antitumor activities of all compounds listed in Tables I–III were evaluated with the total packed cell volume ratio (TPCV %) on the 7th day after the tumor inoculation, as reported previously.[9]

Acknowledgment. One of the authors (S.I.) acknowledges in part the Scientific Research Fund from the Ministry of Education of Japan for the present work. They are gratefully indebted to Drs. K. Kuretani and A. Hoshi of NCC of Japan for making available the antitumor screening results and valuable discussion. They also thank Miss K. Nakaji of Joint Laboratory of this school for the uv and ir spectral measurements.

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Synthesis and Central Nervous System Depressant Activity of Some Bicyclic Amides

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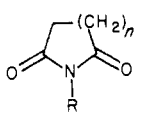
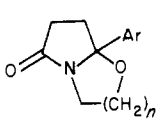
A series of aryl bicyclic analogs of succinimide and glutarimide was prepared and evaluated for CNS depressant activity. The 8a-aryl-3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-ones possessed the best overall spectrum of activity relative to the standard agents glutethimide and phenobarbital.

A large number of five- and six-membered heterocyclic compounds containing a dicarboximide unit (O=CNC=O) have been reported to possess CNS activity.[1-3] The simplest members of this class, the succinimides (Ia) and glutarimides (Ib), have depressant activity and are used as anticonvulsants,[2] sedatives,[1,3] and muscle relaxants.[1]

In the present work we have prepared a series of aryl bicyclic analogs II[4] and III[4] where one of the carbonyl groups in I has been incorporated as part of a second heterocyclic ring and evaluated these compounds for CNS depressant activity.



Ia, $n = 1$
Ib, $n = 2$



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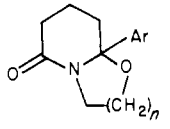


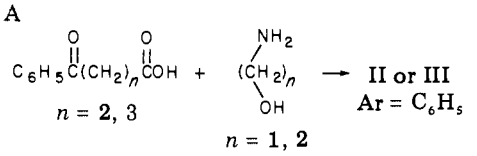
IIIa, $n = 1$
IIIb, $n = 2$

Chemistry. The phenyl analogs of II and III described in this work were prepared by the previously reported[5] condensation of the corresponding oxo acid with an alkanolamine (method A).

Substituted phenyl and 2-thienyl derivatives of IIb were obtained by thermal cyclizations of the *N*-hydroxyalkylamides IV in refluxing xylene in the presence of an acid catalyst (method B). The uv spectra of several hydroxyamides indicated they prefer to exist in the open-chain ketone IV form rather that the cyclic tautomer V.

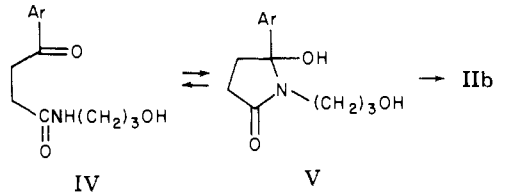
Pharmacology. The results obtained when the bicyclic amides II and III were evalulated in a series of behavioral

method A



$n = 2, 3$ $n = 1, 2$ II or III, Ar = C_6H_5

method B



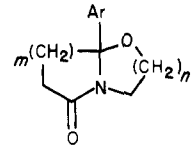
IV V IIb

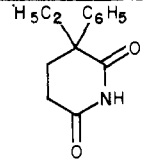
and drug-interaction tests in mice designed to uncover CNS depressant activity are given in Table I. Anticonvulsant activity was studied in mice, using as criteria the antagonism to *N*-sulfamoylhexahydroazepine[6] (N-SA) and maximal electroshock[7] (MES). General CNS-depressant activity was defined by the ability of a substance to reinduce "anesthesia" following loss of righting reflex obtained with hexobarbital.[8]

Evaluation of the phenyl analogs 1–4 of the four ring systems given in formulas II and III revealed that the 3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-one (IIb) derivative **2** possessed the best overall spectrum relative to the standards glutethimide (VI) and phenobarbital (VII).

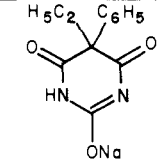
In an attempt to improve the activity of **2** the phenyl ring was substituted with F (**5**), Cl (**6**), CH_3 (**7**), OCH_3 (**8**), Cl_2 (**9**), and $(CH_3)_2$ (**10**) groups or replaced by a 2-thienyl

Table I





VI

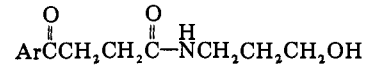


VII

No.	m	n	Ar	LD_{50}, mg/kg ip[a]	Behavior,[b] ED_{50}, mg/kg ip: Ataxia$_{50}$	Behavior,[b] ED_{50}, mg/kg ip: LRR$_{50}$	Anticonvulsant act.: N-SA[c] (ED_{50}, mg/kg ip)	Anticonvulsant act.: MES[d] (ED_{50}, mg/kg ip)	Barbiturate reinduction[e] (RD_{50}, mg/kg ip)
1	1	1	C_6H_5	300	<50	150	Na at 200	Na at 200	37.5
2	1	2	C_6H_5	500	37.5	150	169	92	34.0
3	2	1	C_6H_5	Nt	<150	>150	150	158	69.0
4	2	2	C_6H_5	500	<50	150	122	<150	75.0
5	1	2	4-FC_6H_4	600	75	100	50.0	68.7	66.0
6	1	2	4-ClC_6H_4	675	75	81.2	91.7	58	>100
7	1	2	4-$CH_3C_6H_4$	675	<50	160	Na at 200	Na at 100	>100
8	1	2	4-$CH_3OC_6H_4$	Nt	<150	<150	138.5	93.8	<150
9	1	2	3,4-$Cl_2C_6H_3$	550	<150	<150	<75	112.5	>150
10	1	2	2,4-$(CH_3)_2C_6H_3$	600	<50	150	<150	>150	<150
11	1	2	2-Thienyl	467	<75	>75	>75	112.5	46.5
VI	Glutethimide			350	100	229.0	Na at 400	24.7	112.5
VII	Phenobarbital			225	62.5	83.0	8.0	15.4	65.6

[a] Acute toxicity studies were carried out with paired male Royal Hart Wistar rats, 136–160 g, placed in 7 × 7 × 14 in. wire cages. The LD_{50} values were obtained 2 hr postadministration of compounds using four rats per substance and estimated by probit analysis. [b] Analyses of behavior used a modification of the method of S. Irwin ("Animal and Clinical Pharmacologic Techniques in Drug Evaluation," Year Book Publishers, 1964, pp 36–54); LRR = loss of righting reflex; ten animals per dose. [c] N-SA = *N*-sulfamoylhexahydroazepine; methods of ref 6; ten animals were used per dose. [d] MES = maximal electroshock; method of ref 7 was used with ten animals per dose. [e] Modified method of ref 8 was used in which the animals were administered compound immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time.

Table II. Neuropharmacological Data on *N*-(3-Hydroxypropyl)-3-aroylpropionamides



No.	Ar	LD_{50}, mg/kg ip[a]	Behavior,[b] ED_{50}, mg/kg ip: Ataxia$_{50}$	Behavior,[b] ED_{50}, mg/kg ip: LRR$_{50}$	Anticonvulsant act.: N-SA[c] (ED_{50}, mg/kg ip)	Anticonvulsant act.: MES[d] (ED_{50}, mg/kg ip)	Barbiturate reinduction[e] (RD_{50}, mg/kg ip)
12	4-FC_6H_4	>800	300	500	>400	>400	>400
13	4-ClC_6H_4	633	300	325	>300	>300	<300
14	4-$CH_3C_6H_4$	750	300	700	>300	>300	<300
15	4-$CH_3OC_6H_4$	800	150	800	>600	>600	<600
16	3,4-$Cl_2C_6H_3$	500	300	500	>600	450	>300
17	2,4-$(CH_3)_2C_6H_3$	633	150	150	>150	>150	<150
18	2-Thienyl	475	300	300	>300	>300	>300

[a-e] See corresponding footnotes in Table I.

group (11). Only the 4-fluorophenyl analog **5** gave a profile that showed an increase in anticonvulsant activity.

The overall CNS activity of these compounds relative to phenobarbital did not show any significant improvement and additional analogs were not prepared.

The neuropharmacological data on the *N*-(3-hydroxypropyl)-3-aroylpropionamides IV (**12–18**, Table II) reveal that these substances are devoid of any interesting level of activity.

Experimental Section

Chemical Synthesis. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. For all compounds listed in Table III ^1H NMR spectra were obtained on a Varian Associates A-60 spectrometer in $CDCl_3$ or Me_2SO-*d*6 and ir spectra (KBr) were determined using a Perkin-Elmer Infracord. In all cases the spectra were consistent with the assigned structure. The uv spectra for a selected group of compounds IV were obtained in 95% EtOH solvent on a Cary Model 15 spectrophotometer.

ω-Aroylalkanoic Acids. The acids required to prepare compounds **1–4**, **8**, **10**, and **11** were obtained from the Aldrich Chemical Co.

The acids required to prepare compounds **5–7** and **9** were prepared by the Friedel–Crafts condensations of succinic anhydride with an excess of the appropriate substituted benzene derivative in the presence of aluminum chloride. There was obtained 3-(4-fluorobenzoyl)propionic acid (83%) [mp 103–105° (MeOH–H_2O; lit.[10] mp 101–102°)], 3-(4-chlorobenzoyl)propionic acid (66%) [mp 129–131° (MeOH–H_2O; lit.[10] mp 128°)], 3-(3,-4-dichlorobenzoyl)propionic acid (77%) [mp 165–167° (EtOH–H_2O; lit.[11] mp 166–166.7°)], and 3-(4-methylbenzoyl)propionic acid (57%) [mp 125–127° (MeOH–H_2O; lit.[12] mp 129°)].

Method A. General Procedure. A mixture of the appropriate alkanolamine (0.20 mol), ω-benzoylalkanoic acid (0.10 mol), *p*-toluenesulfonic acid (0.5 g), and 250 ml of toluene was placed in a flask equipped with a stirrer and a Dean-Stark tube. The mixture was stirred and refluxed until the level of the "water layer" (mixture of water and alkanolamine) remained constant. The reaction was allowed to cool to room temperature and the solvent removed in vacuo. The residue was crystallized from an appropriate solvent. The characterizing data for compounds **1–4** prepared by this procedure are given in ref 5.

Method B. General Procedure. A mixture of *N*-(3-hydroxypropyl)-3-aroylpropionamide (10 g), *p*-toluenesulfonic acid (0.5 g), and 200 ml of toluene was stirred and refluxed in a flask equipped with a Dean-Stark tube. After the H_2O level in the Dean-Stark tube remained constant the solvent was removed in vacuo and the resultant residue was distilled or crystallized to

Table III. Physical Properties

No.	Method,[a] % yield	Mp, °C (recrystn solvent)[b]	Emperical formula	Analyses[c,d]
1	A, 67	84.5-84.6 (A)	$C_{12}H_{13}NO_2$	
2	A, 74	77-79 (A)	$C_{13}H_{15}NO_2$	
3	A, 52	74-75 (B)	$C_{13}H_{15}NO_2$	
4	A, 45	72-73 (A)	$C_{14}H_{17}NO_2$	
5	B, 83	86-88 (C)	$C_{13}H_{14}FNO_2$	C, H, N
6	B, 77	63-65 (C)	$C_{13}H_{14}ClNO_2$	C, H, Cl, N
7	B, 75	35 (A)	$C_{14}H_{17}NO_2$	C, H, N
8	B, 61	66-68 (C)	$C_{14}H_{17}NO_3$	C, H, N, O
9	B, 91	119-120 (C)	$C_{13}H_{13}Cl_2NO_2$	C, H, Cl, N
10	B, 66	69-71 (C)	$C_{15}H_{19}NO_2$	C, H, N, O
11	B, 90	114-116 (D)	$C_{11}H_{13}NO_2S$	C, H, N, S
12	C, 54	87-89 (D)	$C_{13}H_{16}FNO_3$	C, H, N
13	C, 53	85-87 (D)	$C_{13}H_{16}ClNO_3$	C, H, N, O
14	C, 66	101-102 (D)	$C_{14}H_{19}NO_3$	C, H, N
15	C, 62	100-102 (D)	$C_{14}H_{19}NO_4$	C, H, N, O
16	C, 53	159-162 (D)	$C_{13}H_{13}Cl_2NO_3$	C, H, Cl, N
17	C, 52	65-67 (A)	$C_{15}H_{21}NO_3$	C, H, N, O
18	C, 41	95-97 (D)	$C_{11}H_{15}NO_3S$	C, H, N, S

[a] See Experimental Section. [b] A, Et_2O; B, EtAc; C, CH_2Cl_2-pentane; D, CH_2Cl_2-Et_2O. [c] Unless otherwise stated the analyses are within ±0.4% of the theoretical values. [d] Analyses for 1-4 are given in ref 5.

give the 8a-aryl-3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]-oxazin-6-ones (**5**-11) given in Table III.

Method C. General Procedure. A stirred mixture of 3-aroylpropionic acid (0.10 mol), triethylamine (0.10 mol), and 250 ml of chloroform was cooled to 0° and then treated dropwise with a solution of ethyl chloroformate (0.10 mol) in 100 ml of $CHCl_3$ at such a rate that the internal temperature did not excede 10°. After an additional 2.5 h of stirring the mixture was treated dropwise with 3-aminopropanol (0.10 mol). The cooling was removed and the reaction was stirred for ca. 20 h at room temperature. The $CHCl_3$ layer was decanted, washed with H_2O, 1 N HCl, and saturated NaCl, respectively, and then dried with anhydrous Na_2SO_4. The solution was filtered and the solvent removed in vacuo to give the *N*-(3-hydroxypropyl)-3-aroylpropionamides (**12**-18) in Table III.

Acknowledgment. The authors are grateful to Mrs. Nancy Engstrom and Mr. Urs Stoeckli for instrumental determinations and to Mr. William Bonkoski for the microanalyses.

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Potentiation of the Estrogenic Activity of Stilbestrol by Spiro(cyclohexane-1,2'-indan)-1',4-dione

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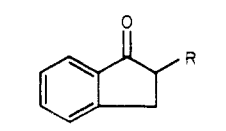
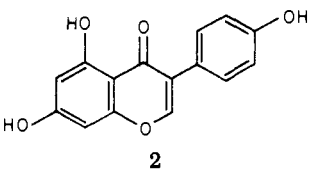
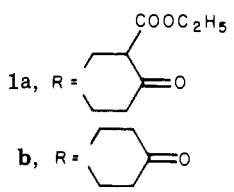
During the investigation of a series of spiro compounds having approximately similar molecular dimensions to naturally occurring estrogens, the novel compound spiro(cyclohexane-1,2'-indan)-1',4-dione was prepared. The pretreatment of mice with this estrogenically inactive compound was found to potentiate the estrogenic activity of stilbestrol.

The present investigation is concerned with the synthesis and biological activity of one of a series of spiro compounds having approximately similar molecular dimensions to some naturally occurring estrogens. During a routine pharmacological screening program it was found that pretreatment with the estrogenically inactive compound spiro(cyclohexane-1,2'-indan)-1',4-dione (**1b**), which is structurally related to the estrogenic isoflavone genistein (**2**),[1] potentiated the estrogenic activity of stilbestrol.





2



Chemistry. 2,2-Bis(β-ethoxycarbonylethyl)indanone was prepared by a two-step Michael condensation between indanone and ethyl acrylate. Ring closure was accomplished by a Dieckmann reaction followed by hydrolysis and decarboxylation to give spiro(cyclohexane-1,2'-indan)-1',4-dione (**1b**).

Pharmacological Activity. Quantitative estimations of estrogenic activity were made using the immature mouse uterine response assay procedure previously described by Rubin et al.[2]

The results presented in Table I show that, whereas **1b** alone is devoid of any significant estrogenic activity at doses of up to 100 μg per mouse, it does produce a marked potentiation in the estrogenic activity of stilbestrol when the two drugs are given in combination. Furthermore, an indication of the potency of **1b** was revealed when it was found that this effect is consistently detectable, although not statistically significant, at a dose level as low as 0.1 μg per mouse. However, in order to attain significant ($p < 0.05$ at 100 μg) potentiation it was essential that **1b** was given at least 24 h before stilbestrol, since experiments in which this pretreatment period was absent revealed no