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Synthesis of Spirofluorenes of Biological Interest

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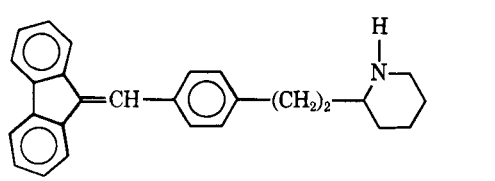
Abstract □ 1′-Substituted spiro[fluorene-9,3′-pyrrolidine-2′,5′-diones], 1′,1‴ - (1,4-piperazinediyldimethylene)bis[spiro[fluorene-9,3′-pyrrolidine-2′,5′-dione]], and 1′-arylspiro[fluorene-9,3′-pyrrolidines] were synthesized from spiro[fluorene-9,3′-tetrahydrofuran-2′,5′-dione]. The rat passive cutaneous anaphylaxis assay showed that one compound possessed slight antiallergic activity. Synthesis of 3-substituted 1-aryl-4-oxospiro[azetidine-2,9′-fluorenes] and 1,1″-*p*-phenylenebis[4-oxospiro[azetidine-2,9′-fluorenes]] was achieved *via* the reaction of appropriate *N*-fluorenylideneanilines with *tert*-butylcyanoketene and cyclopentamethyleneketene, respectively.

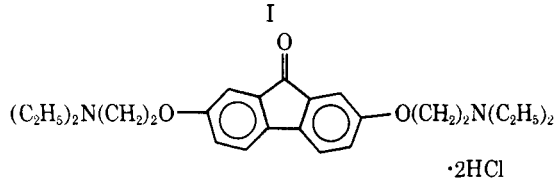
Keyphrases □ Spirofluorenes, various—synthesized, evaluated for antiallergic activity □ Fluorene spiro compounds, various—synthesized, evaluated for antiallergic activity □ Antiallergic activity—various spirofluorenes evaluated □ Structure–activity relationships—various spirofluorenes evaluated for antiallergic activity

The fluorene nucleus is a structural unit in several biologically active drugs such as I, which inhibits platelet aggregation (1), or tilorone hydrochloride (II), which exhibits antiviral activity (2).

The marked growth inhibitory effects of certain azaspiranes such as III were first observed in 1963 (3). Many azaspiranes and azaspirodiones have shown a wide span of biological activity (4, 5). These observations and the interest in II and related systems (6–8) prompted the incorporation of the fluorene moiety into selected azaspirodiones and azaspiranes to examine the effect of structural changes on biological activity.



I



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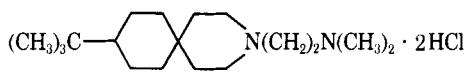


III

DISCUSSION

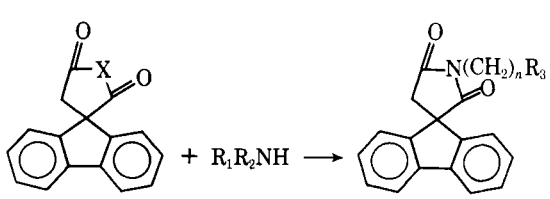
Spiro[fluorenepyrrolidinediones] VI*a*–VI*e* (Table I) were prepared *via* the reaction of spiro[fluorene-9,3′-tetrahydrofuran-2′,5′-dione] (IV) with different primary amines, followed by cyclization of the intermediate amic acids with acetyl chloride as the dehydrating agent (Scheme I). Attempts to cyclize the intermediate amic acids thermally led to decarboxylation (9).

Spiro[fluorenepyrrolidinediones] VII*a*–VII*c* (Table I) were synthesized *via* the reaction of secondary amines with spiro[fluorene-9,3′-pyrrolidine-2′,5′-dione] (V) and formaldehyde under Mannich conditions.

Compound V was prepared by the ammonolysis of IV and cyclization of the intermediate with acetyl chloride (10).

Alkylation of the potassium salt of V with 2-diethylaminoethyl chloride hydrochloride afforded VIII (Table I) (Scheme I).

Spiro[fluorenepyrrolidines] IX*a* and IX*b* (Table II) were prepared by the reduction of the corresponding diones with lithium aluminum hydride in dry ether for 2 hr [a similar procedure was reported to take 40 hr (11)]. Since the study of azaspiranes revealed that the activity of these compounds is due to the azaspiranyl moiety (12), it was felt that compounds containing two azaspiranyl functions could be of interest to elucidate the relationship between structure and activity among central nervous system (CNS) drugs. Accordingly, the bis[spiro[fluorenepyrrolidinedione]] X (Table II) was prepared from IV, formaldehyde, and piperazine hexahydrate in the presence of *p*-toluenesulfonic acid as the catalyst.



IV: X = O
V: X = NH

VI: *n* = 0
VII: *n* = 1
VIII: *n* = 2

Scheme I

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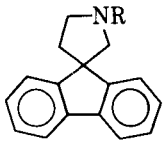
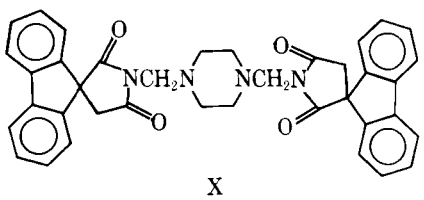


IX*a*: R = 4-$CH_3C_6H_4$
IX*b*: R = 4-FC_6H_4



X

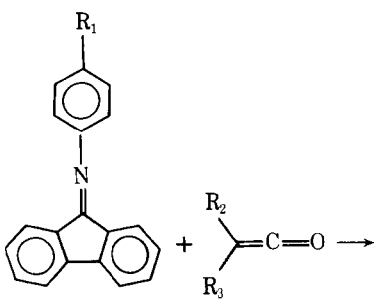
Previous interest in ketene chemistry (13–16) led to the preparation of several oxospiro[azetidinefluorenes] (Table III). 1-Aryl-[3-*tert*-butyl-4-oxospiro[azetidine-2,9′-fluorene]-3-carbonitriles (XII*a* and XII*b*) and the corresponding 3-cyclopentamethylene derivative (XII*c*) were synthesized *via* the reaction of *tert*-butylcyanoketene and cyclopentamethyleneketene with *N*-fluorenylidineanilines (XI*a*–XI*c*) (17) (Scheme II).

Since X was the first example of a bis[spiro[fluorenepyrrolidinedione]], some bis[oxospiro[azetidinefluorenes]] (Table III) also were prepared.

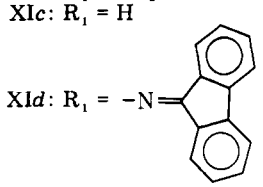
1,1″ - *p*-Phenylenebis[3-*tert*-butyl-4-oxospiro[azetidine - 2,9′-fluorene]]-3-carbonitrile (XIII*a*) and the 3-cyclopentamethylene derivative (XIII*b*) were synthesized by the reaction of *N,N*-difluorenylidene-*p*-phenylenediamine (XI*d*) with *tert*-butylcyanoketene and cyclopentamethyleneketene, respectively (Scheme II).

Compounds VI*a*–VI*c*, VII*a*, and VII*b* were tested for antiallergic activity *in vivo* by the rat passive cutaneous anaphylaxis method. Commercial cromolyn sodium[1] was used as the standard, and IgE antibody was used as the sensitizer (subcutaneously injected). Only VI*b* at 5 mg/kg showed antiallergic activity.

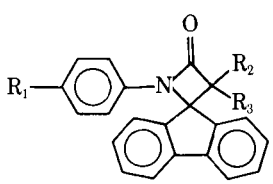
From the limited number of compounds tested, the following structure–activity relationship was noted for spiro[fluorenepyrrolidines]:



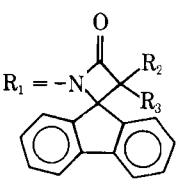
XI*a*: R_1 = Cl
XI*b*: R_1 = CF_3
XI*c*: R_1 = H



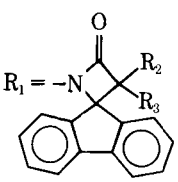
XI*d*: R_1 = –N=



XII*a*: R_1 = Cl, R_2 = $(CH_3)_3C$, R_3 = CN
XII*b*: R_1 = CF_3, R_2 = $(CH_3)_3C$, R_3 = CN
XII*c*: R_1 = H, R_2 = R_3 = $-(CH_2)_5-$



XIII*a*: R_1 = –N, R_2 = $(CH_3)_3C$, R_3 = CN



XIII*b*: R_1 = –N, R_2, R_3 = $-(CH_2)_5-$

Scheme II

maximum antiallergic activity is obtained when n = 0 and R is an electron-withdrawing group in the $>N(CH_2)_nR$ moiety.

The other compounds are still under biological testing for possible CNS or anticancer activity.

EXPERIMENTAL

IR spectra were obtained as potassium bromide disks. PMR spectra were recorded using tetramethylsilane as an internal standard. All chemical shifts are given in the δ scale. Mass spectra were determined with an ionizing potential of 30 ev.

Spiro[fluorene-9,3′(2′*H*)-furan-2′,5′(4′*H*)-dione] (IV)—This compound was prepared as the key starting material by condensing fluorenone with ethyl cyanoacetate, using ammonium acetate as the catalyst. Addition of hydrogen cyanide to the fluorenylidineethyl cyanoacetate, followed by hydrolysis to the diacid and cyclization with acetyl chloride, afforded the corresponding cyclic anhydride in a 90% yield (10, 18).

1′-Substituted Spiro[fluorene-9,3′-pyrrolidine]-2′,5′-diones] (VI*a*–VI*e*)—To a hot benzene solution of IV (0.1 mole) was added a solution of the appropriate primary amine (0.1 mole) in benzene. The mixture was refluxed for 1 hr, and the temperature was raised slowly until all of the benzene was removed. Acetyl chloride (50 ml) was added to the remaining solid, and the mixture was refluxed for 2 hr. Excess acetyl chloride was removed under reduced pressure, and the residue was recrystallized from absolute ethanol (Table I).

1′-Substituted Methylspiro[fluorene-9,3′-pyrrolidine]-2′,5′-diones] (VII*a*–VII*c*)—Imide V was prepared by ammonolysis of IV, followed by cyclization of the intermediate amic acid with acetyl chloride (10). Compound V (0.06 mole) was mixed thoroughly with the appropriate secondary amine (0.2 mole), and formaldehyde (1 ml) was added with vigorous stirring.

The white solid that formed was removed by filtration and recrystallized (Table I).

1′-Diethylaminoethylspiro[fluorene-9,3′-pyrrolidine-2′,5′-dione] (VIII)—To a solution of 1.6 g (0.003 mole) of V in 20 ml of *tert*-butyl alcohol was added 1.5 g (0.012 mole) of potassium *tert*-butoxide, and the mixture was refluxed for 5 min. The solvent was removed by distillation, and 1.12 g (0.003 mole) of 2-diethylaminoethyl chloride hydrochloride in 40 ml of dry dimethylformamide was added to the residue.

The mixture was heated to 140–160° for 2 hr, cooled, and poured into ice water with stirring. The solid that formed was separated and recrystallized (Table I).

1′-Arylspiro[fluorene-9,3′-pyrrolidines] (IX*a* and IX*b*)—Lithium aluminum hydride (0.2 g) was dissolved in 30 ml of dry ether, and to this solution was added the appropriate spiro[fluorenepyrrolidinedione] (0.002 mole) over 15 min. The solution was refluxed for 2 hr and then cooled, and the excess lithium aluminum hydride was destroyed. The solution was filtered, washed with water, and dried with anhydrous sodium sulfate. Removal of the solvent yielded the desired azaspiranes (Table II).

1′,1‴- (1,4-Piperazinediyldimethylene)bis[spiro[fluorene-9,3′-pyrrolidine-2′,5′-dione]] (X)—Imide V (1.4 g, 0.006 mole), piperazine hexahydrate (0.6 g, 0.003 mole), and 0.5 ml of formaldehyde were mixed thoroughly. Benzene (30 ml) was added to the solid that formed, and the mixture was refluxed in the presence of a trace of *p*-toluenesulfonic acid for 2 hr. The cooled solution was filtered, and the residue was washed first with a dilute sodium carbonate solution and then with water (Table II).

***N*-Fluorenylidine-*p*-trifluoromethylaniline (XI*b*)**—Boron trifluoride etherate (1.5 ml) was added to a solution of 9 g (0.05 mole) of fluorenone and 12 g (0.08 mole) of freshly distilled *p*-trifluoromethylaniline in 100 ml of chloroform and a few milliliters of ethanol. The solution was refluxed for 15 min, concentrated to 25 ml, and cooled. The resulting yellow needles (15.5 g, 96.2% yield) were recrystallized from chloroform–ethanol (1:1), mp 146–148°.

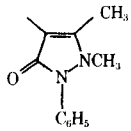
Anal.—Calc. for $C_{20}H_{12}F_3N$: C, 74.29; H, 3.74; N, 4.33. Found: C, 74.02; H, 3.83; N, 4.30.

3-Substituted 1′-Aryl-4-oxospiro[azetidine-2,9′-fluorenes] (XII*a*–XII*c*) and 1′,1‴-*p*-Phenylenebis[4-oxospiro[azetidine-2,9′-fluorenes]] (XIII*a* and XIII*b*)—Compounds XII*a*, XII*b*, and XIII*a* were prepared by adding the appropriate imine (0.005 mole) to a solution of 2,5-diazido-3,6-bis(*tert*-butyl)-1,4-benzoquinone (1.4 g, 0.005 mole) in 30 ml of dry toluene (19).

The solution was refluxed for 12 hr, allowed to cool, and filtered. The toluene was evaporated under reduced pressure, and the combined solids were recrystallized from appropriate solvents (Table III). Compounds XII*c* and XIII*b* were prepared similarly from the appropriate imine and

[1] Intal R.

Table I—1′-Substituted Spiro[fluorene-9,3′-pyrrolidine-2′,5′-diones]

Compound	R_3	Melting Point[a]	Yield[b], %	IR, ν C=O	NMR ($CDCl_3$), δ	Formula	Analysis[c,d], %	Calc.	Found
VI*a*	4-$CH_3C_6H_4$	190–192°	80	1730, 1700	2.35 (s, 3H), 3.32 (s, 2H), 7–7.3 (m, 12H)	$C_{23}H_{17}NO_2$	C	81.39	81.41
							H	5.05	5.22
							N	4.12	3.97
VI*b*	4-FC_6H_4	204–205°	78	1740, 1700	3.25 (s, 2H), 7.3–7.7 (m, 12H)	$C_{22}H_{14}FNO_2$	C	76.95	77.03
							H	4.10	4.40
							F	5.53	5.47
							N	4.07	3.99
VI*c*	3,4,5-$(OCH_3)_3C_6H_2$	228–229°	79	1770, 1710	3.37 (s, 2H), 3.85 (s, 9H), 6.65 (s, 2H), 7.25–7.9 (m, 8H)	$C_{25}H_{21}NO_5$	C	72.28	71.99
							H	5.10	4.88
							N	3.37	3.21
VI*d*		201–203°	63	1760, 1700	3.4 (s, 2H), 7.25–7.85 (m, 12H)	$C_{21}H_{14}N_2O_2$	C	77.29	77.46
							H	4.32	4.36
							N	8.58	8.29
VI*e*		254–256°	83	1730, 1705	—[e]	$C_{26}H_{21}N_3O_3$	C	74.46	74.61
							H	4.86	5.10
							N	9.64	9.62
VII*a*		171–173°	89	1750, 1700	2.7 (t, 4H), 3.25 (s, 2H), 3.8 (t, 4H), 4.6 (s, 2H), 7.3–7.9 (m, 8H)	$C_{21}H_{20}N_2O_3$	C	72.40	72.61
							H	5.79	5.84
							N	8.04	7.92
VII*b*		178–180°	84	1750, 1700	1.55 (broad, 6H), 2.7 (broad, 4H), 3.26 (s, 2H), 4.7 (s, 2H), 7.3–7.7 (m, 8H)	$C_{22}H_{22}N_2O_2$	C	76.28	76.40
							H	6.40	6.48
							N	8.09	7.88
VII*c*		200–202°	66	1750, 1700	1.6 (broad, 4H), 2.6 (broad, 4H), 3.25 (s, 2H), 4.6 (s, 2H), 7.3–7.7 (m, 8H)	$C_{21}H_{20}N_2O_2$	C	75.88	75.99
							H	6.06	5.95
							N	8.43	8.68
VIII	$-N(C_2H_5)_2$	107–109°	53	1760, 1700	0.85–1.1 (t, 6H), 2.4–2.7 (q, 4H), 2.6–2.85 (t, 2H), 3.6–3.9 (t, 2H), 3.25 (s, 2H), 7.35–7.85 (m, 8H)	$C_{22}H_{24}N_2O_2$	C	75.83	75.80
							H	6.94	6.78
							N	8.04	8.05

[a] Melting points are uncorrected. [b] Yield of analytically pure material. [c] Analytical results are within ±0.4% of calculated values. [d] Compounds VI*a*–VI*c* were recrystallized from absolute ethanol, VII*a*–VII*c* were recrystallized from petroleum ether (bp 30–60°)–benzene (1:1), and VIII was recrystallized from petroleum ether (bp 30–60°). [e] Because of the insolubility of VI*e* in suitable solvents, a satisfactory NMR spectrum could not be obtained; *m/e* 435 (M^+).

Table II—Spiro[fluorenepyrrolidines] and Bis[spiro(fluorenepyrrolidinedione)]

Compound	Melting Point[a]	Yield[b], %	IR, ν C=O	NMR ($CDCl_3$), δ	Formula	Analysis[c,d], %	Calc.	Found
IX*a*	179–181°	82	—	2.25 (s, 3H), 2.49–2.25 (t, 2H), 3.9–3.65 (t, 2H), 3.65 (s, 2H), 6.5–7.85 (m, 12H)	$C_{23}H_{21}N$	C	88.71	88.49
						H	6.80	7.03
						N	4.50	4.48
IX*b*	175–177°	85	—	2.27–2.55 (t, 2H), 3.6 (s, 2H), 3.6–3.9 (t, 2H), 6.4–7.9 (m, 12H)	$C_{22}H_{18}FN$	C	83.78	83.52
						H	5.75	6.01
						F	6.02	6.29
						N	4.44	4.23
X	272°	88	1750, 1700	—[e]	$C_{38}H_{32}N_4O_4$	C	74.97	74.68
						H	5.30	5.48
						N	9.20	9.00

[a] Melting points are uncorrected. [b] Yield of analytically pure material. [c] Analytical results are within ±0.4% of calculated values. [d] Compounds IX*a* and IX*b* were isolated analytically pure and not recrystallized. Compound X was recrystallized from dimethyl sulfoxide–benzene (2:1). [e] Because of the insolubility of X in suitable solvents, a satisfactory NMR spectrum could not be obtained; *m/e* 608 (M^+).

Table III—3-Substituted 1-Aryl-4-oxospiro[azetidine-2,9′-fluorenes] and 1,1″-*p*-Phenylenebis[4-oxospiro[azetidine-2,9′-fluorenes]]

Compound	Melting Point[a]	Yield[b], %	IR, ν C=O	NMR ($CDCl_3$), δ	Formula	Analysis[c,d], %	Calc.	Found
XII*a*	188–190°	79	1750	1.15 (s, 9H), 6.85–7.95 (m, 12H)	$C_{26}H_{21}ClN_2O$	C	75.62	75.56
						H	5.12	5.31
						Cl	8.58	8.66
						N	6.78	6.77
XII*b*	143–145°	80	1770	1.17 (s, 9H), 6.95–7.9 (m, 12H)	$C_{27}H_{21}F_3N_2O$	C	72.63	72.42
						H	4.74	4.66
						N	6.27	6.19
XII*c*	195–196°	58	1750	1.15–1.55 (m, 6H), 1.50–1.92 (m, 4H), 6.95–7.05 (m, 5H), 7.30–7.60 (m, 8H)	$C_{26}H_{23}NO$	C	85.45	85.34
						H	6.34	6.25
						N	3.83	3.76
XIII*a*	267–268°	76	1800	0.8 (s, 18H), 6.95–7.55 (m, 20H)[e]	$C_{46}H_{38}N_4O_2$	C	81.38	81.44
						H	5.64	5.77
						N	8.25	8.20
XIII*b*	300°	69	1750	0.30–1.95 (m, 20H), 6.69 (s, 4H), 7.05–7.50 (m, 12H), 7.60–7.92 (m, 4H)	$C_{46}H_{40}N_2O_2$	C	84.63	84.40
						H	6.18	6.01
						N	4.29	4.35

[a] Melting points are uncorrected. [b] Yield of analytically pure material. [c] Analytical results are within ±0.4% of calculated values. [d] Compounds XII*a* and XII*b* were recrystallized from aqueous ethanol, XII*c* was recrystallized from methanol, XIII*a* was recrystallized from acetone, and XIII*b* was recrystallized from chloroform–acetone (1:4). [e] NMR in CF_3CO_2H, *m/e* 678 (M^+).

cyclopentamethyleneketene (generated from α-bromocyclohexanecarboxylic acid bromide, zinc, and diglyme).

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Effect of Diazepam on Cognition *via* Pupillometry

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Abstract □ Continuous pupillary readings in response to a random-digit cognition task were obtained for 20 male subjects. Ten subjects were given 10 mg of diazepam, and 10 subjects were given placebos. Additional pupillary curves were recorded for both groups at 1 and 2 hr and compared to the initial curve. Subjects were required to repeat the exact sequence of verbalized randomized digits as a measure of performance. The results indicated that the diazepam treatment group differed significantly from the placebo group in terms of a depressed pupillary response. Furthermore, the performance recall measure was significantly reduced in the diazepam group. The relationships were clarified by an analysis of covariance and variance.

Keyphrases □ Diazepam—effect on recall ability evaluated by pupillometry, humans □ Pupillometry—used to evaluate effect of diazepam on recall ability in humans □ Sedatives—diazepam, effect on recall ability evaluated by pupillometry in humans

Pupillometrics is the aspect of psychology that deals with pupillary alterations elicited by any stimulus other than light (1). Because the pupil of the human eye is innervated by both sympathetic and parasympathetic fibers in close association with the central nervous system, pupillometrics affords an excellent method of observing the effects of many different types of stimuli such as near vision, lid closure, nystagmus, fatigue, color contrast, hippus, psychopathic states, noise, exercise, and drugs on pupil size (2–12). Furthermore, the degree of pupillary dilation has been positively correlated with human cognition and retention. Peavler (9) described a sensitive means of generating pupillary cognition curves by presenting randomized digits verbally to subjects.

Tranquilizers, in addition to their antipsychotic effects, have been correlated with several pupillary responses in humans. The major tranquilizer chlorpromazine produced a miotic effect in relation to dosage form and temporal measures (12). Critical flicker fusion, which is partly a measure of pupillary functions, has been studied extensively (13). Two studies attempted to relate minor tranquilizers, benzodiazepines, to critical flicker fusion with different conclusions (14, 15).

Diazepam was selected for investigation for several reasons. The drug is absorbed rapidly, with peak blood levels occurring in 1–2 hr (16). The diazepam metabolite, desmethyldiazepam, peaks only after repeated doses of several days (17). Furthermore, diazepam and other benzodiazepines have been studied for their relation to motor and cognition tasks, which suggest a relation between pupillary changes and diazepam. For example, auditory reaction times, complex visual reaction times, and their corresponding error rates appear to be increased by the benzodiazepines (18–20). However, simulated car driving tests were not affected by diazepam administration (21).

The hypotheses of this project were that the oral administration of diazepam would affect the pupillary response curve obtained during the execution of a cognition task and would influence the ability of human subjects to perform successfully the task as measured by recall.

EXPERIMENTAL

Twenty male subjects, 18–28 years old, were assigned to either a control or a treatment group. They were instructed to fast for 2 hr prior to the experiment. The treatment subjects allowed their eyes to adapt to the

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