Analgesic Activity of Novel Spiro Heterocycles. 2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-enes and Related Compounds

Noal Cohen,* Bruce L. Banner, Rocco J. Lopresti,

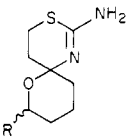
Chemical Research Department

and Herman W. Baruth

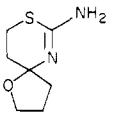
Department of Pharmacology, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received September 19, 1977*

(±)-2-Amino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (1a) and many of its derivatives exhibit significant activity in the phenylquinone writhing and yeast inflamed foot assays. In order to develop structure–activity relationships, the related spiroheterocycles, (±)-2-amino-7-oxa-3-thia-1-azaspiro[5.4]dec-1-ene (2), (±)-2-amino-3-thia-1-azaspiro[5.5]undec-1-ene (3), and (±)-2-amino-7-oxa-1-azaspiro[5.5]undec-1-ene (4), were examined. Of these, only 4 failed to show activity indicating that the analgetic properties displayed by compounds 1–3 are associated, mainly, with the 2-amino-1,3-thiazine ring system. In the 2-acylimino series, evidence is presented suggesting a contribution to the observed activity on the part of the spiroannulated ether ring as well. Both 1a and its *p*-fluorobenzoyl derivative 33 exhibit analgesic activity in the rat tail-flick assay.

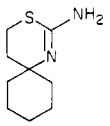
In a previous publication,[1] we described the synthesis and structure determination of the novel spiro[thiazine-pyrans] represented by 1. Pharmacological evaluation of



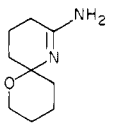
1a ; R=H
1b ; R=C_6H_5
1c ; R=CH_3



2



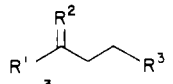
3



4

certain of these compounds revealed significant analgesic activity, a discovery which encouraged us to prepare a variety of derivatives and analogues.[2] A major goal of this program was to determine which structural features or combinations thereof in these unusual molecules were required for the observed pharmacological activity.[3] In this report, we wish to present preliminary analgesic testing data obtained for several of the original compounds[1,2] as well as certain related substances including the amines 2, 3,[4] and 4 which were synthesized in order to develop structure–activity relationships involving the spiro-heterocyclic system.

Chemistry. A. Spiro[thiazinefuran] (2). The synthesis of this compound was patterned after that employed for the homologue **1a**.[1] Thus, vinyl keto ester

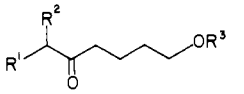


5; R' = Cl, R^2 = O, R^3 = CO_2Me
6; R' = $(CH_2)_2Cl$, R^2 = O, R^3 = CO_2Me
7; R' = $CH=CH_2$, R^2 = O, R^3 = CO_2Me
8; R' = $CH=CH_2$, R^2 = H,OH, R^3 = CH_2OH
9; R' = $(CH_2)_2NEt_2$, R^2 = O, R^3 = CH_2OH
10; R' = $(CH_2)_2Cl$, R^2 = $-O(CH_2)_2O-$, R^3 = CO_2Me
11; R' = $(CH_2)_2Cl$, R^2 = $-O(CH_2)_2O-$, R^3 = CH_2OH

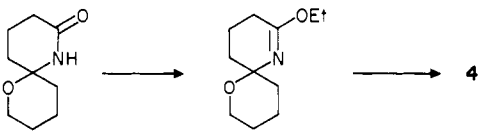
7 was prepared from the commercially available acid chloride 5 via chloro ketone 6, as described by Taylor.[5] Reduction of 7 with $LiAlH_4$ then gave a mixture composed of mainly the vinyl diol 8[6] along with minor amounts of the saturated diol resulting from reduction of the conjugated double bond. Upon oxidation of this mixture with activated manganese dioxide in the presence of diethylamine,[7] the desired Mannich base 9 was formed which yielded compound 2 when treated with thiourea in refluxing toluene–acetic acid.[1]

Alternatively, the chloro ester 6 was converted into the corresponding ethylene ketal 10 which, in turn, gave the alcohol 11 when reduced with $LiAlH_4$. Condensation of 11 with thiourea in moist acetic acid then afforded 2. This route offered little advantage over that proceeding through Mannich base 9 due to the relative instability of the intermediates 10 and 11.

B. Spiro[pyridinepyran] (4). Michael addition of β-keto ester 12[1] to methyl acrylate in the presence of



12 ; R' = CO_2Me, R^2 = H, R^3 = $CH_2C_6H_5$
13 ; R' = CO_2Me, R^2 = $(CH_2)_2CO_2Me$, R^3 = $CH_2C_6H_5$
14 ; R' = H, R^2 = $(CH_2)_2CO_2H$, R^3 = $CH_2C_6H_5$
15 ; R' = H, R^2 = $(CH_2)_2CO_2H$, R^3 = H



16 17 4

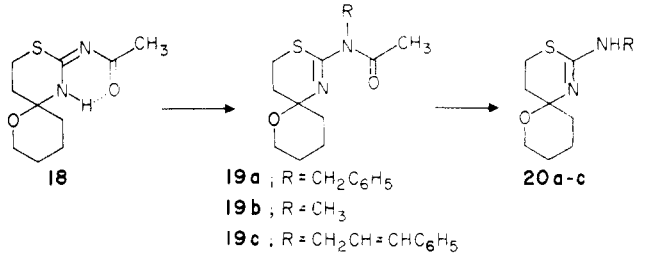
$NaOMe$[8] produced the expected diester 13 which subsequently gave the keto acid 14 upon alkaline hydrolysis and decarboxylation. Catalytic hydrogenolysis of the latter material yielded hydroxy acid 15 which was converted into the spirolactam 16 by treatment with ammonium acetate in DMF.[9] Exposure of 16 to triethyloxonium tetrafluoroborate[10] followed by $NaHCO_3$ gave the very unstable imino ether 17. Methanolic ammonia then transformed 17 into the desired amidine 4 which was purified and characterized as its maleic acid salt.

C. Miscellaneous Derivatives and Analogues. Acylation of the amines 1 using acid chlorides and anhydrides has been described previously.[1] The same procedures were utilized for production of many of the new acyl derivatives and similar derivatives of compounds 2 and 3 (Table I). In addition, several of the compounds in the table were prepared using the acylimidazole method of Rimpler and Schöberl.[11]

The synthesis of *N*-alkyl derivatives of **1a** by condensation of the Mannich base 21[1] with substituted thioureas was generally unrewarding in that complex mixtures were usually formed. These results led to the development of an alternative approach in which the *N*-acetyl compound

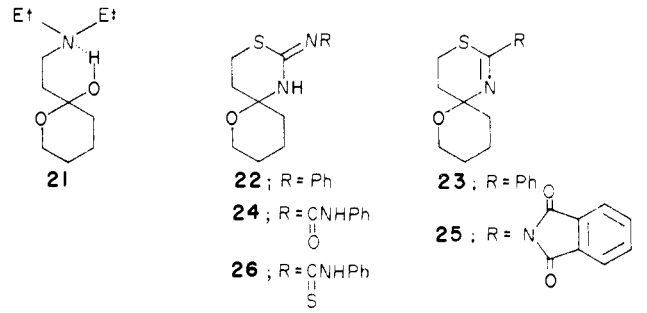
0022-2623/78/1821-0895$01.00/0

18 was converted into its sodium salt with sodium hydride



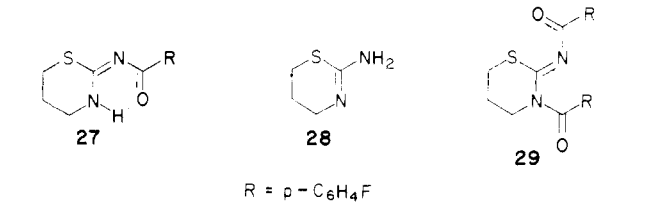
in DMF and alkylated with various reactive halides. Acidic hydrolysis of the resultant products **19a–c** then gave the desired secondary amines **20a–c**. This alkylation process is apparently highly regiospecific since products arising from alkylation of the more sterically encumbered endocyclic nitrogen atom could not be detected.

Treatment of the Mannich base **21**[1] with phenylthiourea gave the desired product **22** albeit in low yield. We assume that this compound is the phenylimino tautomer shown on the basis of structural studies carried out with related monocyclic thiazines.[12] The 2-phenylthiazine **23** was produced by condensation of **21** with thiobenzamide.



Treatment of **1a** with phenyl isocyanate, phthalic anhydride, and phenyl isothiocyanate gave the expected derivatives **24–26**, respectively. Compounds **24** and **26** were assigned the exocyclic double bond structure by analogy with the *N*-acyl derivatives.[1]

For comparison purposes, the monocyclic, monoacyl compound **27** was prepared by treatment of the known



aminothiazine **28**[13,14] with *p*-fluorobenzoyl chloride in pyridine. This reaction produced, in addition to **27**, a substantial amount of the diacyl material **29**[15] which could readily be converted into **27** by heating in ethanol. It is interesting to note that no such diacylated materials could be detected, under identical conditions, starting from the amines **1–3**, again testifying to the relative steric inaccessibility of the endocyclic N atom in these spirocyclic substances.

Pharmacology. Compounds were screened for analgesic activity in mice using the phenylquinone writhing assay[16] and in rats by means of the yeast inflamed foot test.[17] The results are presented in Table II. Compounds 1a, **3**, **33**, and **45** were also evaluated using the rat tail-flick test.[18] The results are contained in Table III along with acute toxicity data for three of these substances. All compounds in Table II except **1b,c**, **4**, **22–24**, **26**, **53**, and **55** were screened by means of the acute adjuvant arthritis test;[19] however, none exhibited significant antiinflammatory activity relative to standard drugs.

Structure–Activity Relationships. The parent amino spiro[thiazinepyran] **1a**[1] shows potent activity in both the writhing and inflamed foot assays, relative to standard drugs. Substitution at the 8 position as in compounds **1c**[1] and especially **1b**[1] leads to decreased activity as does substitution on the exocyclic N atom (compounds **20a,b**). The homologous spiro[thiazinefuran] **2** is somewhat less active than **1a**.

Acylation of the amines **1** and **2** provides a series of derivatives generally maintaining activity. It is interesting to note, however, that **34**, **36**, **38**, and **51–53** are active only in the yeast inflamed foot test. In the series derived from aromatic, carboxylic acids, both electron-donating (e.g., **31**) and electron-withdrawing (e.g., **42**) substituents on the aromatic nucleus provide active compounds. Diminished activity appears to be associated with ortho substitution (e.g., **41**, **50**, and **56**). In contrast to most of the monoacyl derivatives, the urea **24** and thiourea **26** are essentially inactive, as is the 2-phenylimino compound **22**. On the other hand, the phthalimide **25** exhibits substantial potency. The 2-phenylthiazine **23**, a substantially different structural type, lacking the amidine system, is devoid of analgesic properties.

The enantiomers of compound **33** (**54**[1] and **55**[1]) were screened in an attempt to ascertain the relationship of the spiro center chirality to pharmacological activity. Although both compounds are active, the (+) enantiomer appears to be approximately three times as active as its antipode in the writhing test but of essentially equivalent potency in the inflamed foot assay.

The data obtained for compounds **3** and **4** tend to indicate that the aminothiazine ring is the primary structural feature required in order to elicit the observed pharmacological response. Thus, the spirocyclic amidine **4**, in which the S atom in **1a** has been replaced with a methylene group, exhibits no analgesic activity. On the other hand, the spiro[thiazinecyclohexane] **3**, having the 7-oxa moiety in **1a** similarly replaced, shows activity similar to **1a**. It should be noted, however, that whereas acylation of **1a** and **2** generally produces active derivatives (e.g., **33** and **46**), the one acyl derivative of **3** assayed (**57**) is inactive as is the model, monocyclic thiazine **27**. These results suggest that, in the acylimino series, the presence of the spiro-annulated ether ring may be important for maintaining activity.

It was found that the compounds exhibiting activity in the yeast inflamed foot test significantly increased the pain threshold in both the inflamed and noninflamed rat paws. We conclude from these results and from the relative lack of potency in the acute adjuvant arthritis test that these novel compounds resemble centrally acting analgesics rather than nonsteroidal antiinflammatory agents.

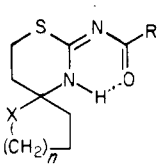
In the rat tail-flick assay, compounds **1a** and **33** are active; however, **45** is inactive in the same dose range. It should be noted that the analogue **3**, which is of nearly comparable activity to **1a** in the writhing assay and quite active in the inflamed foot test, is relatively inactive in the tail-flick test.

In summary, the preliminary studies described herein have led to the discovery of a novel class of analgetic agents which exhibit potency, in certain cases, comparable or superior to standard drugs. Of particular interest are the aroylimino derivatives of aminothiazine **1a** such as **33** and **45**. A determination of the ultimate utility of these compounds must await further evaluation.

Experimental Section

Unless otherwise noted, all reactions were carried out under

Table I. Compounds of Formula



no.	n	X	method[d]	R	mp, °C	crystd from[a]	formula[b,c]
18	2	O	A	CH_3	110–111.5	B-H	$C_{10}H_{16}N_2O_2S$
24	2	O	*d*	NHC_6H_5	177–178	M	$C_{15}H_{19}N_3O_2S$
30	2	O	A	C_6H_5	129.5–130.5	B–H	$C_{15}H_{18}N_2O_2S$
31	2	O	A	*p*-$OCH_3C_6H_4$	104–107	B–H	$C_{16}H_{20}N_2O_3S$
32	2	O	B	3,4-$(OCH_3)_2C_6H_3$	129.5–131	E	$C_{17}H_{22}N_2O_4S$
33[e]	2	O	A	*p*-FC_6H_4	150.5–151.5	B-H or E	$C_{15}H_{17}FN_2O_2S$
34[e]	2	O	A	*p*-BrC_6H_4	128.5–129	B-H or E	$C_{15}H_{17}BrN_2O_2S$
35	2	O	A	*p*-ClC_6H_4	128.5–130	E	$C_{15}H_{17}ClN_2O_2S$
36	2	O	A	1-adamantyl	158–160	E	$C_{19}H_{28}N_2O_2S$
37·HCl	2	O	A	$C_6H_5CH{=}CH$	177.5–179	E	$C_{17}H_{20}N_2O_2S{\cdot}HCl$
38	2	O	A	*m*-$CF_3C_6H_4$	101–102	E	$C_{16}H_{17}F_3N_2O_2S$
39	2	O	B	*m*-FC_6H_4	85–86	E	$C_{15}H_{17}FN_2O_2S$
40	2	O	A	*o*-ClC_6H_4	115.5–117	E	$C_{15}H_{17}ClN_2O_2S$
41	2	O	A	2,4,6-$(CH_3)_3C_6H_2$	120–121.5	A	$C_{18}H_{24}N_2O_2S$
42	2	O	A	*p*-$NO_2C_6H_4$	170.5–172	A	$C_{15}H_{17}N_3O_4S$
43	2	O	A	3,4,5-$(OCH_3)_3C_6H_2$	142.5–143.5	E	$C_{18}H_{24}N_2O_5S$
44	2	O	A	*p*-CNC_6H_4	170.5–172	A	$C_{16}H_{17}N_3O_2S$
45	2	O	A	*p*-$CH_3C_6H_4$	173.5–175	E	$C_{16}H_{20}N_2O_2S$
46·HCl	1	O	A	*p*-FC_6H_4	193–194	M	$C_{14}H_{15}FN_2O_2S{\cdot}HCl$
47	2	O	A	2-furyl	101–103	E	$C_{13}H_{16}N_2O_3S$
48	2	O	B	2-thenyl	115–116	E	$C_{13}H_{16}N_2O_2S_2$
49	2	O	A	$(CH_3)_3C$	124.5–125.5	E	$C_{13}H_{22}N_2O_2S$
50	2	O	A	2,6-$(OCH_3)_2C_6H_3$	187.5–188.5	E	$C_{17}H_{22}N_2O_4S$
51	2	O	B	1-methyl-1-cyclohexyl	103–104	E	$C_{16}H_{26}N_2O_2S$
52	2	O	A	*m*-$NO_2C_6H_4$	126–127	A	$C_{15}H_{17}N_3O_4S$
53	2	O	B	1-naphthyl	139.5–140.5	A	$C_{19}H_{20}N_2O_2S$
54[e]	2	O		*p*-FC_6H_4(+)	108.5–109.5		$C_{15}H_{17}FN_2O_2S$
55[e]	2	O		*p*-FC_6H_4(−)	109–110		$C_{15}H_{17}FN_2O_2S$
56	2	O	B	*o*-OHC_6H_4	149.5–150.5	A	$C_{15}H_{18}N_2O_3S$[f]
57	2	CH_2	A	*p*-FC_6H_4	96–97.5	E	$C_{16}H_{19}FN_2OS$
58[g]	2	CH_2	A	CH_3	89–90.5	B-H	$C_{11}H_{18}N_2OS$

[a] A = acetonitrile, B = benzene, E = ethanol, H = hexane, M = methanol. [b] All compounds were analyzed for C, H, N, and S and gave analytical values within 0.4% of theory. [c] All compounds gave compatible UV, IR, NMR, and mass spectra. [d] See Experimental Section. [e] Compound described in ref 1. [f] Analysis for S not obtained. [g] Compound described in ref 4.

an atmosphere of nitrogen. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The "usual workup" consists of dilution of the reaction mixture with saturated brine followed by three extractions with the indicated solvent. The organic extracts were then combined, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated at 40–50 °C under water aspirator pressure using a rotary evaporator. The residue was dried to constant weight under high vacuum. Column chromatography was performed using Merck (Darmstadt) silica gel (0.05–0.2 mm). The progress of reactions was usually monitored by thin-layer chromatography which was performed using Brinkman, silica gel G plates with UV indicator. Plates were developed with one of the following mobile phases: A, 9:1 benzene–triethylamine; B, 1:1 benzene–ethyl acetate; C, 1:1 hexane–ethyl acetate. Spots were detected with UV light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating. The ultraviolet spectra were recorded on a Cary 14M spectrophotometer in 95% ethanol. Tetrahydrofuran (THF), pyridine, and DMF were dried by slurrying over Woelm grade I, neutral alumina just prior to use. Where microanalyses are indicated only by the symbols of the elements, the analytical values obtained were within 0.4% of the theoretical values.

Pharmacological Methods. General. All compounds having a water solubility less than 1% were micronized prior to administration. Drugs were administered as solutions or suspensions in distilled water.

Phenylquinone-Induced Writhing Assay. The writhing test described by Siegmund et al.[16] as modified by Hendershot and Forsaith[20] was used to test compounds for analgesic activity in mice. Five male CF-1 mice obtained from Carworth Farms, weighing 20–22 g, were used per dose level. Five vehicle-treated control mice typically produce 100–125 writhing episodes during the 5-min observation period beginning 10 min after the intraperitoneal injection of 0.25 mL of a 0.02% 19:1 aqueous–ethanolic solution of 2-phenyl-1,4-benzoquinone. The test compounds were administered 15 min prior to the phenylquinone. The percent of protection afforded by an analgetic substance was determined for each experimental group of five mice as follows.

$$\% \text{ protection} = [(\text{no. of writhes by control group} - \text{no. of writhes by exptl group})/\text{no. of writhes by control group}] \times 100$$

The ED_{50} is the dose which reduces the expected number of writhes by 50%. The statistical method used to estimate the ED_{50} values (and 95% confidence limits) has been described by Litchfield and Wilcoxon.[21]

Rat Tail-Flick Assay.[18] A Model 33 Tail Flick Analgesia Meter (Innovators in Instrumentation, Landing, N.J.) was used to measure the animal reaction time to a thermal stimulus produced by an intense light beam. Male Sprague–Dawley rats obtained from Charles River Laboratories weighing from 126 to 140 g were used only once in the test procedure. Each rat was placed into a plastic restraining cage. The animal's tail was passed through a slot at one end of the holder and positioned in a groove in the plastic base of the analgesia meter so as to occlude an opening over a photocell. When the test switch was turned on, a highly accurate LED timer was activated and an intense light beam focused on the tail approximately 1.5 cm from the tip. When the animal sensed the thermal stimulus, it flicked its tail which permitted the light to fall on the photocell which automatically stopped the timer. A switch permitted the operator to stop the timer for manual determinations and to turn off the lamp in the event that the reaction time equaled or exceeded the cutoff time

Table II. Phenylquinone Writhing and Yeast Inflamed Foot Tests

compd	PQW,[a] ED_{50}, mg/kg[b]	YIF,[j] ED_{50}, mg/kg
1a[c,d]	3.6 (1.9-6.8)	0.6
1b[c,d,f]	64 (35.6-115.2)	>200
1c[c,d,g]	25 (11.9-52.5)	3.2
2[d]	15 (7.5-30.0)	4.0
3[d,i]	6.6 (3.5-12.5)	19
4[d]	>200	>50
18	3.1 (1.6-6.2)	1.9
20a	>200	>100
20b	52 (27.4-98.8)	21
22[e]	>200	>100
23[e]	>200	>200
24	>200	>200
25	14.8 (7.4-29.6)	7.0
26	~200 (-48%)[h]	>200
27	>100	>200
30	5.0 (2.3-11.0)	2.6
31	62 (36.5-105.4)	6.0
32	~200 (-75%)[h]	4.5
33[c]	49 (25.8-93.1)	2.0
34[c]	>200	3.2
35	1.1 (0.6-1.9)	2.4
36	>200	14
37[e]	17 (8.9-32.3)	2.5
38	>200	11
39	9.2 (5.1-16.6)	1.3
40	>200	N.T.
41	>200	>200
42	28 (14.7-53.2)	0.9
43	>200	>200
44	60 (30.0-120.0)	1.0
45	60 (30.0-120.0)	0.9
46[e]	14.8 (8.5-25.9)	2.0
47	42 (24.7-71.4)	N.T.
48	48 (29.1-79.2)	3.8
49	~200 (-53%)[h]	29
50	>200	>200
51	>200	16
52	>200	8.2
53	>200	28
54[c]	8.8 (4.0-19.4)	2.0
55[c]	28 (14.7-53.2)	1.8
56	>200	>200
57	>200	>100
acetylsalicylic acid	82 (41.0-164.0)	50
phenylbutazone	45 (23.7-85.5)	25
indomethacin	8.8 (5.1-15.3)	1.2
d-propoxyphene	48 (24.0-96.0)	60
codeine phosphate	18 (9.0-36.2)	40
morphine sulfate	4.8 (3.0-7.7)	25

[a] Mice, po; see the Experimental Section. [b] 95% confidence limits in parentheses. [c] See ref 1. [d] Maleic acid salt tested. [e] HCl salt tested. [f] Mixture of epimers converted to the maleic acid salt without separation; mp 169-170 °C dec (from CH_3CN). Anal. ($C_{14}H_{18}N_2OS \cdot C_4H_4O_4$) C, H, N, S. [g] Mixture of epimers converted to the maleic acid salt without separation; mp 135-144 °C (from CH_3CN). Anal. ($C_9H_{16}N_2OS \cdot C_4H_4O_4$) C, H, N, S. [h] Percent reduction in number of writhing episodes at the dose tested. [i] See ref 4. [j] Rat, po; see the Experimental Section.

(10 s). Animals were sometimes observed to reposition their tails so that the light beam fell on another portion of the tail. The intensity of the emitted light was adjusted by a built-in rheostat so that the normal preinjection reaction time latency occurred at from 2 to 4 s. The rats were divided into groups of five and control reaction times were measured in duplicate and averaged to constitute the initial or control reaction time. Each group was then treated with logarithmically spaced oral doses and determinations were made in duplicate again at 30, 60, 90, 120, 150, and 180 min after administration of the test compound. Tissue damage was minimized by limiting the exposure time to 10 s for any single determination. The differences between the initial control reaction times and posttreatment reaction times were tested for statistical significance by an analysis of variance and Student's *t* test.

Table III. Rat Tail-Flick Test and Acute Mouse Toxicity

compd	ED_{50}, mg/kg[a-c]	$LD_{50} \pm SE$, mg/kg[c]
1a maleate	12.0 (9.3-16.2)	120 ± 76[d,e]
3 maleate	>50[h]	N.T.
33	22.3 (16.1-40.6)	630 ± 73[f]
45	>25[h]	1120 ± 122[g]
morphine sulfate	29.3 (24.6-34.0)	

[a] Peak effect; 95% Fieller's limits in parentheses. [b] Volume of aqueous suspending vehicle was 1 mL/100 g of body weight. [c] po. [d] Based on only three animals per dose level. [e] 33 ± 1.2 mg/kg ip. [f] 1370 ± 99 mg/kg ip. [g] >400 mg/kg ip. [h] Not tested at higher dose levels.

The percent of maximum possible response (% MPR) for each dose and time interval was calculated from the formula described by Dewey and Harris.[18]

$$\% \text{ MPR} = \frac{\text{test latency} - \text{control latency}}{\text{cutoff time} - \text{control latency}} \times 100$$

The % MPR for each group was plotted against the log dose, and the ED_{50} and 95% Fieller's limits were computed from a line fitted to the data by the Berkson minimum logic chi-square test.

Yeast Inflamed Foot Test. The method of Randall and Selitto[17] was employed. Five male Sprague–Dawley rats obtained from Charles River Laboratories, weighing 125–150 g, were used per dose level. Pain threshold measurements were taken 2 h after administration of the drug on both the inflamed and noninflamed paws. The ED_{50} is the dose that raises the average pain threshold by 50 mm of mercury in the inflamed paw. ED_{50} values were obtained from dose vs. response plots. At least three doses were used to obtain the plots.

Acute Toxicity. Carworth Farms CF-1S mice of both sexes weighing 17-25 g were used. The compound was suspended in a gum acacia solution and administered orally and intraperitoneally to groups of six to ten mice per dose level. The mice receiving the compound intraperitoneally were observed 24 h for mortality and those dosed orally were observed for 5 days for mortality. The LD_{50} was calculated by the method of Miller and Tainter.[22]

Methyl 4-Oxo-5-hexenoate (7). This material was prepared starting from 5 (Aldrich Co.), via the chloro ester 6, using the procedures of Taylor.[5] There was obtained a colorless liquid, bp 110–114 °C (18 mm), in 41% overall yield [lit.[5] bp 96 °C (10 mm)].

Hex-5-ene-1,4-diol (8). A slurry of 6 g (0.158 mol) of $LiAlH_4$ in 200 mL of dry THF was stirred with ice bath cooling while a solution of 15 g (0.105 mol) of keto ester 7 in 50 mL of dry THF was added dropwise over 1 h. The resulting mixture was stirred at 0–5 °C for 1 h and then at room temperature for 1.75 h. With ice bath cooling, the reaction mixture was cautiously decomposed by dropwise addition of 12 mL of H_2O and 9.6 mL of 10% aqueous NaOH. After stirring for several hours, the mixture was filtered and the solids were washed well with CH_2Cl_2. The filtrate and washes were combined and concentrated in vacuo giving 12.6 g of oily residue. This material was combined with 10.2 g of crude product from another run and distilled. There was obtained 16.6 g (69.7%) of diol 8 as a viscous, colorless oil, bp 74–77 °C (0.3 mm) [lit.[6] bp 98–100 °C (1.8 mm)].[23]

6-Diethylamino-4-oxo-1-hexanol (9). The procedure described previously[1] for preparation of the homologue 21 was employed for conversion of 8 to 9. The Mannich base 9 was obtained in 39% yield as a yellow oil.[23]

6-Chloro-4,4-ethylenedioxy-1-hexanol (11). A solution of 1.8 g (0.01 mol) of crude keto ester 6,[5] 2.5 mL of ethylene glycol, 2.5 mL of trimethyl orthoformate, 0.1 mL of concentrated sulfuric acid, and 30 mL of THF was stirred at room temperature for 4.5 h and then poured into excess saturated aqueous $NaHCO_3$ solution. The resulting mixture was worked up with ether in the usual manner, giving 2.3 g of crude, brown, oily ketal ester 10.

A solution of 7 mL of sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in toluene) in 10 mL of toluene was stirred with ice-bath cooling while a solution of 2.2 g of this crude ester in 10 mL of toluene was added dropwise during 15 min. The

resulting solution was stirred at room temperature for 1.75 h and then cautiously poured onto a mixture of ice and 10% aqueous sodium hydroxide solution. Workup with ether in the usual manner gave 1.2 g of crude hydroxy acetal 11 as a brown oil which was used without further purification.

(±)-2-Amino-7-oxa-3-thia-1-azaspiro[5.4]dec-1-ene (2). A. From Mannich Base 9. A mixture of 0.8 g (4.3 mmol) of Mannich base 9, 0.33 g (4.3 mmol) of thiourea, 13.5 mL of toluene, and 4.3 mL of glacial acetic acid was stirred and heated at reflux for 3 h.[1] The resulting solution was concentrated at reduced pressure. The residue was chilled and treated with excess 10% aqueous NaOH solution and the alkaline mixture was worked up with CH_2Cl_2 in the usual manner giving 0.4 g (54%) of pale-yellow crystalline residue. Recrystallization from CH_3CN gave pure spiro[thiazinefuran] (2) as a pale-yellow solid, mp 143–145 °C.[23] Anal. ($C_7H_{12}N_2OS$) C, H, N, S. The maleic acid salt was a colorless solid, mp 143–144 °C (recrystallized from EtOH). Anal. ($C_7H_{12}N_2OS \cdot C_4H_4O_4$) C, H, N, S.

B. From Chloro Ketal 11. A mixture of 1.2 g (6.17 mmol) of crude chloro ketal 11, 0.47 g (6.17 mmol) of thiourea, 6.2 mL of glacial acetic acid, 0.2 mL of water, and 20 mL of toluene was stirred at room temperature for 1.5 h and then at reflux for 2.75 h. The resulting mixture was concentrated at reduced pressure and the residue was treated with ether and washed twice with dilute aqueous HCl. The acid extracts were combined and washed again with ether. The acid solution was made alkaline with K_2CO_3 and worked up with CH_2Cl_2 as usual giving 0.7 g of yellow, solid spiro[thiazinefuran]. TLC analysis of this material (system A) showed essentially a single spot with R_f identical with the amino compound prepared in part A. This material was dissolved in hot EtOH and treated with 0.47 g of maleic acid. Upon cooling there was obtained 0.32 g of 2 maleate as a colorless solid, mp 143–144 °C.

Dimethyl 2-(5-Benzyloxypentanoyl)pentanedioate (13). A mixture of 22.2 g (0.084 mol) of keto ester 12[1] and 2.2 mL of 0.84 M methanolic NaOMe was evacuated to remove most of the methanol and then brought to 110 °C whereupon 7.8 mL (0.086 mol) of methyl acrylate was added, with stirring, over a 10-min period. Stirring and heating were continued for 30 min during which time the temperature was raised to 132 °C.[8] After cooling, the reaction mixture was worked up with ether in the usual manner giving 28.5 g (97%) of diester 13 as an orange oil which was used without further purification. In a separate experiment, a sample of crude 13 was purified by chromatography on silica gel (50 parts). Elution with 1:1 hexane–ether gave the pure (TLC, system C) diester as a pale-yellow oil.[23] Anal. ($C_{19}H_{26}O_6$) C, H.

5-Oxo-9-benzyloxynonanoic Acid (14). A mixture of the diester from the preceding experiment (28.5 g) and 180 mL of 2 N aqueous NaOH was stirred and refluxed for 4 h, then cooled, and extracted with ether. The aqueous, alkaline solution was acidified with 3 N aqueous HCl and worked up with CH_2Cl_2 in the usual manner giving 22.6 g (97%) of 14 as an orange liquid which was used without further purification.[23]

(±)-7-Oxa-1-azaspiro[5.5]undecan-2-one (16). A mixture of 13.7 g (0.049 mol) of acid 14, 1.5 g of 5% palladium on carbon, and 250 mL of ethyl acetate was stirred in an atmosphere of hydrogen for 6 h during which time 99% of the theoretical H_2 volume was taken up. The catalyst was filtered and the filtrate was concentrated in vacuo giving a yellow oily residue of the hydroxy acid 15 (IR and NMR compatible) which was immediately dissolved in 60 mL of DMF and treated with 60 g of NH_4OAc.[9] After heating the resulting mixture at 85 °C for 20 h, the solvent was removed in vacuo and the residue was worked up with CH_2Cl_2 in the usual manner (the organic extracts were additionally washed with $NaHCO_3$ solution). There was obtained 5.1 g (61.6%) of the spirolactam 16 as a pale-yellow solid which was essentially homogeneous on TLC analysis (system B). A sample from another run was recrystallized from EtOH giving a colorless solid, mp 116–118.5 °C.[23] Anal. ($C_9H_{15}NO_2$) C, H, N.

(±)-2-Amino-7-oxa-1-azaspiro[5.5]undec-1-ene Maleate (4 Maleate). To a solution of 2 g (11.84 mmol) of spirolactam 16 in 20 mL of CH_2Cl_2 there was added a solution of 3.04 g (16 mmol) of triethyloxonium fluoroborate[10] in 16 mL of CH_2Cl_2. The resulting solution was stirred at room temperature for 3.5 h, then treated with saturated aqueous $NaHCO_3$, and rapidly worked up with CH_2Cl_2 as usual to give 2.2 g of the crude, oily, very unstable imino ether 17 which was used immediately: IR (film) 1670 cm^{-1} (C=N), NH absent.

To this material there was added 30 mL of methanolic ammonia (4.4 g of NH_3/50 mL of MeOH) and the resulting solution was stirred at room temperature for 17 h and then concentrated in vacuo. The solid residue (1.98 g) was treated with 1.37 g of maleic acid and 20 mL of CH_3CN, and the mixture was warmed until solution occurred. After storage at room temperature for 24 h, a small amount of a colorless solid impurity was filtered off and the filtrate was diluted with 20 mL of ether which led to the precipitation of 4 maleate (1.4 g, 42%), isolated as a colorless solid, mp 126–129 °C. The analytical sample, obtained from a separate experiment, exhibited mp 127–129 °C.[23] Anal. ($C_9H_{16}N_2O \cdot C_4H_4O_4$) C, H, N.

(±)-2-Benzylamino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (20a). A slurry of 0.624 g (0.013 mol) of 50% sodium hydride–mineral oil dispersion in 12 mL of dry DMF was stirred with ice-bath cooling while a solution of 2.7 g (0.0118 mol) of amide 18 in 30 mL of dry DMF was added dropwise over a 10-min period. Hydrogen was evolved and the mixture was stirred for 10 min at 0–5 °C and then for 1 h at room temperature. The reaction mixture was once again cooled in an ice bath while 1.45 mL (0.0125 mol) of benzyl chloride in 15 mL of DMF was added over 5 min. The ice bath was removed and the slurry was stirred at room temperature for 4 h before addition of 3 mL of water. The resulting solution was concentrated to dryness in vacuo and the residue was taken up in ether and washed three times with 3 N aqueous HCl. The acidic washes were combined and extracted once with ether. The ether extracts were discarded. The acidic extracts were made alkaline with 10% aqueous NaOH solution and then worked up with ether as usual giving 2.96 g of yellow oily product composed of a mixture of 19a and 20a. TLC analysis showed essentially two spots, R_f 0.37 and 0.15 (system B); IR (film) 3340 (NH), 1680 (C=O), 1620 cm^{-1} (C=N). This material was stirred and refluxed with 25 mL of 2 N aqueous HCl for 2 h. After cooling, the mixture was made alkaline with 10% NaOH solution and worked up in the usual manner with CH_2Cl_2. This gave 2.5 g of crude crystalline 20a. Recrystallization from EtOH furnished 1.68 g (51.6%) of colorless crystals, mp 94–95 °C. TLC analysis showed a single spot, R_f 0.5 (system A). The analytical specimen was a colorless solid, mp 94.5–95.5 °C.[23] Anal. ($C_{15}H_{20}N_2OS$) C, H, N, S.

(±)-2-Methylamino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (20b). This material was prepared in 57% yield as a colorless solid, mp 107.5–109 °C (from EtOH), starting from 18 and CH_3I, using the procedure of the preceding experiment.[23] Anal. ($C_9H_{16}N_2OS$) C, H, N, S.

(±)-2-Cinnamylamino-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (20c). This material was prepared starting from 18 and cinnamyl bromide using the procedure described above for the *N*-benzyl analogue. There was obtained a colorless solid: mp 107–108 °C; UV max 253 nm (ε 21 990).[23] Anal. ($C_{17}H_{22}N_2OS$) C, H, N, S.

(±)-2-Phenylimino-7-oxa-3-thia-1-azaspiro[5.5]undecane (22). A solution of 3 g (0.0149 mol) of Mannich base 21,[1] 2.28 g (0.015 mol) of phenylthiourea, 15 mL of glacial acetic acid, and 50 mL of toluene was stirred and heated at reflux for 18 h using a Dean-Stark trap to remove water. The solution was then concentrated to dryness in vacuo. The residue was treated with ether and washed three times with dilute aqueous HCl. The acid extracts were combined and washed once with ether. The ether extracts were discarded. The aqueous solution was made alkaline with 10% NaOH solution and worked up in the usual manner with CH_2Cl_2 giving 2.1 g of red gum. This material was chromatographed on 100 g of silica gel. The fractions eluted with 9:1 benzene–ether afforded 0.922 g of yellow, semicrystalline material rich in the desired product 22 (TLC R_f 0.45, system B). A sample of this material was recrystallized twice from benzene–hexane giving pure 22 as a tan solid: mp 103–104.5 °C; UV max 261 nm (ε 12 700).[23] Anal. ($C_{14}H_{18}N_2OS$) C, H, N, S. The HCl salt was a colorless solid, mp 166.5–168 °C (from EtOH). Anal. ($C_{14}H_{18}N_2OS \cdot HCl$) C, H, N, S.

(±)-2-Phenyl-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (23). A 20-g (0.1 mol) sample of Mannich base 21[1] was condensed with thiobenzamide (14 g, 0.1 mol) using the procedure described in the preceding experiment except that the reaction mixture was

refluxed for 3 h. The crude, basic product (14 g) was chromatographed on silica gel (400 g). Elution with 19:1 benzene–ether gave 8.0 g (32.4%) of pure **23** as an orange oil: UV max 239 nm (ε 13 100).[23] Anal. ($C_{14}H_{17}NOS$) C, H, N, S. The hydrochloride was a colorless, hygroscopic solid, mp 134–136 °C dec (from acetone; many samples exhibited melting points in the range of 110–115 °C). Anal. ($C_{14}H_{17}NOS \cdot HCl$) C, H, N.

(±)-2-(3-Phenylcarbamoyl)imino-7-oxa-3-thia-1-azaspiro[5.5]undecane (24). A solution of 1 g (5.38 mmol) of **1a** and 0.675 g (5.65 mmol) of phenyl isocyanate in 20 mL of CH_2Cl_2 was stirred at room temperature for 1.5 h and then concentrated in vacuo. The residue was triturated with C_6H_6 and then recrystallized from MeOH to give tan crystals of **24** (see Table I): UV max 277 nm (ε 20 000).

(±)-2-(3-Phenylthionocarbamoyl)imino-7-oxa-3-thia-1-azaspiro[5.5]undecane (26). This compound was prepared in 80% yield, from **1a** and phenyl isothiocyanate, using the procedure described in the preceding experiment, as a colorless solid: mp 157–158 °C (from EtOH); UV max 235 nm (ε 11 850), 307 (25 600).[23] Anal. ($C_{15}H_{19}N_3OS_2$) C, H, N, S.

(±)-2-Phthalimido-7-oxa-3-thia-1-azaspiro[5.5]undec-1-ene (25). A solution of 1 g (5.38 mmol) of **1a** and 0.81 g (5.45 mmol) of phthalic anhydride in 15 mL of dry pyridine was stirred at room temperature for 5 h and then worked up with ether in the usual manner. The product (0.9 g) was chromatographed on 50 g of silica gel. Elution with 4:1 and 1:1 benzene–ether afforded 0.55 g of pure **25** as a colorless solid. Two recrystallizations from benzene–hexane gave 0.474 g (27.9%) of a colorless solid: mp 166–167.5 °C; UV max 220 nm (ε 49 000), 293 (2345), 238 sh (14 000).[23] Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N, S.

Acylation Procedures. The monoacyl compounds in Table I were prepared by reaction of the parent amine with the appropriate commercially available acid chloride or anhydride in pyridine solution as described previously[1] (method A) or by treatment of the parent amine with an acylimidazole (generated in situ from a commercially available carboxylic acid) in THF solution[11] (method B). The products were purified by column chromatography and/or recrystallization. Purity was determined by TLC analysis (system B). Yields were generally in the range of 80–90% by either method.

2-*p*-Fluorobenzoylimino-3,4,5,6-tetrahydro-2*H*-1,3-thiazine (27). A mixture of 5.12 g (0.026 mol) of the HBr salt of aminothiazine **28**[13,14] and 50 mL of pyridine was stirred with ice-bath cooling while 3 mL (4.12 g, 0.026 mol) of *p*-fluorobenzoyl chloride was added dropwise over a 5-min period. The resulting slurry was stirred at 0–5 °C for 15 min and at room temperature for 1.75 h and then poured into excess saturated aqueous $NaHCO_3$ solution. Workup with CH_2Cl_2 in the usual manner gave 5.05 g of tan solid. TLC analysis showed two spots of approximately equal intensity, R_f 0.50 (**29**) and 0.36 (**27**) (solvent system B). This material was dissolved in C_6H_6 and the solution was washed twice with 20 mL of 1.5 N aqueous H_2SO_4. The acid extracts were combined and extracted once with C_6H_6 and set aside. The C_6H_6 solutions were processed as usual giving 2.9 g (31%) of essentially pure, colorless solid diamide, **29**. A purified sample had mp 149–151.5 °C; UV max 253 nm (ε 10 100), 306 (8750).[23]

The acid solution was made alkaline with K_2CO_3 and worked up with CH_2Cl_2 in the usual manner giving 1.5 g (24.4%) of a pure, colorless solid, **27**. Two recrystallizations from ethanol gave colorless crystals: mp 116.5–117.5 °C; UV max 247 nm (ε 9600), 289 (23 000).[23] Anal. ($C_{11}H_{11}FN_2OS$) C, H, N, S.

Heating the above diamide **29** in boiling EtOH (30 mL) for 30 min gave a quantitative conversion (TLC) to **27** and ethyl *p*-fluorobenzoate. This mixture was separated by partition between 1.5 N H_2SO_4 and C_6H_6 as above, affording an additional 1.6 g of pure **27**.

Acknowledgment. The analgesic testing data were obtained by Mrs. D. Kelly and Mrs. J. Ploski, whose contributions are greatly appreciated. The acute toxicity data were supplied by Ms. D. Hane and Dr. W. Pool. Most of the spectral and microanalytical determinations were carried out by the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N.J. The assistance provided by Mr. L. A. Dolan and his associates, involving the preparation of certain starting materials, greatly facilitated these studies. The support and encouragement provided by Dr. G. Saucy must also be acknowledged.

References and Notes

(1) N. Cohen, B. L. Banner, J. F. Blount, G. Weber, M. Tsai, and G. Saucy, *J. Org. Chem.*, **39**, 1824 (1974).
(2) West German Patent 2 241 140 (March 1, 1973) (Hoffmann-LaRoche Inc.); *Chem. Abstr.*, **78**, 159642t (1973).
(3) Related monocyclic 2-arylamino-5,6-dihydro-4*H*-1,3-thiazines are reported to possess pharmacological activity; cf. (a) Belgium Patent 634 552 (Farbenfabriken Bayer AG) [*Chem. Abstr.*, **61**, 4369c (1964)]; (b) West German Patent 1 173 475 (Farbenfabriken Bayer AG) [*Chem. Abstr.*, **61**, 13323e (1964)]; (c) A. Schöberl and K-H. Magosch, *Justus Liebigs Ann. Chem.*, **742**, 74 (1970), and references cited therein.
(4) N. Cohen and B. L. Banner, *J. Heterocycl. Chem.*, **14**, 717 (1977).
(5) H. T. Taylor, *J. Chem. Soc.*, 3922 (1958).
(6) S. F. Birch, R. A. Dean, and N. J. Hunter, *J. Org. Chem.*, **23**, 1390 (1958).
(7) N. Cohen, B. L. Banner, J. F. Blount, M. Tsai, and G. Saucy, *J. Org. Chem.*, **38**, 3229 (1973), and references cited therein.
(8) The procedure of H. Kappeler, D. Staubfacher, A. Eschenmoser, and H. Schinz, *Helv. Chim. Acta*, **37**, 957 (1954), was employed.
(9) G. Nominé, G. Amiard, and V. Torelli, *Bull. Soc. Chim. Fr.*, 3664 (1968).
(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 1210.
(11) M. Rimpler and A. Schöberl, *Tetrahedron Lett.*, 3185 (1968).
(12) A. Kálmán, G. Argay, B. Ribar, and L. Toldy, *Tetrahedron Lett.*, 4241 (1977), and references cited therein.
(13) H. W. Schubert and O. Behner, *Arch. Pharm. (Weinheim, Ger.)*, **301**, 750 (1968).
(14) A. Schöberl, M. Kawohl, and G. Hansen, *Justus Liebigs Ann. Chem.*, **614**, 83 (1958).
(15) The facile diacylation of **28** has been reported previously; see ref 3c.
(16) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957).
(17) L. O. Randall and J. J. Selitto, *Arch. Int. Pharmacodyn. Ther.*, **111**, 409 (1957).
(18) W. L. Dewey and L. S. Harris in "Methods in Narcotics Research", S. Ehrenpreis and A. Neidle, Ed., Marcel Dekker, New York, N.Y., 1975, pp 101–108.
(19) B. B. Newbould, *Br. J. Pharmacol.*, **21**, 127 (1963).
(20) L. C. Hendershot and J. J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1959).
(21) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(22) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).
(23) This compound exhibited compatible IR, NMR, and MS data.