(16.8 g, 0.10 mole) in dry hexamethylphosphoramide (HMPA, 110 ml) with NaH (4.1 g of a 58.6% NaH dispersion in mineral oil, 0.10 mole of NaH) at 60–80° under N_2 until the evolution of hydrogen ceased.

Likewise, the sodium salt of 2,6-dichloro-3-methylaniline was prepared by warming a solution of the amine (17.6 g, 0.10 mole) in HMPA (110 ml) with NaH (4.1 g of a 58.6% NaH dispersion in mineral oil, 0.10 mole of NaH) at 50–60° under N_2.

The solution of the amine salt was added to the suspension of the pyrimidine acid salt and the mixture was heated, with stirring, at 120° for 18 hr under N_2.

Most of the HMPA was removed from the reaction mixture in a rotary evaporator. The residue was added to cold water, and the mixture was washed with Skellysolve B (bp 60–80°). The resulting aqueous solution was acidified with 10% aqueous HCl. The precipitated solid was collected, washed with cold water, and partially dried. The damp product was crystallized from ethanol to give several crops of **32** with a total yield of 14.5 g (48.5%). The first crop (8.0 g) had mp 280–282° dec.

A repeat of the above reaction replacing HMPA with a mixture of DMF and diglyme resulted in a 13% of yield **32**.

4-(2,4,6-Trichloroanilino)pyrimidine-5-carboxylic Acid (33).—A solution of the sodium salt of 2,4,6-trichloroaniline was formed by heating a stirred suspension of the amine (4.67 g, 0.0238 mole) and NaH (0.973 g of a 58.6% NaH dispersion in mineral oil, 0.0238 mole of NaH) in diglyme (20 ml) at 50° under N_2 until hydrogen evolution ceased. The solution was added to a stirred suspension of sodium 4-ethoxypyrimidine-5-carboxylate prepared by treating a suspension of the acid[16] (4.0 g, 0.0238 mole) and NaH (0.973 g of a 58.6% NaH dispersion in mineral oil, 0.0238 mole of NaH) in diglyme (50 ml) at 140°. The resulting mixture was heated, with stirring, at 140° for 20 hr under N_2. It was cooled to 25° and the solid material was collected and washed successively with cold diglyme and ether. An aqueous solution of the product was acidified to pH 4 with concentrated HCl. The precipitate was collected and crystallized from ethylene glycol dimethyl ether to give **33** (0.82 g, 10.8%), mp 269–270° dec.

Acknowledgment.—The authors are grateful to Dr. Max E. Bierwagen and his staff for the pharmacological test results and to the analytical and spectroscopic departments for their services.

Derivatives of Fluorene. XXIV.[1] Synthesis and Antitumor Activities of Some Imidazolidine-2,5-diones

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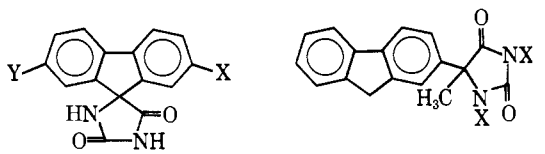
Because of the biological activity of certain imidazolidinediones,[2,3] we are synthesizing a number of such compounds incorporating variously substituted fluorene nuclei, connected through their 9 positions (spirohydantoins), and through their 2 positions (4-fluorenyl-4-methylimidazolidinediones). This is part of a program aimed at exploiting the fact that a number of fluorene compounds (particularly halogen-substituted derivatives) have shown antitumor activity.[4]

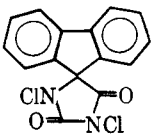
The method of synthesis was a modification of the Bucherer–Bergs method.[2] The ketone was treated with KCN and $(NH_4)_2CO_3$ in a closed system. High yields of **1a** and **2a** were obtained from fluorenone and 2-acetylfluorene. Fluorenones with halogens substituted at both the 2 and 7 positions were less reactive than the unsubstituted ketone.

Chlorination and nitration of spiro[fluoren-9,4′-imidazolidine]-2′,5′-dione (**1a**) gave the 2,7-disubstituted derivatives **1c** and **1e**, respectively. Structures were confirmed as in Scheme I.



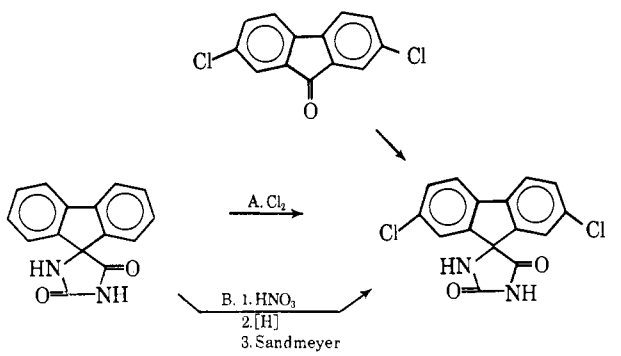
1a, X = Y = H
b, X(Y) = Br; Y(X) = H
c, X = Y = Cl
d, X = Y = NH_2
e, X = Y = NO_2

2a, X = H
b, X = Cl



3

SCHEME I



Bromination of **1a** in acetic acid–water–ferric chloride at 80–100° gave **1b** in good yields. N-Chlorination of **1a** and **2a** with *t*-butyl hypochlorite gave **3** and **2b**, respectively.

In order to elucidate the structure of **1a**, 9-cyanofluoren-9-amine was prepared from the bisulfite addition compound of 9-fluorenylidenimine. Reaction of the cyanoamine with KCNO gave an α-ureidonitrile which, upon hydrolysis and ring closure, gave **1a**.

Attempts to prepare spiro[fluoren-9,4′-imidazolidine]-2′,5′-dithione from fluorenone, KCN, NH_4Cl, and CS_2 in dilute methanol in a closed system failed to give the desired compound. Instead, 9,9′-difluorenyl disulfide was formed. Apparently formation of H_2S and NH_3 (*i.e.*, $(NH_4)_2S$) occurred in the reaction. Subsequent reaction between $(NH_4)_2S$ and fluorenone gave the disulfide.[5]

Antitumor screening results are presented in Table I. Compounds **1b**, **1c**, and **2a** showed some activity against Lewis lung carcinoma. Compound **3** also showed activity against Sarcoma 180.

(1) (a) Supported in part by a grant (CA-01744) from the National Cancer Institute, National Institutes of Health, and in part by Research Career Development Award 5-K3-CA-14,991. (b) Paper XXIII in this series: T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *J. Med. Chem.*, **10**, 936 (1967).

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(4) (a) H.-L. Pan and T. L. Fletcher, *ibid.*, **7**, 31 (1964); (b) H.-L. Pan and T. L. Fletcher, *ibid.*, **8**, 491 (1965).

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TABLE I
ANTITUMOR SCREENING DATA FOR SOME IMIDAZOLIDINE-2,5-DIONES[a]

Compd no.	Tumor system[b]	Daily dose, mg/kg	Survivors	Tumor wt, mg, or survival days (test/control)	% T/C
1b	Sarcoma 180	500	5/6	296/485	61
	Lewis lung	350	6/6	423/965	43
	carcinoma	350	6/6	277/1208	22
		350	5/6	722/848	85
1c	Sarcoma 180	500	6/6	500/485	103
	Lewis lung	400	6/6	510/965	52
	carcinoma	400	6/6	805/1208	66
	L1210	400	6/6	9.0/8.3	108
2a	Sarcoma 180	500	6/6	224/485	46
		500	6/6	1900/1268	149
	Lewis lung carcinoma	400	6/6	599/965	62
	L1210	400	6/6	8.0/8.3	96
3	Sarcoma 180	50	5/6	780/1398	55
	Lewis lung carcinoma	35	6/6	693/965	71
	L1210	35	6/6	8.0/9.1	87

[a] The screening data were supplied through the kindness of Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md. Assays were performed according to CCNSC specifications as reported in *Cancer Chemotherapy Repl.*, **25**, 1 (1962). [b] Sarcoma 180 was tested in Swiss albino mice; Lewis lung carcinoma and L1210 lymphoid leukemia were tested in BDF_1 mice.

Experimental Section[6]

Spiro[fluoren-9,4′-imidazolidine]-2′,5′-dione (1a). A.—Fluorenone (27 g, 0.15 mole), KCN (19.5 g, 0.3 mole), $(NH_4)_2CO_3 \cdot H_2O$ (68.4, 0.6 mole), and 50% ethanol (530 ml) were placed in a 1-l. stainless steel reaction vessel (Parr medium-pressure apparatus, Series 4500). The mixture was stirred at 125–130° for 3.5 hr, cooled, and diluted with water (600 ml), and the product was collected on the filter, washed with water, and dried giving 35.2 g (94%), mp 328–336° dec. Recrystallization from ethanol gave shiny, stubby needles: mp 348–349° dec (lit.[5] mp 352–356° dec); ν_{max} in cm^{-1} 3175 (amide N–H), 1770, 1705 (C=O) (lit.[5] ν_{max} in cm^{-1} 3200, 1780, 1710).

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.93; H, 4.57; N, 11.22.

B.—N-9-(9-Cyanofluorenyl)urea (see below) (0.1 g) was refluxed for 2 hr in 10% H_2SO_4 (20 ml). The lustrous crystals were separated giving 0.1 g, mp 348–349° dec. No melting point depression was observed when the product was mixed with the material obtained in A. The infrared spectra of the two products are identical.

Spiro[2-bromofluoren-9,4′-imidazolidine]-2′,5′-dione (1b). A.—2-Bromofluorene (Aldrich Chemical Co.) was oxidized by sodium dichromate to 2-bromo-9-oxofluorene. The latter (13 g, 0.05 mole) was treated as in A at 130–135° for 3 hr with KCN (6.5 g, 0.1 mole) and $(NH_4)_2CO_3 \cdot H_2O$ (22.7 g, 0.2 mole) in 50% ethanol (400 ml). The crude product (13.8 g) was recrystallized from ethanol giving shiny, white needles: 10.3 g (63%); mp 351–352°; ν_{max} in cm^{-1} 3175 (amide N–H), 1770, 1720 (C=O).

Anal. Calcd for $C_{15}H_9BrN_2O_2$: N, 8.51. Found: N, 8.41.

B.—Spiro[fluoren-9,4′-imidazolidine]-2′,5′-dione (5 g, 0.02 mole) was suspended in a hot mixture of AcOH (250 ml) and water (25 ml) containing $FeCl_3$ (2 g). A solution of Br_2 (8 g, 0.05 mole) in AcOH (25 ml) was added dropwise to the stirred suspension at 80–85° (2.5 hr). The mixture was heated at 85–90° for 18 hr then at 90–100° for 9 hr and diluted with water. The product was isolated and recrystallized twice from ethanol giving 4.2 g (64%). No mixture melting point depression was observed when the product was mixed with the compound obtained in A.

Spiro[2,7-dichlorofluoren-9,4′-imidazolidine]-2′,5′-dione (1c). A.—A mixture of spiro[fluoren-9,4′-imidazolidine]-2′,5′-dione (5 g, 0.02 mole), $FeCl_3$ (0.5 g), and AcOH (350 ml) was stirred at 75° while a solution of Cl_2 (3.6 g, 0.05 mole) in AcOH (50 ml) was added in one portion. The mixture was continuously stirred without heating for 24 hr and diluted with water. The product thus obtained was recrystallized three times from ethanol giving 0.9 g (14%): mp 357–358° dec; ν_{max} in cm^{-1} 1760, 1710 (C=O), 815 (two adjacent ring hydrogens).

Anal. Calcd for $C_{15}H_8Cl_2N_2O_2$: C, 56.45; H, 2.53; Cl, 22.22; N, 8.78. Found: C, 56.57; H, 2.61; Cl, 22.00; N, 8.64.

B.—2,7-Dichloro-9-oxofluorene[8] (5 g, 0.02 mole) in methanol (500 ml) was mixed with a solution of $(NH_4)_2CO_3 \cdot H_2O$ (34.2 g) in water (100 ml) and a solution of KCN (13 g) in water (20 ml). The mixture was heated under reflux at 60–65° for 12 days. Then the volume of the mixture was reduced by distillation to one-half of the original. It was diluted with some water, strongly acidified with concentrated HCl, heated to boiling with stirring, and cooled. The product (6.9 g) was isolated and recrystallized from ethanol, mp 358–359° dec; mixture with the product in A showed no depression of the melting point, and the infrared spectra of both are identical.

C.—Tetrazotization of the 2,7-diamino derivative obtained below and reaction with Cu_2Cl_2 gave a 56% yield of the dichloro compound (mixture melting point and ir spectra).

Spiro[2,7-dinitrofluoren-9,4′-imidazolidine]-2′,5′-dione (1e).—Powdered spiro[fluoren-9,4′-imidazolidine]-2′,5-dione (12.5 g) was added in small portions, with stirring, to a mixture of HNO_3 (*d* 1.42) (20 ml) and 60% H_2SO_4 (100 ml) at 55–60° over a period of 1 hr. The suspension was stirred at the same temperature for 4 hr and cooled. After water dilution the crystalline solid was separated and recrystallized from acetic acid giving 5.4 g (31.5%), mp 333–335° dec. Another recrystallization from acetic acid gave an analytical sample, mp 335–336° dec.

Anal. Calcd for $C_{15}H_8N_4O_6$: C, 52.95; H, 2.37; N, 16.47. Found: C, 53.06; H, 2.26; N, 16.43.

Spiro[2,7-diaminofluoren-9,4′-imidazolidine]-2′,5′-dione (1d).—The 2,7-dinitro compound (5.1 g, 0.015 mole) was suspended in 95% ethanol (1.5 l). To the stirred suspension 85% hydrazine hydrate (30 ml) and Raney nickel (~1 g) were added.[9] The mixture was gradually heated to refluxing and continuously refluxed with stirring for 1 hr then filtered. The filtrate, upon evaporation, gave 3.5 g (83%) of lustrous blades, mp 344–345° dec.

Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.31; H, 4.38; N, 19.77.

4-(2-Fluorenyl)-4-methylimidazolidine-2,5-dione (2a).—2-Acetylfluorene (Aldrich Chemical Co.) (10.4 g, 0.05 mole), KCN (6.5 g, 0.1 mole), $(NH_4)_2CO_3 \cdot H_2O$ (22.8 g, 0.2 mole), and 50% ethanol (200 ml) were stirred in the Parr apparatus described above at 120–130° for 3 hr and diluted with water. The lustrous leaflets thus obtained weighed 13 g (90%), mp 305–307° dec. Recrystallization from ethanol gave an analytical sample, mp 309–310° dec.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.25; H, 5.06; N, 10.19.

1,3-Dichloro-4-(fluoren-2′-yl)-4-methylimidazolidine-2,5-dione (2b).—Compound **2a** (5.6 g, 0.02 mole) was suspended in 4% methanolic sodium tetraborate decahydrate (100 ml). The stirred mixture was cooled at ~10° and *t*-butyl hypochlorite (5.5 g, 0.05 mole) was added dropwise over a period of 10 min. After 1 hr of further stirring at 0–5° and 2 hr at room temperature, the reaction mixture was diluted with water (200 ml). The precipitate was collected, washed with water then with a little methanol, and dried giving 6.9 g (100%), mp 207.5–209°.

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_2$: Cl, 20.42; N, 8.07. Found: Cl, 20.00; N, 8.26.

Spiro[fluoren-9,4′-imidazolidine]-1′,3′-dichloro-2′,5′-dione (3).—Spiro[fluoren-9,4′-imidazolidine]-2′,5′-dione was also N-chlorinated in the same way giving a 44% yield, mp 226–227°.

Anal. Calcd for $C_{15}H_8Cl_2N_2O_2$: Cl, 22.22; N, 8.78. Found: Cl, 21.91; N, 8.97.

9-Cyanofluoren-9-amine.—9-Fluorenylideneimine[10] (20 g, 0.17

(6) Melting points below 250° were taken on a Fisher-Johns block and are corrected to standards. Melting points above 250° were taken in a capillary on the Hoover apparatus and are uncorrected. The infrared absorption spectra were run on a Beckman IR-5 (KBr disks). Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by A. Bernhardt, Mülheim (Ruhr), Germany.

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(8) J. Schmidt and H. Wagner, *Ann.*, **387**, 147 (1912).

(9) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

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mole) was stirred in 95% ethanol (200 ml) while a solution of $NaHSO_3$ (18 g, 0.17 mole) in water (30 ml) was added dropwise over a period of 10 min. The reaction mixture was stirred at room temperature for 0.5 hr then in an ice bath for 1 hr. The crystals were collected, washed with a small amount of cold methanol and then ether, and dried, giving 45 g (95%) of **sodium 9-amino-9-fluorenesulfonate** which was mixed with water (750 ml) and cooled in ice. To the stirred mixture a solution of KCN (21 g) in water (100 ml) was added dropwise over a period of 25 min. The mixture was stirred in the ice bath for 1 more hr and at room temperature for several hours and the 9-amino-9-cyano derivative was isolated giving 23 g (70%). Recrystallization from ether–petroleum ether (bp 30–60°) gave a pure product, mp 95–96.5° (lit.[10] mp 95–96°).

N-Acetyl derivative, mp 237.5–238°.

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.19; H, 4.76; N, 11.48.

N-9-(9-Cyanofluorenyl)urea.—9-Cyanofluoren-9-amine (1.1 g, 5 mmoles) was dissolved in AcOH (30 ml) containing concentrated HCl (0.5 ml). To the stirred solution KCNO (0.4 g, 5 mmoles) was added. The mixture was then heated at 65–75° for 1 hr and diluted with water. The product was isolated and recrystallized from methanol–benzene giving lustrous crystals (0.5 g), mp 270° dec (with a preheated bath).

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.56; H, 4.55; N, 17.01.

9,9′-Difluorenyl Disulfide.—Fluorenone (9 g), CS_2 (25 ml), methanol (200 ml), water (100 ml), KCN (13 g), and NH_4Cl (10.8 g) were mixed and stirred in a Parr apparatus at 115–125° for 2 hr and the solvent evaporated. The residual gummy solid was triturated in water and boiled in 95% ethanol (200 ml). The crystalline material was collected on a filter giving 4.6 g (23%), mp 165–167°. Recrystallization from benzene–methanol gave silky crystals, mp 168–169° (lit.[5] mp 170–171°).

Anal. Calcd for $C_{26}H_{18}S_2$: S, 16.26. Found: S, 16.20.

Acknowledgment.—The authors are grateful to Misses Norma K. Naimy and Carol-Ann Cole for running the infrared spectra.

Drug Latentiation. II.[1] Labile Ether Derivatives of Phenolic Analgesics

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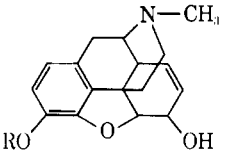
Received April 27, 1967

The main metabolic pathway for the elimination from the body of analgesics bearing phenolic hydroxyl groups is conjugation with glucuronic acid; the main site of conjugation is the phenolic hydroxyl group.[3]

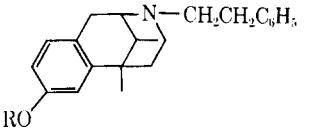
Interference with this mechanism by masking the site may well have a profound effect upon the nature and duration of activity of such analgesics. Etherification is a better means of achieving such masking than is acylation since acylated phenols, such as diacetylmorphine (heroin), are rapidly hydrolyzed *in vivo*.[3] Although the potency of phenolic analgesics is considerably reduced when they are alkylated (*e.g.*, morphine → codeine), it was considered of interest to examine ethers that are much less stable chemically than simple alkyl ethers, *e.g.*, methoxymethyl ethers. The *in vivo* rate of breakdown of methoxymethyl ethers of phenolic analgesics may be such that the speed of conjugation is reduced while allowing sufficient free phenol to be liberated at the site of action to produce a potent analgesic response.

The phenolic analgesics selected for this study were morphine (I) and phenazocine (II). Methoxymethylmorphine (III) was first reported by Mannich[4] and later used by Rapoport, Baker, and Reist,[5] in a synthesis of morphinone, as a derivative in which the phenolic moiety is stable to oxidizing agents. No reports of pharmacological studies have been found. The procedure of Mannich was repeated and gave the desired derivative in 50% yield; isopropyl ether–ethanol was found to be far superior to the described solvent, dilute alcohol, as a crystallization solvent for the product.

Difficulties were encountered in applying the same process to phenazocine. The sodio derivative of morphine, prepared by dissolving the base in sodium ethoxide–ethanol–water, precipitated when its solution was diluted with ether and was readily collected, washed, and dried. In contrast, the sodium salt of phenazocine did not precipitate and needed to be dried by azeotropic distillation with benzene followed by storage in a vacuum desiccator over concentrated sulfuric acid. The dry product was soluble in $CHCl_3$ (in contrast to sodium morphinate) and after reaction with chloromethyl methyl ether gave an oil (insoluble in aqueous NaOH), that could not be induced to solidify. This was chromatographed on neutral alumina. Benzene eluates yielded the desired ether (IV) as an oil, characterized as the crystalline acid succinate (salts with strong acids were avoided due to the lability of the ether group). Elution with 1% methanol in benzene gave unchanged starting material. The latter should normally have been removed by the isolation procedure, but it was observed that phenazocine base was sparingly soluble in aqueous NaOH, in contrast to morphine; furthermore, the hydroxyl stretching band of the phenol was not apparent in the infrared spectrum of phenazocine either as the free base or hydrobromide salt. A better yield of the methoxymethyl ether of phenazocine (IV) was obtained by treating the phenolic base with sodium naphthyl followed by the halide, conditions previously found suitable for forming sodio derivatives of secondary alicyclic alcohols.[1a] The product from this reaction was further characterized as a methiodide.



I, R = H
III, R = CH_3OCH_2



II, R = H
IV, R = CH_3OCH_2

Pharmacological Evaluation.—In the mouse hot plate test for analgesic activity, 3-methoxymethylmorphine (III) showed a mouse ED_{50} of 28.0 mg/kg (25.0–33.2) with a duration of 168 min[6] (*cf.* morphine

(1) (a) Part I: S. M. Kupchan, A. F. Casy, and J. V. Swintosky, *J. Pharm. Sci.*, **54**, 514 (1965). (b) This investigation was supported, in part, by a grant from Smith Kline and French Laboratories.

(2) This author thanks the Wellcome Trust for a travel grant.

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(6) We are indebted to Dr. N. B. Eddy, National Institutes of Health, for these data; *cf.* N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).