The solids were filtered and washed with cold water, 2-propanol, and ether to give 15.44 g (82% overall from 9) of 13h: mp 226-228 °C; IR 3108, 1729, 1622 cm⁻¹. Anal. Calcd for $C_{13}H_7F_3NO_3$: C, 55.12; H, 2.83; N, 4.95. Found: C, 55.08; H, 2.96; N, 5.06.

1-Ethenyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (13c). To 5.89 g (21.7 mmol) of 15^{15} were added 7.5 g (2.5 equiv) of K_2CO_3 and 300 mL of dry DMF. After the mixture was stirred for 30 min at 50 °C, 45 g (11.0 equiv) of 1,2-dibromoethane was added. The temperature was raised to 80 °C, and the mixture stirred vigorously for 48h. It was concentrated to dryness and the residue was partitioned between H₂O and H₂CCl₂. The organic layer was extracted twice more with water. It was dried and concentrated to a dark oil, which was purified by column chromatography (HCCl₃/hexane/2-propanol, 4:5:1) to give 2.58 g (40%) of the ethyl ester 12c, mp 135-136 °C. To 2.2 g (7.4 mmol) of this material were added 40 mL of AcOH and 20 mL of 3 N HCl, and the mixture was heated for 4 h. Dilution with water and filtration gave 1.35 g (68%) of 13c: mp 185-186 °C; IR 1728, 1648 cm⁻¹. Calcd for Anal. C12H16F3NO30.2H2O: C, 52.94; H, 2.35; N, 5.14; H2O, 1.32. Found: C, 52.77; H, 2.41; N, 5.24; H₂O, 0.96. 1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-

pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid 14h. General Coupling Procedure. To 5.00 g (17.65 mmol) of 13h in 50 mL of CH₃CN was added a solution of 2.7 g (1.0 equiv) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2.4 g (1.05 equiv) of N-ethyl-3-pyrrolidinemethanamine in 25 mL of CH₃CN. The mixture was refluxed for 2.5 h and was stirred at room temperature overnight. The solids were filtered and washed with 50 mL of CH₃CN, 20 mL of 80% aqueous CH₃CN, 50 mL of ethanol, and 200 mL of ether to give 6.01 g (87%) of 14h as a white solid: mp 257-258 °C; IR 1730, 1623, 1584 cm⁻¹; NMR (TFA) δ 9.15 (s, 1 H, C₂H), 8.0 (d, J = 12 Hz, 1 H, C₅H), 7.1 (br s, 1 H, NH), 4.1 (m, 5 H, CH₂NHCH₂CH₃ and cyclopropyl CH), 3.4 (m, 4 H, pyrrolidine CH₂N), 2.8 (m, 1 H, pyrrolidine $C_{3}H$), 2.4 (m, 1 H, pyrrolidine $C_{4}H$), 1.9 (m, 1 H, pyrrolidine $C_{4}H$), 1.9 (m, 1 H, pyrrolidine $C_{4}H$), 1.45 (m, 7 H, CH_{3} and $CH_{2}CH_{2}$). Anal. Calcd for $C_{20}H_{23}F_{2}N_{3}O_{3}$: C, 61.38; H, 5.88; N, 10.74. Found: C, 61.08; H, 5.94; N, 10.93.

Data Processing. QSAR analyses were run on an IBM 3081 using the SAS³⁵ program package. In eq 1-14, the figures in parentheses are the standard errors of the regression coefficients. For each equation, n is the number of compounds, r is the correlation coefficient, F is a significance test, and s is the standard error of the estimate. Molecular modeling used the SYBYL program package²⁵ operating on a VAX 11/780.

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Registry No. 8, 1201-31-6; 8 (acid chloride), 94695-48-4; 9, 94695-50-8; 11a, 113220-15-8; 11d, 113220-16-9; 11e, 113220-17-0; **11f**, 113220-18-1; **11g**, 113220-19-2; **11h**, 94695-51-9; **11i**, 113220-20-5; **11j**, 113220-21-6; **11k**, 113220-22-7; **11l**, 113220-23-8; 11m, 113220-24-9; 11n, 113220-25-0; 11o, 113220-26-1; 11p, 106809-20-5; 11q, 105859-07-2; 11r, 113220-27-2; 12a, 113220-28-3; 12c, 91188-95-3; 12d, 93969-13-2; 12e, 113220-29-4; 12f, 100276-66-2; 12g, 113249-33-5; 12h, 94242-51-0; 12i, 113220-30-7; 12j, 113220-31-8; 12k, 113220-32-9; 12l, 113220-33-0; 12m, 113220-34-1; 12n, 113220-35-2; 12o, 113220-36-3; 12p, 104599-93-1; 12q, 105859-09-4; 12r, 106464-85-1; 13a, 79660-45-0; 13b, 75338-42-0; 13c, 91187-99-4; 13d, 79660-52-9; 13e, 113220-10-3; 13f, 100276-67-3; 13g, 113220-11-4; 13h, 94695-52-0; 13i, 98079-84-6; 13j, 113220-12-5; 13k, 99724-24-0; 13l, 113220-13-6; 13m, 99724-27-3; 13n, 99724-28-4; 13o, 99724-30-8; 13p, 104599-99-7; 13q, 103994-87-2; 13r, 106464-84-0; 14a, 91188-03-3; 14b, 91188-00-0; 14c, 91188-02-2; 14d, 91188-01-1; 14e, 99735-14-5; 14f, 103490-74-0; 14g, 113220-14-7; 14h, 99734-97-1; 14i, 99735-25-8; 14j, 99735-16-7; 14k, 99735-15-6; 14l, 99735-19-0; 14m, 99735-20-3; 14n, 99735-21-4; **140**, 99735-24-7; **14p**, 106464-87-3; **14q**, 106486-83-3; **14r**, 106464-86-2; **15**, 79660-46-1; H₃CNH₂, 74-89-5; F(CH₂)₂NH₂·HCl, 460-08-2; $F_3CCH_2NH_2 \cdot HCl$, 373-88-6; $H_3CN(NH_2)CO_2Bu-t$, 21075-83-2; H₃CONH₂·HCl, 593-56-6; (H₃C)₂CHNH₂, 75-31-0; C₆H₅NH₂, 62-53-3; 4-FC₆H₄NH₂, 371-40-4; cyclopropylamine, 765-30-0; 2-methylcyclopropanamine hydrochloride, 89123-14-8; 1-methylcyclopropanamine hydrochloride, 88887-87-0; cyclopropanemethanamine, 2516-47-4; cyclobutanamine, 2516-34-9; cyclopentanamine, 1003-03-8; cyclohexanamine, 108-91-8; 2-thiazolylamine, 96-50-4; N-ethyl-3-pyrrolidinemethanamine, 91187-83-6; propanedioic acid monoethyl ester, 1071-46-1.

Supplementary Material Available: Correlation matrix for the biological potencies, a tabulation showing the development of eq 5-14, and comparisons of calculated and found potencies for all organisms (5 pages). Ordering information is given on any current masthead page.

Potential Anticonvulsants. 11. Synthesis and Anticonvulsant Activity of Spiro[1,3-dioxolane-2,3'-indolin]-2'-ones and Structural Analogues

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A number of spiro[1,3-dioxolane-2,3'-indolin]-2'-ones were synthesized and tested for anticonvulsant activity in the maximal electroshock seizure (MES) and pentylenetetrazole seizure threshold (sc-Met) tests. 5'-Chlorospiro[1,3dioxolane-2,3'-indolin]-2'-one was the most active compound in the MES test and had $ED_{50} = 27.97 \text{ mg/kg}$. Structural analogues spiro[1,3-dioxane-2,3'-indolin]-2'-one, spiro[1,3-dithiolane-2,3'-indolin]-2'-one, spiro[indoline-3,2'-[1,3]oxathiolan]-2-one, and 3,3-dimethoxyindolin-2-one were also evaluated for anticonvulsant activity. Almost all compounds submitted for screening exhibited the ability to protect mice against electrically and chemically induced seizures. The ED_{50} and TD_{50} values for some of the title compounds are reported. Anticonvulsant screenings were carried out through NINCDS, NIH.

The search for potent antiepileptic drugs has resulted in the synthesis and evaluation of compounds having diverse chemical structures.^{1,2} Many of these compounds have structural features quite different from the more popular antiepileptic drugs viz. carbamazepine, phenytoin, phenobarbital, and primidone.³ A closer look reveals the presence of an amide moiety (cyclic or otherwise) and a

tetrahedral carbon in most anticonvulsants. Unique structural features, such as an amide linkage and a β carbonyl (a site for structural modification), make isatin

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⁽a) Swinyard, E. A. In Antiepileptic Drugs; Woodbury, D. M., (1)Penry, J. K., Pippenger, C. E., Eds.; Raven: New York, 1982; p 1. (b) Mercier, J. In Anticonvulsant Drugs; Mercier, J., Ed.; Pergamon: Oxford, 1973; p 203.

Anticonvulsants; Vida, J. A., Ed.; Academic: New York, 1977.

Popp, F. D. In Anticonvulsants; Vida, J. A., Ed.; Academic: New York, 1977; pp 331.

 $(1)^4$ an attractive source for the design of such compounds. Our search for potential antiepileptic drugs has revealed that some isatin derivatives exhibit anticonvulsant activitv.⁵ Recent reports⁶ on anticonvulsant methyl dioxolanylsulfamates prompts us to present our results in the development of such drugs. In a selective preliminary screen of various compounds prepared in our laboratory, we found that spiro[1,3-dioxolane-2,3'-indolin]-2'-one (11) posesses the ability to protect mice against chemically and electrically induced seizures.⁷ The rationale behind having the title compounds screened lies in the fact that these molecules contain two units: an oxindole and a dioxolane moiety. Since both these substructures have independently been seen in other anticonvulsants,^{5,8} we felt a judicious combination of the two units would eventually lead to a novel drug for the treatment of epilepsy. Also, these compounds contain a cyclic amide moiety and a tetrahedral carbon, structural features that have been seen in several anticonvulsants.



Compound 11 served as the lead compound for our structure-activity investigation Structural modification of 11 include incorporation of substituents on the oxindole, substitution of the oxygens in the dioxolane portion of the molecule, and introduction of a different moiety at the spiro center.

Chemistry

Acid catalyzed cyclocondensation reaction of isatin (1) with ethylene glycol, 2-mercaptoethanol, 1,2-ethanedithiol, 1,3-propanediol, and 3-chloro-1,2-propanediol gave compounds 11, 25, 27,⁹ 32, and 33, respectively. Spiro[1,3-

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- (5) (a) Popp, F. D. J. Heterocycl. Chem. 1984, 21, 1641. (b) Rajopadhye, M.; Popp, F. D. J. Heterocycl. Chem. 1984, 21, 289. (c) Pajouhesh, H.; Parson, R.; Popp, F. D. J. Pharm. Sci. 1983, 72, 318. (d) Popp, F. D. J. Heterocycl. Chem. 1982, 19, 589. (e) Popp, F. D.; Pajouhesh, H. J. Pharm. Sci. 1982, 71, 1052. (f) Popp, F. D.; Parson, R.; Donigan, B. E. J. Pharm. Sci. 1980, 69, 1235. (g) Popp, F. D.; Donigan, B. E. J. Pharm. Sci. 1979, 68, 519.
- (6) (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. J. Med. Chem. 1987, 30, 880. (b) Maryanoff, B. E.; Nortey, S. O. U.S. Pat. 4591 601, 1986; Chem. Abstr. 1986, 105, 78920f.
- (7) Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, NINCDS, NIH. The standard screening protocol of that group was followed.
- (8) For examples of anticonvulsant dioxolanes, see: (a) Reference
 3. (b) Hardie, W. R.; Hidalgo, J.; Halverstadt, I. F.; Allen, R. E. J. Med. Chem. 1966, 9, 127.

Table I. Phase I Anticonvulsant Identification Test Results ofSpiro[1,3-dioxolane-2,3'-indolin]-2'-ones

		MES^b		sc-	Met ^c	TOX ^d	
no.	hour	100	300 ^{e,f}	100	300 ^{e,f}	100	300 ^e .g
11	0.5	1/3	1/1	0/1	1/1	1/8	$4/4^h$
12	0.5	2/3	1/1	0/1	1/1	4/8	$4'/4^{h}$
	0.25		•	1/2		2/2	ŕ
13	0.5	0/3	$1/1^{i}$	0/1	1/1	0/8	2/4
	0.25	1/2		0/2		1/4	
14	0.5	0/3	1/1	0/1	1/1	0/8	4/4
	0.25	0/2		1/2		0/4	
15	0.5	3/3	1/1	0/1	1/1	8/8	$4/4^{j}$
	0.25			1/2		2/2	
	1			0/2		2/2	
	4	0/3	1/1	0/1		0/4	$2/2^{k}$
16	0.5	3/3	$1/1^{l}$	0/1	1/1	7/8	$4/4^{h}$
	4	0/3	1/1	0/1	$1/1^{m}$	0/4	1/2
17	0.5	0/3	0/1	0/1	0/1	0/8	0/4
18	0.5	0/3	1/1	0/1	$1/1^n$	0/8	4/4
	0.25	0/2		0/2		1/4	
19	0.5	1/3	1/1	0/1	$0/1^{\circ}$	1/8	4/4
20	0.5	3/3	1/1	0/1	1/1	8/8	$4/4^{h,p}$
	4	0/3	1/1	0/1	0/1	0/4	$2/2^{q}$
21	0.5	3/3	1/1	0/1	1/1	7/8	$4/4^{h}$
	4	0/3	0/1	0/1	$0/1^{m}$	0/4	1/2
22	0.5	3/3	1/1	0/1	1/1	6/8	$4/4^{r}$
23	0.5	2/3	1/1	0/1	1/1	0/8	$4/4^{p}$
24	0.5	0/3	1/1	0/1	$1/1^{s}$	0/8	4/4

^a Anticonvulsant screenings were carried out through the ADD program, NINCDS, NIH. The standard screening protocol of that group was followed. ^bMES = maximal electroshock seizure test. ^c sc-Met = subcutaneous pentylenettrazole (Metrazol) seizure threshold test. ^dTOX = neurotoxicity (rotorod test). ^eDose levels are in milligrams/kilogram. ^fResults are expressed as number of animals protected/number of animals tested. ^gResults are expressed as number of animals protected. ^hUnable to hold on to rotorod. ⁱToxic at 0.5 h. ^j2/4 loss of righting reflex, 2/4 anesthetized. ^k1/2 died before 4-h test. ⁱMES at 0.5 h = 1/1 at 30 mg/kg. ^mToxic at 4 h. ⁿRepeat results: 0/4 protected, 4/4 toxic. ^oClonic seizure followed by continuous seizure action and death. ^pAnesthetized. ^g1/2 unable to hold onto rotorod. ⁱJA toxic.

dioxolane-2,3'-indolin]-2'-ones (12, 15, 16, 19–24) and sulfur analogues 26 and 28 were similarly prepared from commercially available isatins 2–10. Via a procedure similar to that described by us earlier,^{5b} reaction of 11 with aqueous formaldehyde and secondary amines such as morpholine, piperidine, and pyrrolidine gave Mannich products 13, 14, and 18, respectively. Compounds 29 and 30 were similarly synthesized from 27. Treatment of the anion of 11 (prepared by using NaH/DMF) with benzyl bromide furnished 17. Transacetalation of isatin (1) by reaction with trimethyl orthoformate in methanol gave $31.^{10}$

Results and Discussion

The phase I anticonvulsant identification test results for compounds 11-24 are shown in Table I. In this set of compounds substituents have been incorporated in the oxindole moiety of the parent compound (11). Except for the 1'-benzyl analogue (17), all compounds exhibited the ability to protect mice against electrically induced seizures (MES test) at 300 mg/kg. Introduction of a halogen in the oxindole portion of 11 led to more active compounds in phase I. Position of the chlorine (4', 5', or 6') does not seem to affect the activity of these compounds in the identification test. Compound 22 (5'-iodo) was equally active in the MES test, whereas the bromo analogue 12 was less active.

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 (10) Wenkert, E.; Hudlicky, T. Synth. Commun. 1977, 7, 541.



In general a bulky substituent at the 1'-position (oxindole N) tends to decrease the activity of 11 in the MES test, as seen for compounds 13, 14, and 18. The 1'-benzyl group was introduced to make compound 11 more hydrophobic,¹¹ but this led to an inactive compound (17). Compound 20 having a CH₃ at the 1'-position was more active in phase I than 11 and as active as the chlorinated analogues in the MES test. Interestingly, it has been reported¹² that replacement of a small N-alkyl group by a (dialkylamino)alkyl (e.g. piperidinomethyl) group reduces MES and sc-Met activity in succinimides. Isomer 23 (5'-CH₃) was somewhat less active than 20.

Except for compounds 17 and 19, all substituted analogues of 11 prevented pentylenetetrazole (Metrazol) induced convulsions at 300 mg/kg (sc-Met test).

Table II shows the phase I results for compounds 25-33. The lead compound (11) has also been included for comparison. This set of compounds represents analogues in which the dioxolane moiety has been modified. Spiro-[1,3-oxathiolane-2,3'-indolin]-2'-one (25) was as active as 11, whereas the dithio analogue 27 was less active. Introduction of halogens in either 25 or 27 did not enhance anticonvulsant activity, which is contrary to that observed with 11. The homologue 32, having a dioxane moiety,¹³ and compound 31, envisaged as a less rigid analogue of 11, were less potent. The removal of the spiro center¹⁴ does not seem to adversely affect the activity of isatin ketals. Isatin (I) itself displays 100% protection in the MES test

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- (13) (a) Anticonvulsant activity of the related spiro[indoline-3,2'-tetrahydro-1,3-thiazin]-2-one has been investigated: Wolf, M. U.S. Pat. 3 458 525, 1969; Chem. Abstr. 1970, 72, 21715p. (b) A number of oxindoles with a spiro carbon at the 3-position have been synthesized owing to the diverse biological activity associated with such systems. For a review on this aspect, see: Joshi, K. C.; Jain, R.; Chand, P. Heterocycles 1985, 23, 957.
- (14) For recent examples of spiro compounds exhibiting anticonvulsant activity, see: Borenstein, M. R.; Doukas, P. H. J. Pharm. Sci. 1987, 76, 300.

 Table II. Phase I Anticonvulsant Identification Test Results of

 Spiro[1,3-dioxolane-2,3'-indolin]-2'-one Analogues

 25-33^a

		,	-		0			
		М	ES	sc-Met		TOX		
no.	hour	100	300-	100	300	100	300	
11	0.5	1/3	1/1	0/1	1/1	1/8	$4/4^{b}$	
25	0.5	1/3	1/1	0/1	1/1	5/8	$4/4^{b}$	
26	0.5	0/3	1/1	0/1	$0/1^{\circ}$	0/8	3/4	
	4	0/3	1/1°	0/1	0/1°	0/4	2/2	
27	0.5	0/3	1/1°	0/1	0/1	0/8	2/4	
	0.25	2'/2	,	'	'	0/2		
	1	1'/2				0/2		
28	0.5	0/3	0/1	0/1	0/1	0/8	0/4	
29	0.5	0/3	0/1	0'/1	0/1°	0/8	1/4	
30	0.5	0/3	1/1	1/1	0/1	0/8	$0/4^d$	
31	0.5	0/3	1/1	0/1	$1'/1^{e}$	0/8	$4/4^{b}$	
32	0.5	1/3	1/1	0/1	1/1	1/8	$4/4^{b}$	
	0.25			0/2	•	1/2	·	
33	0.5	0/3	0/1	0/1	1/1'	0/8	0/4	

^aSee Table I for explanation of headings. ^bUnable to hold on to rotorod. ^cToxic at 0.5 h. ^dRepeat results: 0/4 protected, 0/4 toxic. ^eRepeat results: 4/4 protected, 4/4 toxic. ^b fRepeat results: 3/4 protected, 0/4 toxic.

Table III. Phase II Quantification Test Results^a

no.	MES, ED ₅₀ [95% CI] ^b	TOX, TD ₅₀ [95% CI] ^b	PI°
11	69.85 [62.09-80.07]	130.49 [97.24-151.53]	1.87
12	46.15 [32.78-67.36]	86.49 [53.59-137.10]	1.87
13	90.03 [76.80-108.10]	170.01 [151.73-185.95]	1.89
14	134.89 [114.30-166.71]	187.22 [159.36-230.35]	1.39
15	$27.97 [19.40 - 39.27]^d$	63.67 [54.63-72.55]	2.28
16	71.97 [51.85-86.96]	120.56 [97.71-150.58]	1.68
20	90.86 [69.89-108.44]	118.36 [107.20-127.34]	1.30
21	95.58 [87.59-110.97]	122.43 [109.25-132.51]	1.24
25	$60.35 \ [51.33-68.28]^d$	99.84 [73.09-136.97]	1.65
27	173.85 [140.63 - 213.33]		
31	$82.03 [77.00-86.82]^d$	202.51 [187.37-227.66]	2.47
32	110.48 [84.16-124.57]	184.73 [190.93-197.14]	1.67

^a Time of test = 0.25 h. ^b ED₅₀ and TD₅₀ are in milligrams/kilogram. 95% CI = 95% confidence intervals. ^c PI (protective index) = TD₅₀/ED₅₀. PI values are for MES tests. ^d sc-Met ED₅₀ [95% CI]: 15, 104.48 [66.32–151.64]; 25, 76.16 [50.31–115.84]; 31, 80.61 [60.20–108.06].

Table IV. Phase II Evaluation at Time of Peak Effect (TPE)^a

no.	MES/TEST, dose ^b	TOX/TEST, dose ^c
11	3/4, 100	8/8, 200
12	4/4, 100	6/8, 150
13	3/4, 100	8/8, 200
14	4/4, 150	5/8, 200
15	4/4, 100	8/8, 100
16	4/4, 125	$6/8, 150^d$
20	2/4, 125	2/4, 125
21	$4/4, 150^{d}$	2/8, 110
25	3/4, 60	5/8, 120
27	3/4, 400	3/8, 500
31	4/4, 100	8/8, 300
32	$4/4, 200^{e}$	7/8, 200

^a TPE for all compounds in the MES and TOX tests is 0.25 h unless otherwise noted. ^bMES/TEST, dose = number of animals protected in the MES test/number of animals tested at the dose level (milligrams/kilogram) indicated. ^cTOX/TEST, dose = number of animals exhibiting neurologic toxicity/number of animals tested at the dose level (milligrams/kilogram) indicated. ^dTPE = 0.5 h. ^eTPE = 0.25 h and 0.5 h.

at 400 mg/kg.³ Compound 33, the 4-chloromethyl analogue of 11, was active in the sc-Met test at 300 mg/kg but was inactive in the MES test. The 4-chloromethyl group in 33 is a potential site for further structural modifications, perhaps via nucleophilic substitution of the halogen.

As seen in Tables I and II most compounds exhibited considerable neurologic toxicity (rotorod test). Methyl analogues 20 and 23 also exhibited anesthetic properties during the rotorod test.

The spiro compounds were also submitted⁷ for phase II quantification testing. The median effective dose (ED_{50}) and the median toxic dose (TD_{50}) for compounds 11–16, 25, 27, 31, and 32 were determined at the time of peak effect and are shown in Table III. The time of peak effect (TPE), for anticonvulsant action (MES) and neurologic toxicity, for these compounds was determined to be 0.25 h. The protection results and the dose levels at the time of peak effect are shown in Table IV. Compound 15 (5'-chloro) was found to be most potent in the MES test showing $ED_{50} = 27.97 \text{ mg/kg}$ and PI = 2.28. In comparison, phenobarbital has PI = 3.16 and $ED_{50} = 21.8 \text{ mg/kg}$ in the MES test.¹⁵ Compound 12 (5'-bromo) is less potent with an $ED_{50} = 46.15 \text{ mg/kg}$. Although 15 and 25 are more potent than the parent compound 11, analogue 26 was found to have poor activity in the MES test and was in-active in the sc-Met test. The high TD_{50} value for 31 resulted in a PI of about 2.5 in the MES and sc-Met tests, which compares well with mephenytoin (PI = 2.54, MES $ED_{50} = 60.5 \text{ mg/kg}$) and methsuximide (PI = 2.46, MES $ED_{50} = 76.3 \text{ mg/kg}$) tested under similar conditions.¹⁵ The PI for compounds 11-14, 16, 25, and 32 is comparable to that of valproic acid (PI = 1.57 in the MES test).

Conclusions

Anticonvulsant screening results indicate spiro[1,3-dioxolane-2,3'-indolin]-2'-ones to be a novel class of anticonvulsants having high potential. X-ray analyses would, perhaps, indicate a suitable model that accommodates the spatial characteristics of the anti-MES active spiro[1,3dioxolane-2,3'-indolin]-2'-ones and the anticonvulsant non spiro phenacyloxindoles.^{5f,16} The structural pattern of **34** seems important for the anticonvulsant activity of substituted oxindoles.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B spectrophotometer. ¹H NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24B instrument. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Elemental analyses were carried out by Spang Microanalytical Laboratory.

Spiro[1,3-dioxolane-2,3'-indolin]-2'-ones (11, 12, 15, 19, and 20). A mixture of the appropriate isatin, ethylene glycol, and *p*-toluenesulfonic acid (catalytic amounts) in benzene was heated at reflux, with azeotropic removal of the water formed, to give the title compounds as reported in the literature. Compound 11 (72%) had mp 131–132 °C (benzene) (lit.¹⁷ mp 134 °C); 12 (54%) had mp 189–190 °C (ethanol) (lit.¹⁷ mp 191–192 °C); 15 (63%) had mp 175–176 °C (ethanol) (lit.¹⁷ mp 178–180 °C); 19 (29%) had mp 216–217 °C (ethanol) (lit.¹⁸ mp 93 °C).

1'-(Morpholinomethyl)spiro[1,3-dioxolane-2,3'-indolin]-2'-one (13). A mixture of 11 (2.25 g, 0.012 mol), morpholine (1.04 g, 0.012 mol), and 37% formaldehyde (1.07 g) in 25 mL of absolute ethanol was heated at reflux for 10 h. The reaction mixture was concentrated in vacuo and kept overnight. The product obtained upon filtration was recrystallized from ethanol to give 13 in 72% yield: mp 133-134 °C; IR (KBr) 3000, 2940, 2880, 2840, 1730,

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1610, 1480, 1460, 1390, 1350, 1260, 1200, 1120, 1040, 940, 860 cm $^{-1}$. Anal. $(C_{15}H_{18}N_2O_4)$ C, H.

1'-(**Piperidinomethyl**)spiro[1,3-dioxolane-2,3'-indolin]-2'one (14). Following the procedure as described for 13 but with 11 (2.25 g, 0.012 mol), piperidine (1.01 g, 0.012 mol), and 37% formaldehyde (1.07 g) gave, after recrystallization from absolute ethanol, 60% of 14: mp 122-123 °C; IR (KBr) 2960, 2875, 2840, 1730, 1615, 1490, 1470, 1350, 1300, 1235, 1190, 1140, 1030, 940, 860 cm⁻¹. Anal. ($C_{16}H_{20}N_2O_3$) C, H.

6'-Chlorospiro[1,3-dioxolane-2,3'-indolin]-2'-one (16). A mixture of 4 (1.46 g, 0.008 mol), ethylene glycol (1.84 g, 0.03 mol), and p-toluenesulfonic acid (0.04 g) in 100 mL of benzene was heated under reflux for 13 h in a Dean-Stark separator. The reaction mixture was cooled, and the solution was concentrated in vacuo and kept overnight at room temperature. The product thus obtained was recrystallized from benzene to give 61% of 16, mp 174-175 °C. Anal. ($C_{10}H_8CINO_3$) C, H.

1'-Benzylspiro[1,3-dioxolane-2,3'-indolin]-2'-one (17). To a well-stirred solution of 11 (2.40 g, 0.0125 mol) and benzyl bromide (1.6 mL, 0.0125 mol) in 15 mL of anhydrous dimethylformamide at room temperature was added 50% sodium hydride in oil (0.91 g, 0.019 mol). After being stirred for 16 h, the mixture was poured onto ice and the product filtered. The crude product was washed with cold water and recrystallized from ethanol to give 17 in 38% yield: mp 114-115 °C; IR (KBr) 2975, 2900, 1720, 1620, 1490, 1470, 1375, 1320, 1180, 1130, 1040, 960 cm⁻¹. Anal. ($C_{17}H_{15}NO_3$) C, H.

1'-(**Pyrrolidinomethyl**)**spiro**[1,3-dioxolane-2,3'-indolin]-2'-one (18). Following the procedure as described for 13 but with 11 (1.91 g, 0.01 mol), pyrrolidine (0.71 g, 0.01 mol), and 37% formaldehyde (0.91 g) gave, after recrystallization from absolute ethanol, 64% of 18, mp 113-114 °C; IR (KBr) 3000, 2950, 2850, 1735, 1620, 1485, 1470, 1370, 1340, 1300, 1220, 1195, 1140, 1035, 960 cm⁻¹. Anal. ($C_{15}H_{18}N_2O_3$) C, H.

4'-Chlorospiro[1,3-dioxolane-2,3'-indolin]-2'-one (21). Following the procedure as described for 16 but with 5 (1.46 g, 0.008 mol) and ethylene glycol (1.84 g, 0.03 mol) gave after recrystallization from benzene 98% of 21, mp 186–188 °C. Anal. ($C_{10}H_8CINO_3$) C, H.

5'-Iodospiro[1,3-dioxolane-2,3'-indolin]-2'-one (22). Following the procedure as described for 16 but with 10 (1.37 g, 0.005 mol) and ethylene glycol (1.53 g, 0.025 mol) gave after recrystallization from ethanol 43% of 22, mp 173–175 °C. Anal. $(C_{10}H_8INO_3)$ C, H, N.

5'-Methylspiro[1,3-dioxolane-2,3'-indolin]-2'-one (23). Following the procedure as described for 16 but with 9 (1.61 g, 0.01 mol) and ethylene glycol (1.05 g, 0.017 mol) gave after recrystallization from ethanol 20% of 23, mp 133-135 °C. Anal. $(C_{11}H_{11}NO_3)$ C, H, N.

7'-(**Trifluoromethyl**)spiro[1,3-dioxolane-2,3'-indolin]-2'-one (24). Following the procedure as described for 16 but with 8 (0.90 g, 0.0042 mol) and ethylene glycol (1.0 g, 0.016 mol) gave after recrystallization from ethanol 73% of 24, mp 138–142 °C. Anal. ($C_{11}H_8F_3NO_3$) C, H, N.

Spiro[indoline-3,2'-[1,3]oxathiolan]-2-one (25). A mixture of 1 (4.41 g, 0.03 mol), 2-mercaptoethanol (3.12 g, 0.04 mol), and p-toluenesulfonic acid (0.04 g) in 100 mL of benzene was heated under reflux for 8 h in a Dean-Stark separator. The reaction mixture was cooled, and the solution was concentrated in vacuo and kept overnight at room temperature. The product thus obtained was recrystallized from benzene to give 3.05 g (49%) of **25**: mp 155-156 °C; IR (KBr) 3200, 3140, 2975, 2925, 2870, 1750, 1620, 1470, 1420, 1325, 1265, 1210, 1110, 1075, 1000, 910 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 7.37-6.73 (aromatic, 4 H), 4.49 (t, 2 H, CH₂O, J = 6 Hz), 3.45 (t, 2 H, CH₂S, J = 6 Hz). Anal. (C₁₀H₉NO₂S) C, H.

5-Chlorospiro[indoline-3,2'-[1,3]oxathiolan]-2-one (26). Following the procedure as described above but with **3** gave after recrystallization from ethanol 53% of **26**, mp 134–136 °C. Anal. $(C_{10}H_8CINO_2S)$ C, H, N.

Spiro[1,3-dithiolane-2,3'-indolin]-2'-one (27) was prepared as reported. Compound 27 had mp 197-198 °C (ethanol) (lit.⁹ mp 200-201 °C).

5'-Bromospiro[1,3-dithiolane-2,3'-indolin]-2'-one (28). A mixture of 2 (2.21 g, 0.01 mol), 1,2-ethanedithiol (1.0 g, 0.011 mol), and p-toluenesulfonic acid (0.02 g) in 80 mL of benzene was heated

⁽¹⁵⁾ For quantification (data) of anticonvulsant activity and neurotoxicity of most antiepileptic drugs marketed in the United States, see: Gladding, G. D.; Kupferberg, H. J.; Swinyard, E. A. In Antiepileptic Drugs; Frey, H. H., Janz, D., Eds.; Springer Verlag: Berlin, 1985; p 341.

under reflux for 36 h. The water formed was azeotropically removed in a Dean-Stark separator. The reaction mixture was allowed to cool to room temperature. The product thus obtained was filtered and recrystallized from ethanol, and then from benzene to give 28 in 57% yield: mp 195-196 °C; IR (KBr) 3160, 3100, 3040, 2960, 2910, 2880, 1710, 1610, 1470, 1440, 1280, 1230, 1185, 1120, 1040 cm⁻¹. Anal. (C₁₀H₈BrNOS₂) C, H.

1'-(Piperidinomethyl)spiro[1,3-dithiolane-2,3'-indolin]-2'-one (29). Following the procedure as described for 13 but with 27 (1.12 g, 0.005 mol), piperidine (0.43 g, 0.005 mol), and 37% formaldehyde (0.45 g) gave, after recrystallization from absolute ethanol, 78% of 29: mp 145-146 °C; IR (KBr) 2960, 2875, 2810, 1715, 1600, 1480, 1465, 1345, 1300, 1240, 1165, 1120, 1040 cm⁻¹. Anal. (C₁₆H₂₀N₂OS₂) C, H.

1'-(Morpholinomethyl)spiro[1,3-dithiolane-2,3'-indolin]-2'-one (30). Following the procedure as described for 13 but with $\mathbf{27}$ (1.12 g, 0.005 mol), morpholine (0.45 g, 0.005 mol), and 37 % formaldehyde (0.45 g) gave, after recrystallization from ethanol, 81% of 30: mp 143-144 °C; IR (KBr) 3000, 2960, 2880, 2845, 1720, 1605, 1480, 1460, 1420, 1340, 1305, 1290, 1260, 1230, 1155, 1120,

1000, 1400, 1400, 1420, 1340, 1300, 1200, 1200, 1200, 1200, 1200, 1120,

Spiro[1,3-dioxane-2,3'-indolin]-2'-one (32). A mixture of 1 (2.94 g, 0.02 mol), 1,3-propanediol (3.04 g, 0.04 mol), and ptoluenesulfonic acid (0.02 g) in 80 mL of toluene was heated under reflux for 13 h. The water formed was azeotropically removed in a Dean-Stark separator. The reaction mixture was allowed to cool to room temperature, decanted, and evaporated in vacuo. The product thus obtained was recrystallized from ethanol to give 32 in 48% yield: mp 150-151 °C; IR (KBr) 3200, 3120, 3010, 2925, 2875, 1700, 1620, 1460, 1325, 1275, 1245, 1210, 1115, 1080, 900, 845 cm⁻¹. Anal. (C₁₁H₁₁NO₃) C, H.

4-(Chloromethyl)spiro[1,3-dioxolane-2,3'-indolin]-2'-one (33). A mixture of 1 (2.94 g, 0.02 mol), 3-chloro-1,2-propanediol (2.61 g, 0.02 mol), and p-toluenesulfonic acid (0.02) in 80 mL of toluene was heated at reflux. After 12 h the solvent was removed in vacuo. The product thus obtained was recrystallized from benzene to give 0.77 g (16%) of 33: mp 158–159 °C; IR (KBr) 3200, 3150, 2960, 2940, 1730, 1620, 1465, 1320, 1225, 1120, 1065, 1000, 930, 850 cm⁻¹; ¹H NMR (Me₂SO-d₆) δ 7.73-7.03 (aromatic, 4 H), 5.05–4.4 (multiplets, 3 H, CH₂O, CH), 4.27 (d, 2 H, CH₂Cl, J = 6 Hz). Anal. ($C_{11}H_{10}$ ClNO₃) C, H. Pharmacological Evaluation.^{7,19,20} Anticonvulsant screenings

(19) For a description of the NINCDS screening protocol, see: (a) Reference 15. (b) Pharmacology section of Conley, J. D.; Kohn, H. J. Med. Chem. 1987, 30, 567. (c) Clark, C. R.; Davenport, T. W. J. Med. Chem. 1987, 30, 1214.

were carried out through the Antiepileptic Drug Development Program, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), NIH. Each compound submitted was tested for its ability to protect mice (male Carworth Farm No. 1) against electrically and chemically induced seizures. This evaluation (phase I) was performed at three dose levels viz. 30, 100, and 300 mg/kg. The compounds were administered ip, generally in PEG. The maximal electroshock seizure test evaluates the ability of a compound to prevent seizure spread through neural tissue. Maximal electroshock seizures are elicited with 60 cycle alternating current of 50-mA intensity delivered for 0.2 s via corneal electrodes. Protection in the MES test was defined as the abolition of the hind limb tonic extension component of the seizure. Pentylenetetrazole (85 mg/kg) is administered as a $0.5\,\%$ solution subcutaneously. The subcutaneous pentylenetetrazole test estimates the ability to raise seizure threshold for excitation of neural tissue. Protection in the sc-Met test was defined as the failure to observe even a single episode of clonic spasms of at least 5-s duration (threshold seizure). All compounds were tested for neurotoxicity. The rotorod test was used to evaluate central nervous system toxicity. Neurologic toxicity was defined as the failure of the dosed animal to remain on a 1-in. diameter knurled plastic rod, rotating at 6 rpm, for 1 min. Compounds exhibiting anticonvulsant activity at 100 mg/kg or less are usually advanced to phase II (quantitative) testing. Phase II determines the time of peak anticonvulsant and toxic effect. The TD_{50} and ED_{50} are then determined (the tests being performed at the time of peak effect).

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(20) Information obtained from ADD Program, NINCDS, NIH.

9-(2-Fluorobenzyl)-6-(alkylamino)-9H-purines. A New Class of Anticonvulsant Agents

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Several substituted aryl and 6-alkylamino analogues of the anticonvulsant purine 9-(2-fluorobenzyl)-6-(methylamino)-9H-purine (1) were synthesized and tested for anticonvulsant activity against maximal electroshock-induced seizures (MES) in rats. Derivatives with a second fluoro substituent in the 5- or 6-position of the aryl moiety were very active with ip ED₅₀'s that ranged from 2 to 4 mg/kg. Congeners in which the purine 6-substituent was varied among a number of alkylamino groups possessed potent activity against MES that was comparable to or several times better than phenytoin.

Although several drugs are used in the treatment of epilepsy, many patients fail to experience satisfactory

seizure control with them, or they do so at the expense of significant side effects.^{1,2} Due to the need for new im-

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