The crude crystalline prod-

uct was slurried in dil. hydrochloric acid and extracted with methylene chloride. The extracts were combined, concentrated *in vacuo* and dried by the addition and distillation of benzene. The product, a mixture of VI and VII, was dissolved in 400 ml. of benzene and 100 ml. of absolute ethanol. The solution was boiled for 2.5 hr., during which time 150 ml. of solvent was distilled. The solution was then concentrated to dryness *in vacuo*. The product was dissolved in methylene chloride and washed twice with 0.1 *N* potassium hydroxide. The organic solution was dried over magnesium sulfate, filtered and concentrated to dryness *in vacuo*, affording 26.7 g. of crude VIII. After one recrystallization from methylene chloride–ether and one from acetone–petroleum ether, 10.6 g. of *exo*-imide VIII was obtained,[14] m.p. 152–160°; λ_{max}^{KBr} 5.65, 5.90, 6.25, 6.69, 6.97, 7.25 μ.

***endo*-7-Diphenylmethylene-N-ethyl-5-norbornene-2,3-dicarboximide (XVII).**—A 15-g. sample (0.065 mole) of diphenylfulvene and an 8.2-g. sample (0.065 mole) of N-ethylmaleimide were combined and dissolved in 65 ml. of benzene and allowed to stand at room temperature for 3.5 days. The benzene was then removed *in vacuo* and a quantitative yield of crystalline material was obtained from ether-petroleum ether. After two recrystallizations from ether-petroleum ether, 17.1 g. (73.5%) of XVII was obtained as crystalline plates, m.p. 118–121°; $\lambda_{max}^{CHCl_3}$ 5.65, 5.92, 6.25 (w), 6.70 (w), 6.92, 7.15, 7.25 μ.

***endo*-7-Diphenylmethylene-N-β-hydroxyethyl-5-norbornene-2,3-dicarboximide (XXVI).**—To 15 g. (0.046 mole) of *endo*-7-diphenylmethylene-5-norbornene-2,3-dicarboximide (IV), almost completely dissolved in a mixture of 350 ml. of hot ethanol and 100 ml. of water containing 3.1 g. (0.055 mole) of potassium hydroxide, was added 4.1 g. (0.0506 mole) of ethylene chlorohydrin. The solution was refluxed for 1 hr. and then treated three more times with 3.1 g. of potassium hydroxide in water and 4.1 g. of ethylene chlorohydrin. The treatments were separated by approximately 1 hr. of refluxing. The resultant solution was concentrated *in vacuo* to remove ethanol. The aqueous mixture was extracted with methylene chloride. The extracts were washed once with water, dried over magnesium sulfate, filtered and concentrated to dryness *in vacuo*. A first crop of 11.2 g. of crystals, m.p. 170.5–172°, was obtained from ether. Treatment of the mother liquor with petroleum ether afforded a second crop of 1.9 g., m.p. 167–169°. The total crude yield amounted to 13.1 g. (76%). After one recrystallization from methylene chloride–ether, pure XXVI was obtained, m.p. 171–172° dec.; λ_{max}^{KBr} 2.85, 3.35, 5.64, 5.92, 6.23, 6.67, 6.90, 7.16, 7.50 μ.

***endo*-7-Diphenylmethylene-N-β-phenethyl-5-norbornene-2,3-dicarboximide (XXVII).**—A 2.5-g. sample (0.0076 mole) of *endo*-7-diphenylmethylene-5-norbornene-2,3-dicarboximide (IV) was added to a solution of 0.54 g. (0.0082 mole) of potassium hydroxide in 15 ml. of water and 30 ml. of ethanol. When all the imide was in solution, 1.53 g. (0.0082 mole) of phenethyl bromide was added. The solution was stirred overnight at room temperature during which time crystals separated. The crystals were removed by filtration, washed with water and dried: 0.3 g. (10%), m.p. 169.5–172°. Potassium hydroxide pellets (0.27 g., 0.0041 mole) and phenethyl bromide (0.77 g., 0.0041 mole) were added to the filtrate which was then heated under reflux for 2.5 hr. The solution was concentrated *in vacuo* to one-half the volume. The crystalline product was filtered and dried, giving 1.33 g. (41.5%), m.p. 166–168°. The two crops were combined and recrystallized from methanol giving 1.5 g. (47%) of XXVII, m.p. 174–176°; $\lambda_{max}^{CHCl_3}$ 5.63, 5.88, 6.2, 6.65–6.73, 6.92–6.95 μ.

7-Diphenylmethylene-*endo*-3-β-phenethylcarbamoyl-5-norbornene-*endo*-2-car-

boxylic acid.—To a solution of 1.27 g. (0.0105 mole) of phenethylamine in 50 ml. of tetrahydrofuran was added 3.28 g. (0.01 mole) of *endo*-7-diphenylmethylene-5-norbornene-2,3-dicarboxylic anhydride (II).[3] The solution turned yellow upon stirring at room temperature for 1 hr. It was then concentrated to dryness *in vacuo*. The residue was slurried in ether, filtered, washed several times with ether and dried to give 4.0 g. (81%) of the *endo*-amide acid, m.p. 131–133°; λ_{max}^{KBr} 2.95, 3.25, 3.35, shl. 5.70, 5.76, 6.0, 6.2, 6.45, 6.65, 6.88 μ; $\lambda_{max}^{CH_3OH}$ 247 mμ (ϵ 17,950).

Anal. Calcd. for $C_{30}H_{27}NO_3$: C, 80.15; H, 6.05; N, 3.12. Found: C, 80.36; H, 6.18; N, 3.10.

***endo*-7-Diphenylmethylene-N-β-phenethyl-5-norbornene-2,3-dicarboximide (XXVII).**—A 2.0-g. sample (0.0045 mole) of 7-diphenylmethylene-*endo*-3-β-phenethylcarbamoyl-5-norbornene-*endo*-2-carboxylic acid was refluxed in toluene for 5 hr. The clear solution turned deep orange-red during the first 15 min. of heating. The toluene was removed *in vacuo*. The residue was dissolved in methylene chloride and washed with aqueous sodium hydroxide. The organic layer was dried and concentrated *in vacuo* to yield 1.7 g. of a red oil. Chromatography over 30 g. of acid-washed alumina gave 0.34 g. of XXVII, eluted with 2:3 ether–petroleum ether. This material, melting at 171–174°, showed $\lambda_{max}^{CH_3OH}$ 247 mμ (ϵ 17,500) and was identical with the sample described above by mixed melting point and infrared spectrum.

***endo*-8-Diphenylmethylene-3a,4,7,7a-tetrahydro-2-methyl-4,7-methanoisoindoline (IX).**—To a slurry of 9.5 g. (0.25 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether was added rapidly, dropwise and with stirring, a solution of 17.5 g. (0.0514 mole) of *endo*-7-diphenylmethylene-N-methyl-5-norbornene-2,3-dicarboximide (V) in 1500 ml. of ether. The mixture was refluxed for 2.5 hr. and allowed to stand at room temperature for 16 hr. The reduction mixture was hydrolyzed carefully by the addition of 50 ml. of ethyl acetate and 20 ml. of water, stirred for 3 hr. and then filtered. The inorganic solids were washed well with ether. The filtrate was dried over magnesium sulfate, filtered and concentrated to dryness *in vacuo*, affording 15.8 g. (98%) of IX as an oil which showed no carbonyl absorption in the infrared spectrum. The base was crystallized from petroleum ether giving IX, m.p. 74–77°; λ_{max}^{KBr} 3.40, 3.60, 5.99, 6.25, 6.69, 6.78, 6.91, 7.05 μ.

The **fumarate** of IX was prepared by adding a solution of 4.8 g. (0.05 mole) of fumaric acid in methanol to a solution of 15.8 g. of IX in methanol. Dilution with ether and scratching afforded a white crystalline salt which was filtered, washed with ether and air-dried to give 18.9 g. (90.5%) of IX fumarate, m.p. 203.5–205.5° dec.; λ_{max}^{KBr} 3.29, 3.37, 4.05, 5.25, 5.85, 6.25, 6.66, 6.80, 6.90 μ.

The **maleate** salt was prepared by adding a solution of 23.2 g. (0.2 mole) of maleic acid in 250 ml. of isopropyl alcohol to a solution of 60.5 g. (0.195 mole) of crude IX in 150 ml. of isopropyl alcohol. The solution was diluted with *ca.* 1 l. of anhydrous ether. After crystallization was completed, the material was collected by filtration, washed three times with ether and dried *in vacuo* over calcium chloride. The yield was 55.7 g., m.p. 136–137.5°. A recrystallized sample, m.p. 136–139°, showed λ_{max}^{KBr} 3.35–3.42, 4.05, 5.90 (w.), shl. 6.18, 6.34, 6.70–6.90 μ; $\lambda_{max}^{CH_3OH}$ 245 mμ (ϵ 18,400).

Anal. Calcd. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.76; H, 6.51; N, 3.20, 3.25.

The **hydrochloride** was prepared by adding an ethereal solution of anhydrous hydrogen chloride to an ethereal solution of IX. The salt, m.p. 258–262° dec.,

showed λ_{max}^{KBr} 2.93, 3.40, 4.0 (br.), 6.25 (w.), 6.69, 6.91 μ; $\lambda_{max}^{CH_3OH}$ 245 mμ (ϵ 15,000); $\lambda_{shl}^{CH_3OH}$ 223 mμ (ϵ 13,100).

Anal. Calcd. for $C_{23}H_{24}ClN$: N, 4.00. Found: N, 3.90.

All of the amines given in Table III were prepared by a procedure similar to that described above for IX except that the reduction to obtain compound XXXII was carried out in diethyleneglycol dimethyl ether while tetrahydrofuran was used as a solvent in preparing compounds XXXVII, XXXVIII, XXXIX, XLI and XLV.

***endo*-7-Diphenylmethylene-N-methyl-2,3-norbornanedicarboximide (XLII).**—A 1-g. sample (0.0029 mole) of *endo*-7-diphenylmethylene-N-methyl-5-norbornene-2,3-dicarboximide (V) was hydrogenated at atmospheric pressure over 8 mg. of 10% palladium-on-carbon in 45 ml. of tetrahydrofuran. After 1.25 hr., the theoretical amount of hydrogen had been consumed and the reduction stopped. The reaction solution was filtered and concentrated to dryness *in vacuo*. The product was crystallized from ether–petroleum ether; yield 92%, m.p. 135–139.5°. After one recrystallization from ether–petroleum ether, 0.72 g. of XLII, m.p. 137–139.5°, was obtained. A sample, recrystallized once more from ether-petroleum ether, melted at 140–140.5°; λ_{max}^{KBr} 5.67, 5.90, 6.28, 6.71, 6.80 (w.), 6.95, 7.03, 7.28 μ.

***endo*-7-Diphenylmethyl-*N*-methyl-2,3-norbornanedicarboximide (XLIV).**—A 5-g. sample of *endo*-7-diphenylmethylene-N-methyl-5-norbornene-2,3-dicarboximide (V) was reduced over 0.45 g. of 10% palladium-on-carbon in 300 ml. of 95% ethanol under 3.1 kg. of hydrogen/cm.^{2}. The uptake of hydrogen stopped after the addition of the required 2 moles. The reduction solution was filtered and concentrated to dryness *in vacuo*. The product was crystallized from methylene chloride–ether. The crystals were filtered, washed with ether and air-dried, affording 3.0 g. (59%), m.p. 192–202; the ultraviolet spectrum showed benzene ring and end absorption only. After a recrystallization from methylene chloride-ether, a 2.3 g. sample of pure XLIV was obtained, m.p. 206–208°; λ_{max}^{Nujol} 5.67, 5.91, 6.25, shl. 6.68, shl. 6.74, 6.87, 7.00 μ.

7-Diphenylmethylene-*endo*-2-methylaminomethyl-5-norbornene-*endo*-3-methanol (XLVI).—To a solution of 3.7 g. (0.097 mole) of lithium aluminum hydride in 250 ml. of tetrahydrofuran (distilled from lithium aluminum hydride) was added 9.3 g. (0.026 mole) of 7-diphenylmethylene-*endo*-2-methylcarbamoyl-5-norbornene-*endo*-3-carboxylic acid (VI) slurried in 450 ml. of dried tetrahydrofuran. After an overnight reflux, 11 ml. of water was added cautiously to hydrolyze the reaction mixture. The inorganic solids were removed by filtration and washed with ether. The organic solution was extracted with 5% hydrochloric acid. The acid extracts were made basic with 35% sodium hydroxide solution and extracted with ether. The ether extracts were combined, washed with water, dried and concentrated to dryness *in vacuo*, giving 6.8 g. (80%) of oily base. This was converted to the *fumarate* salt. After Darco treatment and three recrystallizations from methanol, 2.62 g. (26%) of the pure fumarate of XLVI was obtained, m.p. 212–214°; λ_{max}^{KBr} 3.25–3.65, shl. 6.35, 6.40, shl. 6.51, 6.66, 6.88 μ.

***endo*-8-Diphenylmethylene-3a,4,7,7a-tetrahydro-2,2-dimethyl-4,7-methanoisoindolinium iodide (XLVII).**—A 6.7-g. sample of *endo*-8-diphenylmethylene-3a,4,7n,7a-tetrahydro-2-methyl-4,7-methanoisoindoline (IX) was dissolved in 150 ml. of methanol-benzene and treated with 3.7 g. of methyl iodide. The solution was stirred for 1 hr. at room temperature, refluxed for 15 min., concentrated and diluted with ether. The resultant crystals were removed by filtration, washed with ether and dried, yielding 8.5 g. (86%) of XLVII, m.p. 260–262° dec.

The **methiodide** was recrystallized once from benzene-ether and twice from methanol-ether, affording 5.57 g. of pure XLVII, m.p. 261.5–262.5° dec.; λ_{max}^{Nujol} 4.27 (w), 5.97 (w), 6.24 (w), shl. 6.68 μ.

Synthesis and Diuretic Activity of 3,3-Spiro-Substituted Hydrothiazides[1]

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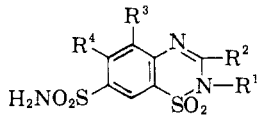
Forty-one 3,3-spiro-substituted hydrothiazides were synthesized by the condensation of substituted 4-amino-1,3-benzenedisulfonamides with cyclic ketones or the corresponding ethylene ketals. Five different synthetic procedures were employed and a comparison of these and other methods was made using the reaction of 4-amino-6-chloro-1,3-benzenedisulfonamide with cyclohexanone as a prototype.

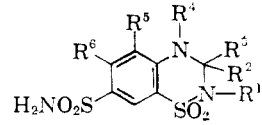
The relative naturetic activity, as determined in rats and dogs, is presented and the structure-activity relationships are discussed. The two most active compounds, 4′-methyl-6-chloro[2H-1,2,4-benzothiadiazine-3(4H)-1′-cyclohexane]-7-sulfonamide-1,1-dioxide and the 6-trifluoromethyl analog, were found to be about ten times as potent as hydrochlorothiazide in dogs and in man.

The advent of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1- dioxide[2-4] (III) as a diuretic and saluretic agent with outstanding

(1) The term "thiazide" is restricted to 2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide derivatives of the general structure I. The term "hydrothiazide" refers to the corresponding 3,4-dihydro derivatives (II). These terms have received wide usage in the biological and medi-



I



II

cal literature for compounds of this type which potentially possess electrolyte excreting or diuretic properties. Adherence to the terminology defined here would serve to differentiate these compounds from the closely related non-diuretic antihypertensive drugs which lack the 7-sulfamoyl group.