Table III—Histological Examination Results [a]

Mixidine–2-Naphthalene-Sulfonic Acid	Animal	Serositis	Myositis	Enteritis	Granuloma (Foreign Body)
1:0	1	—	—	—	—
	2	—	2	2	—
	3	—	2	2	X
	4	—	—	—	—
	5	—	1	1	—
1:1	6	—	—	—	—
	7	—	—	—	—
	8	1	—	—	—
	9	—	—	—	—
	10	—	—	—	—
1:3	11	—	—	—	—
	12	—	—	—	—
	13	2	2	2	—
	14	—	—	—	—
	15	—	—	—	—
1:5	16	1	1	—	—
	17	—	—	—	—
	18	t	t	—	—
	19	—	—	—	—
	20	3	3	3	X

[a] X = present, t = trace, 1 = slight or small, 2 = moderate, 3 = marked, and 4 = severe.

with 1:5 ≫ 1:3 > 1:1 ≈ 1:0 > neutralized 1:3 for the mixidine to 2-naphthalenesulfonic acid ratios. This result is consistent with the trend observed in the lethality studies.

The 1:5 combination produced lethality in two out of three rats. This finding was not anticipated from the lethality studies in which much higher doses in very acidic solutions failed to produce lethality. Possibly, the extensive absorption of the drug combined with the surgical trauma associated with intraduodenal administration and the prolonged administration of anesthetic was fatal to the animals. This hypothesis was not investigated.

The means of the plasma levels following intraduodenal administration are illustrated in Fig. 1. The figure describes more dramatically the differences in the plasma levels, especially the extremely high levels observed during the 1st hr following administration of the 1:5 mixidine–2-naphthalenesulfonic acid combination.

Of particular interest are the low levels of intact mixidine observed following administration of the sodium hydroxide-neutralized 1:3 mixidine–2-naphthalenesulfonic acid combination. The levels were even lower than with mixidine without adjuvant. It may be postulated that the sodium hydroxide has a greater effect on mixidine absorption across the duodenal wall than just neutralization of the sulfonic acid.

Histologic lesions were present in all groups without any apparent relationship to ratios employed (Table III). Some lesions, such as the foreign body granulomas (trichogranuloma), obviously were related to surgical technique, but the cause of the other lesions could not be ascertained. Certainly, the pathology discovered upon histological examination failed to demonstrate a trend that implicates increases in the doses of 2-naphthalenesulfonic acid with increases in the number and severity of lesions.

It is apparent from the lack of counterion lethality (1) and the absence of counterion-related lesions that dose-related lethality and dose-related plasma intact mixidine levels are the results of increased mixidine absorption across the duodenal wall and are not related to toxic or corrosive effects of the counterions. These observations, coupled with the observation of ion-pair-mediated partitioning of mixidine (1), substantiate the conclusion that mixidine absorption may be ion-pair mediated.

Under the proper circumstances, improved drug absorption through ion-pair mediation across the GI tract may occur. However, the application of ion-pairs to improve the absorption of mixidine or other drugs in humans remains a challenge. Ion-pairs exist only in nonaqueous media. Casually releasing a quantity of drug with counterions into the aqueous GI tract environment is not likely to improve drug absorption, as demonstrated by the oral administration studies.

Increasing the quantity of counterion relative to the quantity of drug to overload the GI tract with counterion presents problems regarding dosage form size, particularly if complete absorption is necessary for the clinical activity of a low potency compound. Also, if ion-pair-mediated absorption is site specific, as it appears to be, then a novel means of delivering the drug and counterion simultaneously to that site must be developed since conventional enteric release dosage forms are generally regarded as problematic. Future studies with ion-pair-enhanced absorption will have to address these problems.

REFERENCES

(1) W. D. Walkling, A. C. Bonfilio, and H. I. Jacoby, *J. Pharm. Sci.*, **67**, 945 (1978).

(2) J. Plostnieks and W. A. Cressman, "Biochemical Research Report No. 50: The Absorption and Excretion of Mixidine-^{14}C Fumarate in Dogs," McNeil Laboratories, Fort Washington, Pa., 1971.

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Simple GLC Analysis of Anticonvulsant Drugs in Commercial Dosage Forms

J. R. WATSON ˣ, R. C. LAWRENCE, and E. G. LOVERING

Received September 28, 1976, from the *Drug Research Laboratories, Health Protection Branch, Ottawa, Ontario, Canada, K1A 0L2.*
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Abstract □ A simple, specific GLC procedure is described for the analysis of one sedative and six anticonvulsant drugs in pharmaceutical dosage forms. Sample aliquots of ethotoin, glutethimide, mephenytoin, methsuximide, and phensuximide were shaken with or extracted into ethyl acetate, diluted with the internal standard (diphenyl phthalate) solution, injected into a gas chromatograph, and eluted from a methylsilicone column. Primidone and phenytoin samples (extracted as the free acid) required derivatization with *N,O*-bis(trimethylsilyl)acetamide prior to chromatography. The same temperature programming conditions and flow rate settings were used for all seven drugs. The GLC results agreed well with those obtained using the pharmacopeial methods.

Keyphrases □ GLC—analyses, various anticonvulsants and one sedative in commercial dosage forms □ Anticonvulsants, various—GLC analyses in commercial dosage forms □ Sedatives—glutethimide, GLC analysis in commercial dosage forms

The pharmacopeial procedures (1–3) for the assay of several important anticonvulsant drugs in commercial dosage forms generally involve multiple steps. The sample preparation and measurement techniques vary, depending on the chemical entity and its associated physicochemical characteristics. UV spectrophotometry is employed for the

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Table I—GLC Data on Anticonvulsant Drugs

Drug	Average Retention Time, min	Relative[a] Retention Time ± % CV	Relative[a] Response Factor ± % CV
Ethotoin	10.86	0.372 ± 1.5	1.549 ± 2.3
Glutethimide	11.69	0.400 ± 0.6	1.118 ± 1.8
Mephenytoin	11.20	0.384 ± 1.9	1.205 ± 2.2
Methsuximide	5.86	0.201 ± 1.1	1.131 ± 0.7
Phensuximide	6.21	0.213 ± 1.3	1.209 ± 1.4
Phenytoin[c]	23.56	0.805 ± 0.4	0.777 ± 0.6
Primidone[c]	11.75	0.402 ± 0.8	0.713 ± 0.8

[a] Relative to the internal standard (diphenyl phthalate average retention time = 29.20 min). [b] Each relative response factor represents the average of five determinations at varying weight levels of drug. [c] Eluted as the silylated derivatives; relative response factors are based on the weight of unsilylated compound.

analysis of glutethimide (a sedative), mephenytoin, methsuximide, phensuximide, and primidone. Phenytoin and its sodium salt in commercial preparations are assayed by nonaqueous titration or gravimetry, and ethotoin is assayed by titrimetric determination of nitrogen.

Even within the same monograph, the methods sometimes differ for the content uniformity and drug content (assay) tests. This situation underscores the need to develop more specific methods, incorporating a single technique and unified approach with the eventual aim of an autosampling setup for the analysis of numerous anticonvulsant drugs in dosage forms. GLC appears to be the method of choice for such analyses because of its resolving power, high sensitivity and specificity, and minimum time requirement.

Many GLC methods (4–16) are concerned with analyses of individual anticonvulsants in biological media only. Recent efforts (17–19) were directed toward establishing a universal GLC system for multiple and reproducible analyses applicable to several antiepileptic drugs. This trend has gained impetus because of economic factors and because the more extensive use of these drugs has increased the necessity of monitoring blood levels on a routine basis.

In this work, a group analytical procedural concept was developed for several anticonvulsant (and one sedative) drugs of similar structure in various dosage forms.

EXPERIMENTAL

Materials and Solutions—The following were used: ethotoin[1], glutethimide[2], mephenytoin[3], methsuximide[2], phensuximide[2], phenytoin[2], phenytoin sodium[4], primidone[2], *N,O*-bis(trimethylsilyl)acetamide[5], and ethyl acetate[6] (ACS reagent grade). The structural integrities of the standard ethotoin, mephenytoin, and phenytoin sodium substances were verified by NMR spectroscopy, and the purities of the compounds were confirmed by TLC.

The internal standard solution was diphenyl phthalate[7] in spectrograde dimethylformamide[8], accurately weighed to contain about 15 mg/ml. Diphenyl phthalate was recrystallized from benzene–cyclohexane (activated charcoal) to give white plates, mp 70–71°.

Sample Preparation: Response Factor Calibration Solutions—*Ethotoin, Glutethimide, Mephenytoin, Methsuximide, and Phensuximide*—For each drug, five separate samples, ranging from about 10 to 15 mg, were weighed accurately into 10-ml flasks and dissolved in ethyl acetate (5 ml). The internal standard solution (1.00 ml) was dispensed into each flask from a 5-ml microburet graduated in 0.01 ml.

Phenytoin and Phenytoin Sodium—For each, five separate samples, ranging from about 10 to 15 mg, were weighed accurately into 30-ml separators and dissolved in 0.1 *N* NaOH (3 ml). After acidification with concentrated hydrochloric acid, the solution was extracted for free phenytoin with 10-, 5-, and 5-ml portions of ethyl acetate; the combined extracts were transferred to a 25-ml flask with a septum seal screw cap[5].

The solvent was removed at 60° under a stream of pure dry nitrogen on a heating block module[5]. The residue in the flask was dissolved in spectrograde dimethylformamide (5 ml) and then treated with *N,O*-bis(trimethylsilyl)acetamide (1.5 ml). The internal standard solution (1.00 ml) was dispensed into the flask, and the mixture was shaken and allowed to stand at ambient temperature for 15 min.

Primidone—Five separate samples, ranging from about 10 to 15 mg, were weighed accurately into 10-ml flasks; each sample was dissolved in spectrograde dimethylformamide (5 ml) and then treated with *N,O*-bis(trimethylsilyl)acetamide (1.5 ml). The internal standard solution (1.00 ml) was dispensed into each flask; each mixture was shaken and heated to 60° on a heating block module for 30 min.

Sample Preparation: Commercial Dosage Forms—*Ethotoin, Glutethimide, Mephenytoin, Methsuximide, and Phensuximide*—Ten capsules were emptied, and their contents were weighed and thoroughly mixed. Ten tablets were selected at random, weighed, and finely powdered. An amount of powder equivalent to about 8–12 mg of drug was weighed accurately into a 10-ml flask and shaken with ethyl acetate (5 ml). The internal standard solution (1.00 ml) was dispensed into the flask from a 5-ml microburet graduated in 0.01 ml.

Samples of oral suspensions (equivalent to 600 mg of drug) were pipetted into a 50-ml volumetric flask and then made up to volume with water. A 1-ml aliquot of this solution was pipetted into a 30-ml separator and extracted successively with 3 × 5-ml portions of ethyl acetate. The combined organic extracts were reduced to about 5 ml under a stream of pure dry nitrogen. The internal standard (1.00 ml) was dispensed into the flasks.

Phenytoin and Phenytoin Sodium—Ten capsules were emptied, and their contents were weighed and thoroughly mixed. An amount of powder (or solution) weighed or measured to be equivalent to about 10–15 mg of labeled active ingredient was transferred to a 30-ml separator and then treated exactly as described for phenytoin and phenytoin sodium response factor calibration solutions.

Primidone—Ten tablets were selected at random, weighed, and finely powdered. An amount of powdered tablet equivalent to about 10–15 mg of drug was weighed accurately into a 10-ml flask, shaken with 5 ml of spectrograde dimethylformamide, and then treated exactly as described for primidone response factor calibration solutions.

GLC—Two microliters of solution (or supernate) was injected into a gas chromatograph[9] (flame-ionization detector) fitted with a U-shaped glass column [1.82 m (6 ft) × 6.4 mm o.d. (4.0 mm i.d.)] packed with 5% OV-101[5] on 100–120-mesh Chromosorb 750[10]. The column was preconditioned at 265° for 18 hr.

Temperature conditions were: column, 150° (5 min) and then programmed to 240° at 3°/min; injector port, 250°; and detector, 250°. Gas flows were: nitrogen, 70 ml/min; hydrogen, 40 ml/min; and air, 380 ml/min.

The detector signal was fed to an electronic integrator[11] with an input signal range capacity of 0–1 v. The gas chromatograph input attenuation was 1×10^{-11} amp/mv, and the integrator attenuation was ×16.

RESULTS AND DISCUSSION

In the described GLC system, only phenytoin and primidone, of the seven drugs examined, required derivatization with *N,O*-bis(trimethylsilyl)acetamide to elute as single sharp peaks. The other compounds do not possess hydrogen atoms of sufficient activity to cause tailing through hydrogen bond adsorptive interactions between the drug and stationary phase. Glutethimide is an apparent anomaly in this respect since, by reason of its imide structure, it would be expected to exhibit chromatographic behavior similar to that of phenytoin.

The relevant GLC data for the drugs investigated are given in Table I. The same methylsilicone column packing material, GLC instrumental

[1] Abbott Laboratories Ltd., Montreal, Quebec, Canada.
[2] United States Pharmacopeia-National Formulary Reference Standard, Rockville, Md.
[3] Aldrich Chemical Co., Milwaukee, Wis.
[4] Parke-Davis & Co., Brockville, Ontario, Canada.
[5] Pierce Chemical Co., Rockford, Ill.
[6] Caledon Laboratories Ltd., Georgetown, Ontario, Canada.
[7] Eastman Kodak Co., Rochester, N.Y.
[8] J. T. Baker Chemical Co., Phillipsburg, N/J.
[9] Bendix series 2500.
[10] Applied Science Laboratories, State College, Pa.
[11] Hewlett-Packard series 3380A reporting integrator.

Table II—GLC *versus* Compendial Assay Results for Commercial Anticonvulsant Drug Dosage Forms

Sample	Labeled Active Ingredient	Dosage Form	Dosage Level, mg/unit	Manufacturer	Percent of Label Claim	
					GLC	Compendial
1	Ethotoin	Tablets	500	O	108.2	107.5[a]
					108.3	108.3
2	Glutethimide	Capsules	500	P	97.9	98.8[b]
					98.7	100.0
3	Glutethimide	Tablets	500	P	101.7	101.2[b]
					99.6	100.9
4	Glutethimide	Tablets	250	P	99.8	96.7[b]
					100.2	96.8
5	Mephenytoin	Tablets	100	Q	101.1	101.3[b]
					100.1	102.0
6	Methsuximide	Capsules	300	R	98.1	97.9[b]
					98.8	96.4
7	Phensuximide	Capsules	500	R	100.0	100.7[b]
					99.9	98.5
8	Phensuximide	Oral suspension	300[c]	R	97.4	99.2[b]
					99.1	97.9
9	Phenytoin	Oral suspension	125[c]	R	100.2	101.9[b]
					100.8	99.2
10	Phenytoin sodium	Capsules	100	R	103.3	103.2[d]
					103.6	101.8
11	Phenytoin sodium	Capsules	30	R	102.0	100.5[d]
					103.1	100.8
12	Phenytoin sodium	Capsules	100	S	99.2	96.6[d]
					98.3	95.7
13	Phenytoin sodium	Capsules	30	S	107.5	105.6[d]
					105.9	104.4
14	Phenytoin sodium	Injection	250[c]	T	105.0	107.1[d]
					104.8	108.1
15	Primidone	Tablets	250	U	100.6	100.4[d]
					99.5	100.4
16	Primidone	Tablets	250	U	101.9	101.5[d]
					101.6	100.8
17	Primidone	Tablets	125	U	102.1	100.4[d]
					100.4	101.1
18	Primidone	Tablets	125	U	100.0	102.1[d]
					101.2	104.5
19	Primidone	Tablets	250	V	100.6	101.7[d]
					103.3	101.6

[a] BP (1973) procedure. [b] NF XIV procedure. [c] In milligrams per 5 ml. [d] USP XIX procedure.

settings, temperature, and gas flow conditions were suitable for the analysis of all seven drugs. The method was designed to use these constant experimental conditions and instrumental parameters to be compatible eventually with an automated analysis.

Each relative response factor represents the average of five determinations at varying weight ratios of compound to internal standard. The values in all cases were calculated and expressed as weight/area in terms of the free drug. Thus, phenytoin and primidone, in agreement with theoretical expectations, gave appreciably lower values since trimethylsilylation confers a significant increase in molecular weight and also results in a larger number of ions being formed at the electrode gap of the flame detector. The accompanying net increase in current manifests itself by a proportional increase in the number of integrator area counts per unit weight of free drug. The low coefficients of variation in response factor values readily attest to the precision of the method over a relatively wide linear range.

In Table II, the percentage of label claim values obtained when the GLC technique was applied to the analysis of commercial formulations of the seven drugs from various manufacturers are compared to those obtained with the pharmacopeial procedures. The good agreement between the two sets of results for each of the 19 samples examined demonstrates the reproducibility and feasibility of the GLC procedure as a reliable monitor of drug content in both solid and liquid dosage forms. The high solubility of primidone in dimethylformamide and of the other six drugs in ethyl acetate permitted ready quantitative extraction of the drugs into the organic solvent.

Complete extraction was confirmed by subjecting the residual aqueous layers and further solvent washings of the insoluble portions of the powders to TLC [layer, fluorescent silica gel (0.25 mm); developing system, chloroform–acetone (9:1); and visualization, shortwave UV light]. In no case was any spot corresponding in R_f value to that of the authentic active ingredient observed. Experimentally determined R_f values were: ethotoin, 0.28; glutethimide, 0.40; mephenytoin, 0.35; phensuximide, 0.44; methsuximide, 0.51; phenytoin, 0.17; and primidone, 0.19.

Gas chromatograms of ethotoin, mephenytoin, methsuximide, phensuximide, glutethimide, phenytoin, and primidone extracted from various types of commercial formulations, treated as described, and diluted with the internal standard solution gave no signals from excipient materials or potential drug impurities. For phenytoin, several congeneric compounds (20) were examined from a qualitative standpoint to establish whether they would interfere with the GLC analysis if present in commercial dosage forms as carryovers during drug synthesis. The compounds examined (after trimethylsilylation) and their retention times relative to diphenyl phthalate were: benzophenone, 0.198; benzil, 0.349; ethyl benzilate, 0.419; and benzilic acid, 0.462. There appears to be little doubt that the associated intermediates of the other six drugs would exhibit analogous differences in elution characteristics to those of the parent drugs because of distinct structural variations, particularly in functional groups.

If desired for any particular analysis, it should be possible to reduce the analytical time considerably by utilizing one of the foregoing drugs as the internal standard.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, pp. 379–381, 405, 406.

(2) "British Pharmacopoeia, 1973," Her Majesty's Stationery Office, London, England, 1973, pp. 197, 367, 383.

(3) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, pp. 298, 299, 409, 458, 570, 571, 574.

(4) K. Sabih and K. Sabih, *Anal. Chem.*, **41**, 1452 (1969).

(5) M. A. Evanson, P. Jones, and B. Darcey, *Clin. Chem.*, **16**, 107 (1970).

(6) T. Chang and A. J. Glazko, *J. Lab. Clin. Med.*, **75**, 145 (1970).

(7) H. J. Kupferberg, *Clin. Chim. Acta*, **29**, 283 (1970).

(8) J. MacGee, *Anal. Chem.*, **42**, 421 (1970).

(9) J. C. Van Meter, H. S. Buckmaster, and L. L. Shelley, *Clin. Chem.*, **16**, 135 (1970).

(10) I. A. Muni, C. H. Altshuler, and J. C. Neicheril, *J. Pharm. Sci.*, **62**, 1820 (1973).
(11) R. J. Perchalski, K. N. Scott, B. J. Wilder, and R. H. Hammer, *ibid.*, **62**, 1735 (1973).
(12) E. A. Fiereck and N. W. Tietz, *Clin. Chem.*, **17**, 1024 (1971).
(13) D. Sampson, I. Harasymiv, and W. J. Hensley, *ibid.*, **17**, 382 (1971).
(14) A. R. Hansen and L. J. Fischler, *ibid.*, **20**, 236 (1974).
(15) N. E. Larsen and J. Naestoft, *J. Chromatogr.*, **92**, 157 (1974).
(16) M. W. Couch, M. Greer, and C. M. Williams, *ibid.*, **87**, 559 (1973).
(17) J. Bonitati, *Clin. Chem.*, **22**, 341 (1976).
(18) R. E. Beam, *Am. J. Med. Technol.*, **40**, 211 (1974).
(19) D. P. Ritz and C. G. Warren, *Clin. Toxicol.*, **8**, 311 (1975).
(20) F. F. Matsui and S. J. Smith, *Z. Anal. Chem.*, **275**, 365 (1975).

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Synthesis of Spirofluorenes of Biological Interest

MAGID A. ABOU-GHARBIA, T. T. SU, and MADELEINE M. JOULLIÉ ˣ

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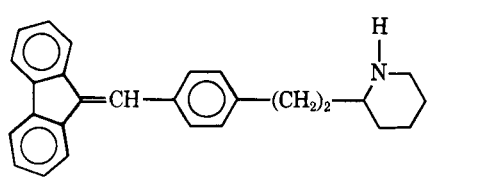
Abstract □ 1′-Substituted spiro[fluorene-9,3′-pyrrolidine-2′,5′-diones], 1′,1‴ - (1,4-piperazinediyldimethylene)bis[spiro[fluorene-9,3′-pyrrolidine-2′,5′-dione]], and 1′-arylspiro[fluorene-9,3′-pyrrolidines] were synthesized from spiro[fluorene-9,3′-tetrahydrofuran-2′,5′-dione]. The rat passive cutaneous 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.



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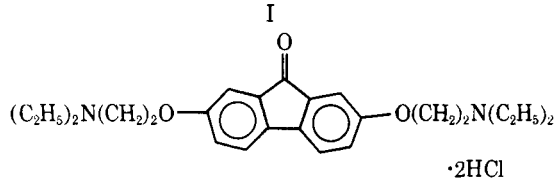

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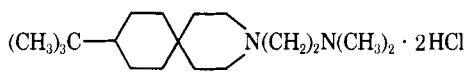


III

DISCUSSION

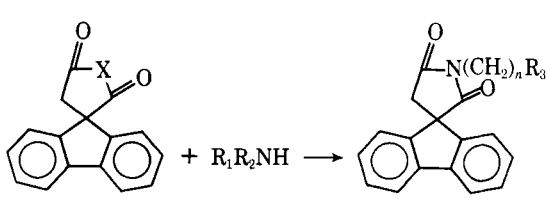
Spiro[fluorenepyrrolidinediones] VI*a*–VI*e* (Table I) were prepared *via* the reaction of spiro[fluorene-9,3′-tetrahydrofuran-2′,5′-dione] (IV) with different primary amines, followed by cyclization of the intermediate amic acids with acetyl chloride as the dehydrating agent (Scheme I). Attempts to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

0022-3549/78/0700/0953$01.00/0