The Chemistry and Pharmacology of a Series of Cycloalkanespiro-5′-hydantoins

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A number of substituted cycloalkanespiro-5′-hydantoins have been prepared and tested for toxicity, for gross effects on behavior, and for anticonvulsant and analgesic activity in mice. Indications of sedative activity were obtained by ability to potentiate hexobarbital anesthesia. A limited number of compounds were tested for antiinflammatory activity in rats. Cyclopentanespiro-5′-hydantoins showed a low toxicity and low sedative activity. Certain cyclohexanespiro-5′-hydantoins showed analgesic and antiinflammatory activity. Some cycloheptanespiro-5′-hydantoins exhibited anticonvulsant activity, while the few cyclooctanespiro-5′-hydantoins tested possessed properties reminiscent of the barbiturates but with lower potency.

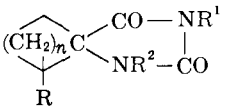
Numerous cycloalkanespiro-5′-hydantoins have been tested[2a-k] for anticonvulsant activity, but little has been reported relating to other types of pharmacological activity in these compounds.

Although 1- and 3-substituted hydantoins have been widely investigated,[3-5] few 1′- and/or 3′-substituted cycloalkanespiro-5′-hydantoins have been described. These include 1′- and/or 3′-methyl[6-8] and 1′-phenyl[9] derivatives, 3′-morpholinomethyl and 3′-piperidinomethylcyclohexanespiro-5′-hydantoins and their corresponding 1′-methyl analogs,[10] 1′-(2-diethylaminoethyl)- and 3′-[2-(4-pyridyl)ethyl]cyclohexanespiro-5′-hydantoins,[11] and certain 3′-phenylcyclopentanespiro-5′-hydantoins.[12]

It was of interest therefore to synthesize a number of novel 1′- and/or 3′-substituted cycloalkanespiro-5′-hydantoins and their known parents so that they could be tested for several types of pharmacological activity.

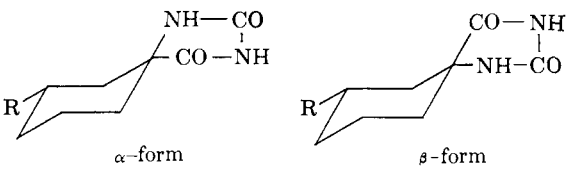
Chemistry.—Cycloalkanespiro-5′-hydantoins (Ia) were conveniently prepared using the Bucherer synthesis.[13]

It is apparent that when R is a group other than hydrogen then two geometric isomers are possible. One isomer (α-form) has been observed to predominate when the Bucherer synthesis is used to prepare the hydantoin from the substituted cycloalkanone, whereas



Ia, $R^1 = R^2 = H$
b, $R^1 = H$
c, R^1 = alkyl
d, R^1 = aryl

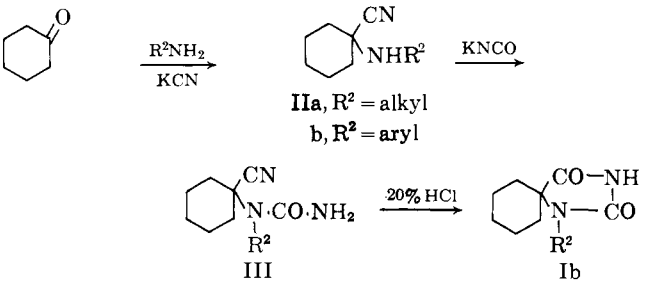
the other isomer (β-form) predominates when the Strecker synthesis is used to prepare the amino acid from the cycloalkanone, and the amino acid is converted to the hydantoin.[12,14-16] Physical evidence[15] has indicated that the isomers have the following configurations.



α-form β-form

It was assumed therefore that Ia (n = 3, R is other than H) was almost completely in the α-form.

Hydantoins cannot usually be substituted directly in the 1-position[3] and consequently the following method was used to prepare Ib.



IIa, R^2 = alkyl
b, R^2 = aryl

III Ib

IIa (R^2 = allyl, 2-hydroxyethyl, benzyl, or methyl) was prepared from the amine hydrochloride in aqueous solution,[17] whereas IIb (R^2 = phenyl, *p*-methoxy, or *p*-ethoxyphenyl) was obtained from the amine in glacial acetic acid. The preparation of III (R^2 = allyl, hydroxyethyl, benzyl, or methyl) was carried out in

(1) Lilly Research Laboratories Ltd., Bromborough Port, New Ferry, Wirral, Cheshire, England.

(2) (a) R. Tiffeneau and M. Beauvallet, *Presse méd.*, **51**, 417 (1943); (b) H. R. Henze, R. C. Wilson, and R. W. Townley, *J. Am. Chem. Soc.*, **65**, 963 (1943); (c) E. S. Rothman and A. R. Day, *ibid.*, **76**, 111 (1954); (d) G. W. Smith and A. R. Day, *ibid.*, **77**, 3541 (1955); (e) J. A. Faust, L. H. Jules, L. Yee, and M. Sahyun, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 118 (1957); (f) L. H. Jules, J. A. Faust, and M. Sahyun, U. S. Patent 2,716,648 (1955); (g) H. C. Brimelow and C. H. Vasey, British Patent 807,679 (1959); (h) W. Reppe, O. Schlichting, F. Westphal, and A. Amann, U. S. Patent 2,732,380 (1956); (i) W. S. Waring, British Patent 796,069 (1958); (j) H. C. Brimelow and C. H. Vasey, British Patent 807,678 (1959); (k) W. J. Close and M. A. Spielman in "Medicinal Chemistry," Vol. 5, W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 1.

(3) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

(4) M. Tiffeneau, B. Tchoubar, M. Saiaslambert, and S. LeTellier-Dupré, *Bull. Soc. Chim. France*, 445 (1947).

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(6) H. C. Carrington, *J. Chem. Soc.*, 681 (1947).

(7) H. C. Carrington, *ibid.*, 684 (1947).

(8) H. C. Carrington and W. S. Waring, *ibid.*, 354 (1950).

(9) H. C. Carrington and W. S. Waring, British Patent 817,745 (1959).

(10) O. O. Orazi and R. A. Corral, *Tetrahedron*, **15**, 93 (1961).

(11) E. Schipper and E. Chinery, *J. Org. Chem.*, **26**, 3597 (1961).

(12) L. Nicole and L. Berlinguet, *Can. J. Chem.*, **40**, 353 (1962).

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(14) H. C. Brimelow, H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, 2789 (1962).

(15) L. Munday, *ibid.*, 4372 (1961).

(16) H. L. Hoyer, *Chem. Ber.*, **83**, 491 (1950).

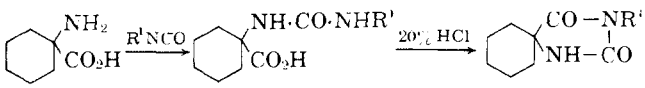
(17) E. Schipper and E. Chinery, *J. Org. Chem.*, **26**, 4480 (1961).

aqueous solution from the aminonitrile hydrochloride.[7] Where R^2 = phenyl, *p*-methoxy, or *p*-ethoxyphenyl, the compounds were obtained from aminonitriles (II) in glacial acetic acid.[9] Conversion of III to Ib was carried out in refluxing hydrochloric acid. The yields were sometimes poor.

Acetylation of hydantoins in the 1-position has been carried out with acetic anhydride[18] or acetyl chloride–pyridine.[19] In our hands several alkali-soluble derivatives of Ib (R^2 = acetyl) were obtained using acetic anhydride.

Cycloalkanespiro-5′-hydantoins Ic (R^1 = hydroxyethyl, ethoxycarbonylmethyl, allyl, benzyl, epoxypropyl, or 2-diethylaminoethyl) were obtained by heating Ia or Ib (sodium salt) with alkyl halide alone, or in a suitable solvent. Ic (R^1 = methyl) was obtained using dimethyl sulfate in alkali. Hydroxymethylation[5,6,20] of Ia was carried out with boiling 37% formalin. Substitution usually occurred in the 3-position. This was not the case with cycloheptanespiro-5′-hydantoin when both 1′,3′-dihydroxymethyl and 3′-hydroxymethyl derivatives were obtained. Attempts to prepare hydroxymethyl derivatives of 1′-methylcyclohexanespiro-5′-hydantoin and 1′-phenylcyclohexanespiro-5′-hydantoin were unsuccessful.

In the preparation of Id (R^1 = phenyl or *p*-methoxyphenyl) the following method was used. IV was obtained by hydrolysis of cyclohexanespiro-5′-hydantoin with 60% sulfuric acid.



IV Id

Pharmacological Methods.—The compounds were formulated in aqueous solution or as suspensions in 0.5% sodium carboxymethylcellulose. They were administered orally to groups of albino mice (Schofield) weighing 19–21 g. and tested for toxicity, for gross effects on behavior, for anticonvulsant activity, and for analgesic properties. The ability of the compounds to potentiate hexobarbital was investigated and, in certain of the compounds, antiinflammatory activity was assessed in rats (see Tables I–VII).

A. Acute Toxicity.—The acute toxicity of each compound was determined in groups of five mice, treated orally with ascending doses. Mortalities were recorded over 48 hr. and any gross behavioral changes which occurred prior to death and at high doses were noted. LD_{50} values were estimated by a graphical method when possible.

B. Anticonvulsant Activity.—The compounds were given orally to groups of ten mice, and 1 hr. after dosing the mice were stimulated by the i.v. injection either of strychnine (625 γ/kg.) or of pentylenetetrazol (100 mg./kg.) or were subjected to electroshock seizures.[21] In each case the per cent inhibition of tonic extensor convulsions which occurred in each group was noted.

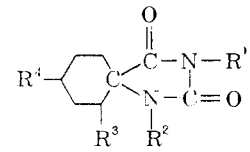
C. Analgesic Activity.—Analgesic activity was assessed by the ability of the compounds to inhibit stretching induced by intraperitoneal injections of acetic acid in mice. The compounds were administered orally to groups of ten animals and 1 hr. later 0.25 ml. of 0.5% v./v. acetic acid was injected intraperitoneally. The mice were observed for 15 min. and the number of mice which failed to show the typical stretching reaction of the hind limbs was recorded.

D. Hexobarbital Potentiation.—Groups of ten mice were given oral doses of the compounds and 1 hr. later all mice received intraperitoneal injections of 100 mg./kg. of hexobarbital sodium. The mice were turned on their backs as soon as anesthesia occurred, and the time from injection to recovery of righting reflex was recorded for each mouse. The mean time for each group was then calculated and compared with a saline-treated control group.

E. Antiinflammatory Activity.—The method used was a modification of that described by Domenjoz.[22] Groups of ten Wister Rats (ARC, Compton), five male and five female per group, weighing about 200 g., were dosed orally with the compounds 1 hr. before the injection of 0.1 ml. of 1.2% formalin subcutaneously into the ventral surface of the right hind foot. The left hind foot was similarly injected with 0.1 ml. of physiological saline. After 2 hr. the rats were killed by gassing and the hind feet were amputated and weighed. The formalin caused swelling, and inflammation was therefore measured in terms of the difference in weight between the hind feet of each rat. The mean increase in weight for each group was calculated, and the results are expressed as a per cent inhibition of swelling, compared to that of a control group.

Results and Discussion

Cyclohexanespiro-5′-hydantoins (Tables I–IV).—Analgesic activity was apparent in this series when



substitution at R^1 or R^4 was a small aliphatic group (**1, 1a, 2, 3, 4, 31,** and **37**) or when R^2 was acetyl (**17, 41,** and **42**). Substitution at R^3 reduced activity and toxicity (*cf.* **1** and **30, 3** and **36, 41** and **42**).

Antiinflammatory activity, in the limited number of compounds tested, was most marked when R^1 was methyl or hydroxymethyl (**2** or **3**). When R^2 was aromatic and R^1 was H, the compounds showed stimulant properties (**19–21**), but when R^2 was aromatic and R^1 substituted, the compounds were depressants (**24–29**). It is of interest that the equivalent R^1-substituted hydantoins with R^2 unsubstituted were stimulants (**7–9**). Most compounds showing depression of behavioral effects potentiated hexobarbital, although certain compounds which were stimulants also had this effect. This was especially marked with **9**, which probably mediated its effect through some action on barbiturate metabolism. Little anticonvulsant activity was apparent in this series.

Cyclopentanespiro-5′-hydantoins (Table V).—This

(18) M. R. Salmon and A. Z. Kozlowzki, *J. Am. Chem. Soc.*, **67**, 2270 (1945).

(19) G. P. Lampson and H. O. Singher, *J. Org. Chem.*, **21**, 684 (1956).

(20) R. Behrend and R. Niemeyer, *Ann. Chem.*, **365**, 38 (1909).

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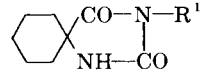
(22) R. Domenjoz, *Ann. N. Y. Acad. Sci.*, **86**, 263 (1960).

TABLE I

PHARMACOLOGICAL ACTIVITY[a] OF CYCLOHEXANESPIRO-5′-HYDANTOINS SUBSTITUTED AT N_3

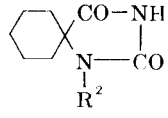


No.	R^1	LD_{50}, mg./kg.	Anticonvulsant activity against: Strychnine	Pentylene tetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
1	H	420	+, 187.5	0	0	+, 250	♁, 500	0	Toxic doses caused convulsions, mydriasis, lachrymation, piloerection, and tail erection.
1a	Na	450	0	0	0	+, 55	0	–	Toxic doses caused convulsions, mydriasis, salivation, piloerection, and tail erection.
2	CH_3	1100	0	0	0	+, 400	♁, 500	+, 800	Near toxic doses caused convulsions. Tail erection was observed.
3	CH_2OH	520	0	0	0	+, 182	0	+, 400	Near toxic doses caused convulsions. Tail erection was observed.
4	CH_2OCOCH_3	887	0	0	♁, 400	+, 400	0	0	Near toxic doses caused convulsions. Tail erection was observed.
5	$CH_2COOC_2H_5$	>2500	0	0	0	0	+, 1000	–	2500 mg./kg. caused depression and slight muscular weakness.
6	CH_2Cl	1500	0	0	0	♁, 1000	0	–	Toxic doses caused convulsions and marked diarrhea.
7	CH_2CH_2OH	2000	♁, 1000	0	+, 500	+, 1000	0	0	Toxic doses caused convulsions.
8	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	1500		0	0	0	0	♁, 1500	Toxic doses caused depression and slight clonic convulsions.
9	$CH_2CH{=}CH_2$	750	♁, 250	0	+, 500	0	+, 31.25	–	Toxic doses caused clonic convulsions.
10	$CH_2CH(-O-)CH_2$	>2000	0	0	0	0	0	0	Appeared inactive.
11	$CH_2C_6H_5$	>2000	0	0	♁, 1000	0	+, 1000	–	Slight increase in activity at high doses.
12	C_6H_5	>4000	0	0	0	0	0	–	Appeared inactive.
13	p-$C_6H_4OCH_3$	>2000	♁, 1000	0	♁, 1000	0	♁, 250	–	Appeared inactive.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = no effect at highest dose given, ♁ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, – = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}.

TABLE II

PHARMACOLOGICAL ACTIVITY[a] OF CYCLOHEXANESPIRO-5'-HYDANTOINS SUBSTITUTED AT N_1

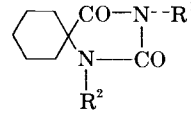


No.	R^2	LD_{50}, mg./kg.	Anticonvulsant activity against — Strychnine	Pentylene tetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
14	CH_3	900	+, 500	0	+, 500	0	0	−	Toxic doses caused CNS depression, muscular weakness, and mydriasis.
15	$CH_2C_6H_5$	>2500	0	+, 1000	0	+, 2000	+, 500	−	2500 mg./kg. caused CNS depression, muscular weakness, and some loss of righting reflex.
16	CH_2CH_2OH	1500	+, 125	+, 500	+, 500	0	♁, 500	−	1000 mg./kg. caused slight CNS depression, muscular weakness, and lachrymation.
17	$COCH_3$	500	0	0	0	+, 125	0	−	Toxic doses caused tonic extensor convulsions.
18	$CH_2CH{=}CH_2$	1000	♁, 500	+, 250	0	+, 500	♁, 125	−	Toxic doses caused deep depression and loss of righting reflex.
19	C_6H_5	>5000	0	0	0	0	♁, 500	−	5000 mg./kg. caused a slight increase in activity, face washing, and muscular weakness.
20	p-$C_6H_4OCH_3$	>5000	+, 1000	♁ 1000	0	0	++, 1000	−	Slight CNS stimulation at 2000 mg./kg.
21	p-$C_6H_4OC_2H_5$	>4000	0	♁ 1000	+, 500	0	+, 500	−	Slight CNS stimulation at 4000 mg./kg.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = effect at highest dose given, ♁ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, −− = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}.

TABLE III

PHARMACOLOGICAL ACTIVITY[a] OF CYCLOHEXANESPIRO-5′-HYDANTOINS SUBSTITUTED AT N_1 AND N_2

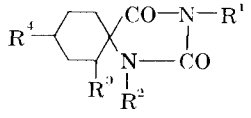


No.	R^1	R^2	LD_{50}, mg./kg.	Anticonvulsant activity against: Strychnine	Pentylene tetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
22	$CH_2CH{=}CH_2$	CH_3	2500	0	0	0	ŏ, 1000	ŏ, 125	–	Near-toxic doses caused initial CNS depression followed by clonic convulsions.
23	$CH_2\underline{CH{-}O{-}CH_2}$	CH_3	2000	0	0	0	0	0	–	2000 mg./kg. caused depression and muscular weakness with some righting loss.
24	$CH_2CH{=}CH_2$	C_6H_5	2000	0	0	0	0	+, 250	–	2000 mg./kg. had no apparent effect.
25	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	C_6H_5	1500	0	0	0	ŏ, 600	++, 60	–	1000 mg./kg. caused deep depression and some righting loss.
26[b]	$CH_2CH_2N^+(C_2H_5)_2CH_3 \cdot I^-$	C_6H_5	73.4	0	ŏ, 40	0	0	ŏ, 40	–	Toxic doses caused marked cyanosis and depression.
27	CH_2CH_2OH	C_6H_5	2000	0	ŏ, 1000	ŏ, 1000	ŏ, 1000	++, 250	–	2000 mg./kg. caused marked depression with some righting loss.
28	CH_2CH_2OH	p-$C_6H_4OCH_3$	2000	0	0	0	0	++, 1000	–	2000 mg./kg. caused marked depression with some righting loss.
29	CH_2CH_2OH	p-$C_6H_4OC_2H_5$	2000	0	0	ŏ, 500	0	+, 200	–	Slight sedation at 2000 mg./kg.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = no effect at highest dose given, ŏ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, – = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}. [b] All tests were made on this compound by the intraperitoneal route.

TABLE IV

PHARMACOLOGICAL ACTIVITY[a] OF MISCELLANEOUS CYCLOHEXANESPIRO-5'-HYDANTOINS

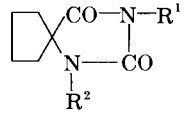


No.	R^1	R^2	R^3	R^4	LD_{50}, mg./kg.	Anticonvulsant activity against: Strychnine	Pentylene tetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
30	H	H	CH_3	H	>2500	δ, 1000	+, 1000	δ, 1000	0	δ, 750	−	2500 mg./kg. caused slight clonic convulsions and righting loss.
31	H	H	H	CH_3	400	0	0	0	++, 125	0	−	Toxic doses caused intermittent clonic convulsions and marked ataxia.
32	H	H	CH_2OH	H	>2000	δ, 1000	0	δ, 1000	0	δ, 250	−	2000 mg./kg. caused a slight increase in irritability.
33	H	H	$COOC_2H_5$	H	5000	δ, 1000	δ, 1000	0	δ, 2000	+, 1000	−	Near-toxic doses caused depression.
34	H	H	COOH	H	>4000	0	0	0	0	0		Slight sedation and diarrhea at 4000 mg./kg. Increased irritability at 2000 mg./kg.
35	$CH_2CH{=}CH_2$	H	$COOC_2H_5$	H	>2000	0	0	0	0	+, 200	−	2000 mg./kg. caused depression and some righting loss after initial hyperactivity.
36	CH_2OH	H	CH_3	H	1500	δ, 1000	+, 1000	+, 500	+, 250	++, 1000	−	Toxic doses caused intermittent clonic convulsions.
37	CH_2OH	H	H	CH_3	200	0	0	0	+, 62.5	0	δ, 150	Toxic doses caused intermittent clonic convulsions and tail erection.
38	CH_2OH	H	$COOC_2H_5$	H	>2500	0	0	0	0	0	−	2500 mg./kg. had no apparent effect.
39	CH_2CH_2OH	H	$COOC_2H_5$	H	>2500	0	0	0	0	δ, 1250	−	2500 mg./kg. caused sedation and mydriasis.
40	$CH_2CH_2{-}O{-}CH_2$	H	H	CH_3	>4000	0	δ, 1500	−	++, 1500	δ, 1500	−	No apparent effects at 2000 mg./kg.
41	H	$COCH_3$	H	CH_3	125	0	0	0	+, 50	0	−	Near-toxic doses caused clonic convulsions.
42	H	$COCH_3$	CH_3	H	2000	0	0	0	+, 326	+, 750	−	Near-toxic doses caused intermittent clonic convulsions and tail erection.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = effect at highest dose given, δ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, − = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}.

TABLE V

PHARMACOLOGICAL ACTIVITY[a] OF CYCLOPENTANESPIRO-5′-HYDANTOINS

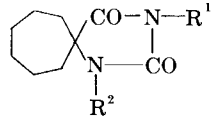


No.	R^1	R^2	LD_{50}, mg./kg.	Anticonvulsant activity against: Strychnine	Pentylene tetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
43	H	H	>4000	0	ŏ, 2000	ŏ, 2000	0	+, 1000	–	2000 mg./kg. had no apparent effects.
44	CH_2OH	H	1500	0	0	0	0	+, 500	ŏ, 750	Near-toxic doses caused deep sedation.
45	CH_2CH_2OH	H	4500	0	0	0	0	++, 250	–	Near-toxic doses caused deep sedation.
46	H	$COCH_3$	3000	0	0	0	+, 1500	0	–	Near-toxic doses caused deep sedation.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = no effect at highest dose given, ŏ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, – = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}.

TABLE VI

PHARMACOLOGICAL ACTIVITY[a] OF CYCLOHEPTANESPIRO-5′-HYDANTOINS



No.	R^1	R^2	LD_{50}, mg./kg.	Anticonvulsant activity against: Strychnine	Pentylene tetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
47	H	H	>1000	+, 500	+, 250	+, 250	0	++, 1000	–	1000 mg./kg. caused sedation and ataxia; active against nicotine.
48	CH_2OH	H	1700	0	+, 250	+, 500	0	ŏ, 750	–	Toxic doses caused deep depression and righting loss.
49	CH_2CH_2OH	H	1500	0	+, 500	0	0	0	–	Toxic doses caused deep depression.
50	$CH_2CH{=}CH_2$	H	1340	+, 300	ŏ, 600	+, 600	+, 600	+, 50	–	Toxic doses caused severe clonic convulsion followed by deep depression.
51	$CH_2CH{-}O{-}CH_2$	H	>2000	+, 1000	ŏ, 1000	+, 1000	0	ŏ, 500	–	2000 mg./kg. caused deep depression.
52	H	$COCH_3$	2500	+, 1500	+, 375	+, 750	+, 1500	+, 750	–	Near-toxic doses caused depression.
53	CH_2OH	CH_2OH	2500	+, 810	+, 360	+, 525	0	+, 250	–	1000 mg./kg. caused intermittent clonic convulsions.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = no effect at highest dose given, ŏ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, – = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}.

TABLE VII

PHARMACOLOGICAL ACTIVITY[a] OF CYCLOOCTANESPIRO-5′-HYDANTOINS

No.	R^2	LD_{50}, mg./kg.	Anticonvulsant activity against— Strychnine	Pentylenetetrazol	Electroshock	Analgesic activity	Hexobarbital potentiation	Antiinflammatory activity	Remarks
54	H	>3000	+, 480	+, 240	+, 240	0	+, 480	−	750 mg./kg. caused loss of righting reflex, followed by recovery.
55	CH_3	1500	0	+, 300	0	0	δ, 75	−	Toxic doses caused initial hyperexcitability followed by deep depression and righting loss.
56	$COCH_3$	>2000	δ, 150	+, 150	+, 150	0	δ, 300	−	1000 mg./kg. caused deep CNS depression and righting loss. 500 mg./kg. caused CNS depression and partial righting loss.

[a] The symbol representing the activity is given, followed by the dose of compound: 0 = no effect at highest dose given, δ = slight effect at highest dose given, + = 50% effect, or 100% increase in hexobarbital test, ++ = much greater than 50% effect, − = not tested. Doses are given in mg./kg. The highest dose normally given was about half the LD_{50}.

series of compounds showed little activity, except at near toxic doses when sedation occurred.

Cycloheptanespiro-5′-hydantoins (Table VI).—Anticonvulsant activity was evident in this series. Generally, they were most effective against pentylenetetrazol-induced convulsions. They all showed a low toxicity.

Cyclooctanespiro-5′-hydantoins (Table VII).—Only three of this series were prepared and each showed anticonvulsant and sedative activity, reminiscent of the barbiturates.

Experimental[23]

Cycloalkanespiro-5′-hydantoins.—The ketone (1.0 mole), KCN (1.5 moles), and $(NH_4)_2CO_3$ (3.0 moles) were stirred in 50% aqueous ethanol (700–800 ml.) at 55–60° for 5–6 hr. The mixture was cooled and the product was removed by filtration, washed well with water, and recrystallized (see Table VIII).

2-Carboxycyclohexanespiro-5′-hydantoin.—2-Ethoxycarbonylcyclohexanespiro-5′-hydantoin (11.5 g.) was refluxed with 18% HCl (50 ml.) for 2 hr. A white solid was obtained on cooling which was removed by filtration, dried, and recrystallized (see Table VIII).

1-Alkylaminocyclohexanecarbonitriles.—Potassium cyanide (1 mole) in water (130 ml.) was added to a stirred, cooled solution of cyclohexanone (1 mole) and alkylamine hydrochloride (1 mole) in 50% aqueous methanol (200 ml.). The mixture was stirred overnight at room temperature and refluxed for 2 hr. The mixture was extracted with ether and the ethereal extract was dried (Na_2SO_4). Hydrogen chloride was passed into the solution causing the aminonitrile hydrochloride to be precipitated. Alternately the aminonitrile was obtained by concentration of the ethereal solution *in vacuo* and fractional distillation of the residual oil. Yields were between 50–70%. The following 1-substituted cyclohexanecarbonitriles were prepared in this manner: 1-methylamino, b.p. 114–117° (40 mm.), $n^{20}D$ 1.4468; 1-allylamino, b.p. 109–115° (12 mm.), $n^{20}D$ 1.4795; 1-benzylamino, m.p. 166–167° (hydrochloride) (lit.[17] m.p. 134–135°); 1-(2-hydroxyethyl)amino, m.p. 78–79°; hydrochloride, m.p. 102°.

1-Arylaminocyclohexanecarbonitriles.—Potassium cyanide (1.2 moles) in water (130 ml.) was slowly added to a stirred solution of cyclohexanone (1.0 mole) and arylamine (1.0 mole) in glacial acetic acid (300 ml.) at 0°. The mixture was stirred at 0–5° for 1 hr. and filtered. The solid was washed with dilute acetic acid and water, and recrystallized. Yields were between 75–100%. The following 1-substituted cyclohexanecarbonitriles were prepared in this manner: 1-anilino, m.p. 77–78° (lit.[17] m.p. 74–76°); 1-*p*-anisidino, m.p. 76–78° (lit.[17] m.p. 74–76°); 1-*p*-phenetidino, m.p. 68°.

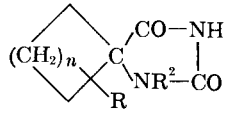
1′-Alkylcyclohexanespiro-5′-hydantoins.—A typical procedure was as follows. 1′-Allylaminocyclohexanecarbonitrile (0.1 mole) was dissolved in 9% HCl (40 ml.), and the solution was treated with potassium cyanate (0.11 mole) in water (15.0 ml.) at 30–35°. The mixture was stirred at 30–35° for 45 min. and cooled. The solid was removed by filtration, washed with water, and refluxed with 12% HCl (45 ml.) for 30 min. The solution was cooled and the hydantoin was removed by filtration, dried, and recrystallized. See Table VIII for details of the 1′-methyl, 1′-hydroxyethyl, and 1′-allyl derivatives.

1′-Benzylcyclohexanespiro-5′-hydantoin.—1-Benzylaminocyclohexanecarbonitrile hydrochloride (0.05 mole) in glacial acetic acid (40.0 ml.) was treated with potassium cyanate (0.1 mole) in water (14.0 ml.) at room temperature. The mixture was stirred at 60° for 1.5 hr., cooled, and poured into water. The solid was removed by filtration and refluxed with 20% HCl (75 ml.) for 30 min. The solution was cooled, and the hydantoin was removed by filtration, dried, and recrystallized (see Table VIII).

(23) Melting points were taken in open capillaries and are uncorrected.

TABLE VIII

CYCLOALKANESPIRO-5′-HYDANTOINS Ia AND Ib

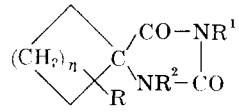


Cycloalkane, C_nH_{2n} n	R	R^2	No.	Yield, % (crude)	M.p., °C.[a]	Purification[b] solvent	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
5[c]	H	H	43	62	207[d]	EtOH	$C_7H_{10}N_2O_2$						
5	H	$COCH_3$	46	70	116–118	EtOAc	$C_9H_{12}N_2O_3$	55.1	55.0	6.17	6.1	14.30	15.5
6[c]	H	H	1	80	218–220[e]	50% EtOH	$C_8H_{12}N_2O_2$						
6	H	CH_3	14	38	175[f]	50% EtOH	$C_9H_{14}N_2O_2$						
6	H	$CH_2C_6H_5$	15	47	179–180	EtOH	$C_{15}H_{18}N_2O_2$	69.8	69.6	7.02	7.0	10.85	10.55
6	H	CH_2CH_2OH	16	19.5	109–110	C_6H_6	$C_{10}H_{16}H_2O_3$	56.6	56.3	7.54	7.50	13.20	13.40
6	H	$COCH_3$	17	53	185–187	EtOAc	$C_{10}H_{14}N_2O_3$	57.1	56.8	6.66	6.66	13.30	13.20
6	H	$CH_2CH{=}CH_2$	18	60	157–159	EtOH	$C_{11}H_{16}N_2O_2$	63.4	62.9	7.75	7.50	13.45	13.15
6	H	C_6H_5	19	23	286–288[g]	95% EtOH	$C_{14}H_{16}N_2O_2$					11.45	11.30
6	H	p-$CH_3OC_6H_4$	20	49	225	EtOH	$C_{15}H_{18}N_2O_3$	65.7	65.9	6.61	6.59	10.20	10.25
6	H	p-$C_2H_5OC_6H_4$	21	61	212–213	95% EtOH	$C_{16}H_{20}N_2O_3$	66.6	66.6	6.99	7.06	9.70	9.65
6	2-CH_3	H	30	74	219–221[h]	EtOH	$C_9H_{14}N_2O_2$	59.3	59.3	7.74	7.76	15.4	15.30
6	4-CH_3	H	31	87	279–280[i]	EtOH	$C_9H_{14}N_2O_2$	59.3	58.8	7.74	7.60	15.4	15.25
6	2-CH_2OH	H	32	36	233–236	MEK	$C_9H_{14}N_2O_3$	54.5	55.0	6.84	7.03	14.15	14.15
6	2-$CO_2C_2H_5$	H	33	61	170	EtOH	$C_{11}H_{16}N_2O_4$	55.1	55.6	6.71	6.55	11.65	11.65
6	2-CO_2H	H	34	76	244–245	EtOAc	$C_9H_{12}N_2O_4$	50.9	50.7	5.70	5.73	13.20	12.75
6	4-CH_3	$COCH_3$	41	61	177–179	EtOAc–petr. ether	$C_{11}H_{16}N_2O_3$	58.9	58.4	7.14	7.33	12.50	12.30
6	2-CH_3	$COCH_3$	42	40	169–171	Aq. EtOH	$C_{11}H_{16}N_2O_3$	58.9	58.5	7.14	7.26	12.50	12.30
7[c]	H	H	47	93	217–218[j]	50% EtOH	$C_9H_{14}N_2O_2$						
7	H	$COCH_3$	52	89	160–161	EtOAc	$C_{11}H_{16}N_2O_3$	58.9	59.2	7.14	7.30	12.50	12.65
8	H	H	54	57	245[k]	Aq. EtOH	$C_{10}H_{16}N_2O_2$	61.2	60.9	8.2	8.2	14.3	14.3
8	H	$COCH_3$	56	83	150–151	EtOAc	$C_{12}H_{18}N_2O_3$	60.5	60.6	7.6	7.7	11.3	11.2

[a] Melting points were taken in open capillaries and are uncorrected. [b] EtOH = ethanol, EtOAc = ethyl acetate, C_6H_6 = benzene, MEK = methyl ethyl ketone, petr. ether = petroleum ether (b.p. 60–80°), aq. = aqueous. [c] Structure supported by infrared spectrum. [d] H. R. Henze and R. J. Speer [*J. Am. Chem. Soc.*, **64**, 522 (1942)] give m.p. 204–205°. [e] Lit.[4] m.p. 222°. [f] Lit.[8] m.p. 174°. [g] Lit.[9] m.p. 283–284°. [h] Lit.[d] m.p. 215–216°. [i] Lit.[d] m.p. 279–280°. [j] Lit.[4] m.p. 217°. [k] Lit.[4] m.p. 246°, lit.[2g] m.p. 241–242°.

TABLE IX

CYCLOALKANESPIRO-5′-HYDANTOINS Ic AND Id



Cycloalkane C_nH_{2n} n	R	R^2	R^1	No.	Yield, % (crude)	M.p., °C.[a]	Purification[b] solvent	Formula	—% carbon— Calcd.	Found	—% hydrogen— Calcd.	Found	—% nitrogen— Calcd.	Found
5	H	H	CH_2OH	44	68	143–144	EtOAc	$C_8H_{12}N_2O_3$	52.1	52.1	6.57	6.60	15.20	15.15
6	H	H	CH_2OH	3	80	170–174	EtOAc	$C_9H_{14}N_2O_3$	54.5	54.6	7.12	7.29	14.15	13.95
6	2-CH_3	H	CH_2OH	36	35	150–152	CH_2Cl_2–CCl_4	$C_{10}H_{16}N_2O_3$	56.6	56.1	7.60	7.51	13.20	12.95
6	4-CH_3	H	CH_2OH	37	60	274–276	EtOAc	$C_{10}H_{16}N_2O_3$	56.6	56.7	7.60	7.69	13.20	13.20
6	2-$CO_2C_2H_5$	H	CH_2OH	38	41	142–143	EtOAc–petr. ether	$C_{12}H_{18}N_2O_5$	53.3	53.0	6.72	6.51	10.40	10.55
7	H	H	CH_2OH	48	59	137–138	EtOAc	$C_{10}H_{16}N_2O_3$	56.6	56.5	7.60	7.66	13.20	13.35
7	H	CH_2OH	CH_2OH	53	59	129–131	CH_2Cl_2	$C_{11}H_{18}N_2O_4$	54.7	54.4	7.52	7.45	11.60	11.20
5	H	H	CH_2CH_2OH	45	65	128–129	EtOAc	$C_9H_{14}N_2O_3$	54.5	54.2	7.12	7.13	14.15	14.10
6	H	H	CH_2CH_2OH	7	42	158–160	EtOAc	$C_{10}H_{16}N_2O_3$	56.6	56.0	7.60	7.51	13.20	12.95
6	2-$CO_2C_2H_5$	H	CH_2CH_2OH	39	18	137–138	EtOAc	$C_{13}H_{20}N_2O_5$	54.9	54.8	7.1	7.3	9.85	10.2
6	H	C_6H_5	CH_2CH_2OH	27	42	126–127	EtOAc	$C_{16}H_{20}N_2O_4$	66.6	66.6	6.99	7.14	9.70	9.55
6	H	p-$CH_3OC_6H_4$	CH_2CH_2OH	28	26	84–86	Et_2O–petr. ether	$C_{17}H_{22}N_2O_5$	64.1	63.9	6.96	7.16	8.80	9.00
6	H	p-$C_2H_5OC_6H_4$	CH_2CH_2OH	29	75	192–193	EtOAc–petr. ether	$C_{18}H_{24}N_2O_5$	65.0	64.6	7.28	7.01	8.45	8.95
7	H	H	CH_2CH_2OH	49	65	126–128	EtOAc–petr. ether	$C_{11}H_{18}N_2O_3$	58.4	57.9	8.02	8.08	12.40	12.70
6	H	H	$CH_2CH{=}CH_2$	9	59	154	EtOAc	$C_{11}H_{16}N_2O_2$	63.5	63.7	7.70	7.77	13.45	13.15
6	2-$CO_2C_2H_5$	H	$CH_2CH{=}CH_2$	35	33	118–120	Aq. EtOH	$C_{14}N_{20}H_2O_4$	59.9	59.4	7.19	7.00	10.0	9.70
6	H	CH_3	$CH_2CH{=}CH_2$	22	75	67	n-hexane	$C_{12}H_{18}N_2O_2$	64.8	65.0	8.12	8.3	12.60	12.50
6	H	C_6H_5	$CH_2CH{=}CH_2$	24	71	133–135	Aq. EtOH	$C_{17}H_{20}N_2O_2$	71.8	71.5	7.09	7.10	9.85	9.70
7	H	H	$CH_2CH{=}CH_2$	50	70	126–128	Aq. EtOH	$C_{12}H_{18}N_2O_2$	64.8	64.1	8.12	8.18	12.60	12.50
6	H	H	$CH_2CH{-}O{-}CH_2$	10	25	146–149	EtOAc–petr. ether	$C_{11}H_{16}N_2O_3$	58.8	58.3	7.19	7.40	12.50	12.15
6	4-CH_3	H	$CH_2CH{-}O{-}CH_2$	40	40	160–164	EtOAc	$C_{12}H_{18}N_2O_3$	60.4	59.9	7.61	7.58	11.75	11.25
6	H	CH_3	$CH_2CH{-}O{-}CH_2$	23	34	106–107	EtOAc–Et_2O	$C_{12}H_{18}N_2O_3$	60.4	60.2	7.61	7.61	11.75	12.20
7	H	H	$CH_2CH{-}O{-}CH_2$	51	96	125–126	EtOAc	$C_{12}H_{18}N_2O_3$	60.4	60.3	7.61	7.67	11.75	11.75
6	H	H	$CH_2CO_2C_2H_5$	5	53	131–132	EtOAc	$C_{11}H_{16}N_2O_4$	56.7	56.6	7.13	7.16	11.00	10.95
6	H	H	$C_6H_5CH_2$	11	50	155–156	Aq. EtOH	$C_{15}H_{18}N_2O_2$	69.8	69.3	7.02	6.84	10.85	10.65
6	H	H	$CH_2CH_2N(C_2H_5)_2$	8	63	85–87	EtOAc	$C_{14}H_{25}N_3O_2$[c]	63.8	63.4	9.41	9.74	15.70	15.25
6	H	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	25	69	51–53	n-hexane	$C_{20}H_{29}N_3O_2$[d,e]	69.9	69.3	8.50	8.40	12.20	12.10
6	H	H	CH_3	2	83	215–218[f]	EtOH	$C_9H_{14}N_2O_2$	59.3	59.3	7.74	7.85	15.35	14.80
8	H	H	CH_3	55	80	168–170	Aq. EtOH	$C_{11}H_{18}N_2O_2$	62.8	62.8	8.6	8.7	13.3	13.3
6	H	H	C_6H_5	12	40	222–224	Aq. EtOH	$C_{14}H_{16}N_2O_2$	68.8	68.7	6.60	6.67	11.45	11.40
6	H	H	p-$CH_3OC_6H_5$	13	46	243–244	EtOH	$C_{15}H_{18}N_2O_3$	65.7	65.6	6.62	6.60	10.20	10.25
6	H	H	$CH_2CO_2CH_3$	4	70	161–162	EtOAc	$C_{11}H_{16}N_2O_4$	55.0	55.0	6.70	6.42	11.65	11.70
6	H	H	CH_2Cl	6	63	176–179	CH_2Cl_2–petr. ether	$C_9H_{13}ClN_2O_2$	49.9	49.9	6.05	5.61	12.95	12.85
7	H	CH_2OH?	CH_2Cl?	-		144	CCl_4–EtOAc	$C_{13}H_{17}ClN_2O_3$[g]	50.7	50.2	6.58	7.22	10.80	10.45

[a] Melting points were taken in open capillaries and are uncorrected. [b] EtOAc = ethyl acetate, CH_2Cl_2 = methylene dichloride, CCl_4 = carbon tetrachloride, petr. ether = petroleum ether (b.p. 60–80°), Et_2O = diethyl ether, EtOH = ethanol, aq. = aqueous. [c] Hydrochloride from diethyl ether, m.p. 189–190°. *Anal.* Calcd. for $C_{14}H_{25}N_3O_2 \cdot HCl$: C, 55.4; H, 8.64; N, 13.85. Found: C, 55.6; H, 8.70; N, 13.75. [d] Hydrochloride from diethyl ether, m.p. 147–150°. *Anal.* Calcd. for $C_{20}H_{29}N_3O_2 \cdot HCl$: Cl, 9.33. Found: Cl, 9.37. [e] Methiodide from ethyl acetate, m.p. 155°. *Anal.* Calcd. for $C_{21}H_{32}IN_3O_2$: C, 51.9; H, 6.64; I, 26.15; N, 8.65. Found: C, 51.1; H, 6.52; I, 26.05; N, 8.55. [f] Lit.[8] m.p. 212–213°. [g] *Anal.* Calcd.: Cl, 13.60. Found: Cl, 13.90.

1′-Acetylcycloalkanespiro-5′-hydantoins.—The cycloalkanespiro-5′-hydantoin (7.0–10.0 g.) was refluxed with acetic anhydride (30–40 ml.) for 1–1.5 hr. The mixture was concentrated *in vacuo*, and the residue was slurried with saturated $NaHCO_3$ solution. The residual 1′-acetylhydantoin was removed by filtration and recrystallized (see Table VIII).

1′-Arylcyclohexanespiro-5′-hydantoins.—1-Arylaminocyclohexanecarbonitrile (0.10 mole) and KCNO (0.11 mole) were stirred in glacial acetic acid (35 ml.) for 3 days at room temperature and then 1 hr. at 50°. The mixture was refluxed with 9% HCl (214 ml.) for 1 hr. and cooled. The precipitated hydantoin was removed by filtration, dried, and recrystallized (see Table VIII).

3′-Hydroxymethylcycloalkanespiro-5′-hydantoins.—The cycloalkanespiro-5′-hydantoin (1 mole) was boiled with 37% formalin (220–320 ml.) until complete solution was obtained. The solution was cooled to 0°, and the product was removed by filtration. It was slurried with a little water, dried *in vacuo* at 70°, and recrystallized (see Table IX). The method was not successful for hydroxymethylating 1′-methylcyclohexanespiro-5′-hydantoin, as the starting material was recovered unchanged.

Hydroxymethylation of 1′-phenylcyclohexanespiro-5′-hydantoin yielded a product having m.p. 158–159° (carbon tetrachloride).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.7; H, 6.62; N, 10.20. Found: C, 64.6; H, 6.40; N, 9.90.

Repeated recrystallization gave no improvement in microanalysis, and the product possessed a persistent odor of formaldehyde. Infrared analysis confirmed that hydroxymethylation had occurred.

3′-Alkylcycloalkanespiro-5′-hydantoins.—3′-Sodiocycloalkanespiro-5′-hydantoin was refluxed (or stirred at 100°) with a two- or threefold excess of alkyl chloride alone, in ethanol or dimethylformamide for several hours. The mixture was concentrated *in vacuo*, and the residue was extracted with a suitable solvent. Removal of the solvent afforded a residue which was suitably recrystallized. Alternatively the residue, obtained by concentration of the reaction mixture, was slurried with water, 2 *N* NaOH solution, or ethanolic 2 *N* NaOH solution, and the insoluble material was recrystallized.

3′-Alkylcycloalkanespiro-5′-hydantoins prepared in this manner were 3′-hydroxyethyl, 3′-ethoxycarbonylmethyl, and 3′-epoxypropyl derivatives (see Table IX).

In a method similar to that described above, equimolar proportions of 3′-sodiocycloalkanespiro-5′-hydantoin and alkyl halide were refluxed in ethanol for several hours. 3′-Alkylcycloalkanespiro-5′-hydantoins prepared in this manner were 3′-allyl, 3′-benzyl, and 3′-(2-diethylaminoethyl) derivatives (see Table IX).

3′-Methylcycloalkanespiro-5′-hydantoins.—A solution of cycloalkanespiro-5′-hydantoin (0.06 mole) in water (30 ml.) containing NaOH (0.074 mole) was treated dropwise with dimethyl sulfate (0.08 mole) over 5 min. The mixture was stirred at room temperature for an additional 10 min., cooled, and filtered. The solid was washed with water, dried, and recrystallized (see Table IX).

3′-(2-Diethylaminoethyl)cyclohexanespiro-5′-hydantoin.—A solution containing cyclohexanespiro-5′-hydantoin (8.4 g.) in absolute ethanol (30 ml.) and *N* NaOH solution (50 ml.) was treated with 2-diethylaminoethyl chloride hydrochloride (11.7 g.) in water (17 ml.) containing NaOH (2.7 g.). The mixture was stirred at room temperature for 2 hr. and refrigerated overnight. The solid was removed by filtration, washed with water, and recrystallized (see Table IX).

3′-Arylcyclohexanespiro-5′-hydantoins.—A solution of 1-aminocyclohexanecarboxylic acid (0.052 mole) in water (75 ml.) containing NaOH (0.05 mole) was stirred rapidly at 0° and treated with aryl isocyanate (0.054 mole) in one portion. The mixture was stirred for 15 min., and any remaining solid was removed by filtration and discarded. The filtrate was acidified with concentrated HCl and the precipitated hydantoic acid was removed by filtration. It was refluxed with dilute HCl (400 ml.) for 6 hr., and the mixture was cooled. The product was removed by filtration and recrystallized (see Table IX).

1-Aminocyclohexanecarboxylic Acid.—Cyclohexanespiro-5′-hydantoin (61.5 g.) was stirred with 60% H_2SO_4 (310 ml.) for 20 hr. at 150°. The solution was poured into water (300 ml.) and the small amount of solid was removed by filtration and discarded. The filtrate was neutralized with barium hydroxide and then made just acid with dilute H_2SO_4. The barium sulfate was removed by filtration, and the hot solution was concentrated to 30 ml. and neutralized with concentrated ammonia solution. 1-Aminocyclohexanecarboxylic acid was filtered off and recrystallized from dilute acetic acid; yield 19.1 g. (36.5%), m.p. 320° dec., lit.[15] m.p. 320–325°.

3′-Acetoxymethylcyclohexanespiro-5′-hydantoin.—3′-Hydroxymethylcyclohexanespiro-5′-hydantoin (5.0 g.) was refluxed with acetic anhydride (40 ml.) for 30 min. The solution was poured into water (200 ml.) and the mixture was stirred. The precipitated 3′-acetoxymethylcyclohexanespiro-5′-hydantoin was removed by filtration and recrystallized (see Table IX). The infrared spectrum was in accordance with that expected for O-acetylation.

Attempt to Prepare 3′-(3,4,5-trimethoxybenzoyloxymethyl)-cyclohexanespiro-5′-hydantoin.—3′-Hydroxymethylcyclohexanespiro-5′-hydantoin (7.4 g.) and 3,4,5-trimethoxybenzoic acid (7.95 g.) were each dissolved in a minimum quantity of methylene chloride containing a small amount of dioxane, and the solutions were mixed. A solution of dicyclohexylcarbodiimide (7.65 g.) in methylene chloride was added and the mixture refluxed for 1 hr. The precipitated dicyclohexylurea, m.p. 217°, was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was slurried with $NaHCO_3$ solution and Soxhlet extracted with methylene chloride. Concentration of the methylene chloride solution afforded a white solid. This was slurried with ethanolic 2 *N* NaOH solution, and the residue (7.9 g.) was removed by filtration, washed with water, and dried. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) gave a product having m.p. 132–134°.

Anal. Calcd. for $C_{19}H_{24}N_2O_7$: C, 58.2; H, 6.16; N, 7.14. Calcd. for $C_{23}H_{34}N_2O_5$ (N,N′-dicyclohexyl-N-3,4,5-trimethoxybenzoylurea): C, 65.60; H, 8.19; N, 6.70. Found: C, 65.65; H, 8.14; N, 6.80.

The infrared spectrum was in accordance with that expected for N,N′-dicyclohexyl-N-3,4,5-trimethoxybenzoylurea.

3′-Chloromethylcyclohexanespiro-5′-hydantoin.—3′-Hydroxymethylcyclohexanespiro-5′-hydantoin (10.0 g.) in methylene chloride (200 ml.) was treated with PCl_5 (10.5 g.) at room temperature. The reaction was slightly exothermic. The solution was stirred for 1 hr., filtered, and evaporated to dryness. The residue was slurried with ether and recrystallized (see Table IX).

1′(3′?)-Chloromethyl-3′(1′?)-hydroxymethylcyclohextanespiro-5′-hydantoin.—1′,3′-Dihydroxymethylcycloheptanespiro-5′-hydantoin (7.0 g.) was stirred with methylene chloride (150 ml.) at room temperature. Powdered PCl_5 (12.1 g.) was added, and the mixture was stirred for 1.5 hr. The mixture was concentrated *in vacuo* leaving an oil. This was dissolved in ethyl acetate and the solution was washed several times with $NaHCO_3$ solution and dried (Na_2SO_4). Concentration afforded a gum which solidified in hexane–methylene chloride. Recrystallization from carbon tetrachloride–ethyl acetate gave material having m.p. 144°.

Anal. Calcd. for $C_{11}H_{17}ClN_2O_3$: C, 50.7; H, 6.58; Cl, 13.80; N, 10.80. Found: C, 50.2; H, 6.22; Cl, 13.90; N, 10.45.

Infrared analysis confirmed that only one hydroxymethyl group had been replaced by chloromethyl.

Other preparations gave products having varying chlorine content and melting point. In no case was 1′,3′-dichloromethylcycloheptanespiro-5′-hydantoin obtained.

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