propanol. Compound I was recovered by neutralization with aqueous NaOH and the identity was confirmed by elemental analysis and infrared and nmr spectra. With the aforementioned quantities of reactants, ephedrine and I were obtained in almost equal yield, 27 and 28%, respectively. Even with an equimolar ratio of reactants, the diamine was isolated in 3% yield which increased to 8% when the reactants were preheated to 60° and maintained at that temperature during the hydrogenation.

Since various catalysts have been reported to be effective in ephedrine synthesis, the effect of the nature of the metal catalyst on the product distribution was briefly investigated. With 5% Pt/C, 5% Pd/C, or PtO_2 as catalyst and 2.5 moles of methylamine/mole of acetylbenzoyl, the ratio of the yield of ephedrine:yield diamine was *ca.* 4:1 compared with 1:1 for the mixed 5% Pt/C–5% Pd/C catalyst. When Raney nickel was used, no evidence for the formation of diamine was observed, even when the methylamine:acetylbenzoyl mole ratio was increased to 4:1. The choice, by Couturier, of Raney nickel as the hydrogenation catalyst was likely responsible for the impression that the synthesis of ephedrine is highly selective and only 1 mole of methylamine may be introduced.[4] It is surprising, however, that diamine formation was not previously observed when other catalysts were employed.

The likely reaction path for the reductive alkylation is hydrogenation of the respective ketimines formed from acetylbenzoyl and methylamine. The initial rapid reaction and absorption of approximately 1 mole of hydrogen occurs most likely at the β-ketimine position. Ketimine formation is reversible and the position of equilibrium between the α-carbonyl and the α-ketimine is apparently influenced by the nature of the metal catalyst to account for the observed product distribution between ephedrine and the diamine.

SCHEME I

$$C_6H_5COCOCH_3 \overset{CH_3NH_2}{\rightleftharpoons} C_6H_5COC(=NCH_3)CH_3 + H_2O \xrightarrow{H_2}$$

$$C_6H_5COCH(NHCH_3)CH_3 \xrightarrow{H_2} \text{ephedrine}$$

$$\Big\downarrow\uparrow CH_3NH_2$$

$$C_6H_5C(=NCH_3)CH(NHCH_3)CH_3 + H_2O \xrightarrow{H_2} \text{I}$$

Pharmacological Activity.—The dihydrochloride of I was tested by a typical behavior screen procedure[10] and found to exhibit weak sympathomimetic properties. Significant stimulatory effects were observed only at concentrations that approached lethal dosage.

Experimental Section[11]

N,N′-Dimethyl-1-phenyl-1,2-propanediamine (I).—A mixture of acetylbenzoyl[12] (29.6 g, 0.20 mole), methanolic methylamine (69 ml, 22%) (15 g, 0.48 mole, of amine), and methanol (120 ml) was hydrogenated in a Parr apparatus in the presence of a mixture of 5.0 g of 5% Pt/C and 5.0 g of 5% Pd/C. The initial absorption of hydrogen was rapid and the temperature rose from 25 to 35°. The reaction then moderated and proceeded slowly. When no further uptake of hydrogen was observed, the shaking was discontinued and the catalyst was separated by filtration. The filtrate was concentrated to one-half the original volume to remove methylamine, made acid with methanolic HCl and concentrated to a waxy solid. Trituration with acetone afforded a solid product that was collected by suction filtration, washed with acetone, and dried. Any pseudoephedrine hydrochloride formed was removed by heating under reflux with two 200-ml portions of $CHCl_3$. The crude product (mp 177–230°) was heated under reflux with two 200-ml portions of 2-propanol. The insoluble fraction was separated by filtration and washed with 2-propanol to afford the dihydrochloride of I (14 g, 28% of theoretical), mp 250–252° dec. Recrystallization from water–2-propanol did not raise the melting point.

Anal. Calcd for $C_{11}H_{20}Cl_2N_2$: C, 52.60; H, 8.03; Cl, 28.23; N, 11.15. Found: C, 52.35; H, 8.10; Cl, 28.04, 28.13; N, 10.85.

Ephedrine hydrochloride was isolated by concentration of the 2-propanol-soluble fraction (11 g, 27% of theoretical), mp 188–189° (lit.[2,3] mp 189°, 185–186°). The hydrochloride was converted to the free base, mp 75° (lit.[2,3] mp 75°).

An aqueous solution of the dihydrochloride of I was made alkaline (NaOH) and extracted twice ($CHCl_3$). The combined extracts were dried (Na_2SO_4), the solvent was removed, and I was obtained by distillation at 143–145° (20 mm) as a clear liquid: $\nu_{max}^{CHCl_3}$ 3300 cm^{-1} (N–H); nmr ($CDCl_3$) (reference TMS), τ 9.17 (CH_3 doublet), 8.60 (NH), 7.85, 7.72 (N–CH_3), 7.40 (CH multiplet), 6.58 (CH doublet), 2.82 (aromatic CH).

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.86; H, 10.16; N, 15.48.

Catalyst Studies.[13]—When 5% Pt/C, 5% Pd/C, or the mixed 5% Pt/C–5% Pd/C was used as the hydrogenation catalyst, 10 g of catalyst was employed for 0.2 mole of acetylbenzoyl. With PtO_2, 0.50 g of catalyst was used. Raney No. 28 active nickel catalyst contains approximately 50% water, and 20 g of wet catalyst was washed with methanol to remove water and used to hydrogenate 0.2 mole of acetylbenzoyl.

All other conditions and procedures were identical.

Acknowledgments.—We wish to thank Mr. Robert Puchalski and Mr. Arnold Lewis of the Warner-Lambert Research Institute for obtaining the elemental analyses and infrared and nmr spectra. We also wish to thank Mr. Puchalski for his assistance in interpretation of the spectra.

(10) Tested at the Warner-Lambert Research Institute by the procedure of S. Irwin, *Science*, **136**, 123 (1962).

(11) All melting points are uncorrected. Analyses and spectra were obtained by the Warner-Lambert Research Institute.

(12) W. W. Hartman and L. J. Roll in "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 20.

(13) The catalysts employed were all commercial samples; 5% Pt/C, 5% Pd/C, and PtO_2 were obtained from Engelhard Industries, Inc., Newark, N. J. Raney No. 28 Active Nickel Catalyst in Water was obtained from W. R. Grace and Co., Raney Catalyst Division, Chattanooga, Tenn.

4-Anilinopyrimidine-5-carboxylic Acids and Esters with Antiinflammatory and Analgetic Properties[1]

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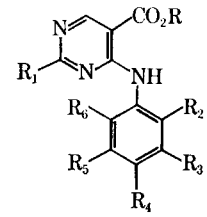
Several N-phenylanthranilic acids and esters have been described which show antiinflammatory, analgetic, and antipyretic activities in both pharmacological and clinical tests. These compounds include N-(3-trifluoromethylphenyl)anthranilic acid[2] and esters,[3] N-

(1) Some of the compounds have been reported by P. F. Juby, U. S. Patents 3,254,086 (1966), 3,254,087 (1966), and 3,300,496 (1967).

(2) (a) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963); (b) E. L. Coodley, *Western Med.*, **4**, 228 (1963); (c) P. Young, *Arthritis Rheumat.*, **6**, 307 (1963).

(3) (a) R. A. Scherrer and F. W. Short, U. S. Patent 3,278,584 (1966); (b) French Patent M2948 (1964).

TABLE I: 4-ANILINOPYRIMIDINE-5-CARBOXYLIC ACIDS AND ESTERS



No.	R	R_1	R_2	R_3	R_4	R_5	R_6	Mp, °C	Crystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Dose, mg/kg	Anti-inflam act., % inhib of edema[b]
										Esters								
1	C_2H_5	H	H	H	H	H	H	103–104[c]	A	$C_{13}H_{13}N_3O_2$							150	0
2	C_2H_5	H	Cl	H	H	H	H	112–114	B–C	$C_{13}H_{12}ClN_3O$[j]	56.22	4.36	15.14	56.50	4.54	15.35	150	0
3	C_2H_5	H	H	Cl	H	H	H	82–83	B–C	$C_{13}H_{12}ClN_3O_2$	56.22	4.36	15.14	56.40	4.41	15.42	150	0
4	C_2H_5	H	H	CH_3	H	H	H	78.5–79.5	B–C	$C_{14}H_{15}N_3O_2$	65.35	5.88	16.33	65.50	5.92	16.44	100	6
5	CH_3	H	H	CF_3	H	H	H	95–96	A	$C_{13}H_{10}F_3N_3O_2$	52.52	3.39	14.14	52.75	3.47	14.25	150	32
6	C_2H_5	H	H	CF_3	H	H	H	72–73	B–C	$C_{14}H_{12}F_3N_3O_2$	54.00	3.89	13.50	54.05	3.90	13.48	100	46
7	C_2H_5	H	H	$COCH_3$	H	H	H	130.5–131	B–C	$C_{15}H_{15}N_3O_3$	63.15	5.30	14.73	62.90	5.12	15.00	150	26
8	C_2H_5	H	H	SO_2CH_3	H	H	H	149–150	B–C	$C_{14}H_{15}N_3O_4S$	52.38	4.71	13.08	52.60	4.74	13.38	150	15
9	C_2H_5	H	H	H	Cl	H	H	111.5–113	B–C	$C_{13}H_{12}ClN_3O_2$	56.22	4.36	15.14	56.35	4.38	15.27	150	4
10	C_2H_5	H	H	H	CH_3	H	H	85–87	B–C	$C_{14}H_{15}N_3O_2$	65.35	5.88	16.33	65.10	5.87	16.53	100	12
11	C_2H_5	H	H	H	OCH_3	H	H	79.5–80	B–C	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.38	61.65	5.50	15.32	150	19
12	C_2H_5	H	H	H	CO_2CH_3	H	H	139–140	D	$C_{15}H_{15}N_3O_4$	59.79	5.02	13.95	59.90	5.04	14.10	150	20
13	C_2H_5	H	CH_3	CH_3	H	H	H	89–90	D–C	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49	66.10	6.17	15.70	100	0
14	C_2H_5	H	Cl	H	H	CF_3	H	111–112	D	$C_{14}H_{11}ClF_3N_3O_2$	48.64	3.21	12.16	49.00	3.18	12.20	150	5
15	C_2H_5	H	H	Cl	H	Cl	H	127–128	B	$C_{13}H_{11}Cl_2N_3O_2$	49.99	3.55	13.46	50.00	3.64	13.55	150	10
16	C_2H_5	CH_3	H	CF_3	H	H	H	77–78	B–C	$C_{15}H_{14}F_3N_3O_2$	55.40	4.34	12.91	55.70	4.43	13.08	100	1
17	C_2H_5	C_6H_5	H	CF_3	H	H	H	130–132	B	$C_{20}H_{16}F_3N_3O_2$	62.00	4.16	10.84	62.30	4.28	10.95	100	17
										Acids								
18	H	H	H	H	H	H	H	272–275[d,e]		$C_{11}H_9N_3O_2$	61.39	4.22	19.53	61.10	4.41	19.55	150	21
19	H	H	Cl	H	H	H	H	274–275.5 dec	B–C	$C_{11}H_8ClN_3O_2$	52.92	3.23	16.83	52.80	3.40	17.02	150	9
20	H	H	H	Cl	H	H	H	288–289 dec	E	$C_{11}H_8ClN_3O_2$	52.92	3.23	16.83	52.75	3.09	17.00	150	9
21	H	H	H	CH_3	H	H	H	261–263 dec	D	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33	63.00	5.10	18.10	100	6
22	H	H	H	CF_3	H	H	H	236–237[f]		$C_{12}H_8F_3N_3O_2$	50.89	2.85	14.84	51.10	3.12	15.05	100	61
23	H	H	H	$COCH_3$	H	H	H	214–215.5	B	$C_{13}H_{11}N_3O_3$	60.69	4.31	16.34	60.50	4.43	16.52	150	13
24	H	H	H	SO_2CH_3	H	H	H	254 dec	C	$C_{12}H_{11}N_3O_4S$[g]	47.67	4.00	13.90	47.75	4.07	13.75	150	0
25	H	H	H	H	Cl	H	H	283.5–284 dec	B–C	$C_{11}H_8ClN_3O_2$	52.92	3.23	16.83	53.00	3.57	16.65	150	1
26	H	H	H	H	CH_3	H	H	257–258 dec	B	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33	62.85	4.93	18.33	100	22
27	H	H	H	H	OCH_3	H	H	277–278 dec	E	$C_{12}H_{11}N_3O_3$	58.75	4.63	17.14	58.70	4.62	17.25	150	21
28	H	H	H	H	CO_2H	H	H	318–318.5 dec[h]		$C_{12}H_9N_3O_4$	55.60	3.50	16.21	55.65	3.69	16.22	150	0
29	H	H	CH_3	CH_3	H	H	H	255–256	B	$C_{13}H_{13}N_3O_2$	64.18	5.39	17.28	63.99	5.44	17.50	100	37
30	H	H	Cl	H	H	CF_3	H	256.5–258 dec	B	$C_{12}H_7ClF_3N_3O_2$	45.37	2.22	13.23	45.68	2.50	13.14	150	11
31	K	H	H	Cl	H	Cl	H	>400	C–F	$C_{11}H_6Cl_2KN_3O_2$	41.00	1.88	13.05	41.30	1.77	13.15	150	22
32	H	H	Cl	CH_3	H	H	Cl	281–281.5 dec	B	$C_{12}H_9Cl_2N_3O_2$	48.34	3.04	14.10	48.05	3.07	14.26	150	50
33	H	H	Cl	H	Cl	H	Cl	277–279 dec	B	$C_{11}H_6Cl_3N_3O_2$	41.47	1.90	13.19	41.70	2.19	13.41	150	2
34	H	CH_3	H	CF_3	H	H	H	273–274	B	$C_{13}H_{10}F_3N_3O_2$	52.52	3.40	14.14	52.75	3.50	14.15	100	9
35	H	C_6H_5	H	CF_3	H	H	H	274–275	B	$C_{18}H_{12}F_3N_3O_2$	60.17	3.37	11.69	60.40	3.38	11.75	100	10

[a] A = Skellysolve B (bp 60–80°), B = ethanol, C = water, D = methanol, E = dimethylformamide, F = 1-butanol. [b] Any result of more than 30% inhibition is greater than three times the standard deviation of the result in control animals and is considered to indicate significant activity. [c] See ref 9. [d] This compound was prepared by Dr. R. A. Partyka of these laboratories. [e] The compound was sublimed at 180–200° (0.05–0.1 mm). [f] The compound was sublimed at 190° (0.01 mm). [g] Hemihydrate. [h] The compound was purified by reprecipitation.

(2,3-dimethylphenyl)anthranilic acid,[4] N-(2,6-dichloro-3-methylphenyl)anthranilic acid,[5] and some N-(fluorophenyl)anthranilic acids.[6] In this paper we describe the preparation and preliminary pharmacology of a series of pyrimidine analogs of these anthranilic acids and esters. Pyridine[7] and quinoxaline[8] analogs have already been reported.

Chemistry.—All of the substituted 4-anilino-5-carbethoxypyrimidines (**1–4** and **6–17**, Table I) were prepared by a method similar to that described by Bredereck and co-workers[9] for the preparation of the unsubstituted parent product (**1**). A 5-carbethoxy-4-chloropyrimidine was treated with an appropriately substituted aniline in benzene. The resulting 4-anilino-5-carbethoxypyrimidines were converted to the 4-anilinopyrimidine-5-carboxylic acids (**18–31**, **34**, and **35**) by alkaline hydrolysis.

5-Carbethoxy-4-(2,6-dichloro-3-methylanilino)pyrimidine, however, could not be isolated from the reaction of the sterically hindered 2,6-dichloro-3-methylaniline with 5-carbethoxy-4-chloropyrimidine in benzene or toluene. Use of the sodium salt of the 2,6-dichloro-3-methylaniline in dimethylformamide or diglyme did result in an uncharacterized mixture which upon alkaline hydrolysis gave the desired 4-(2,6-dichloro-3-methylanilino)pyrimidine-5-carboxylic acid (**32**), albeit in very poor yield.

An improved yield of **32** was obtained from the reaction of sodium 4-ethoxypyrimidine-5-carboxylate[10] with the sodium salt of 2,6-dichloro-3-methylaniline in hexamethylphosphoramide, followed by an acid work-up. The limited solubilities of the reactants might account for lower yields of product obtained in alternative solvents such as dimethylformamide and diglyme.

Structure–Activity Relationships.—The 4-anilinopyrimidine-5-carboxylic acids and esters were tested orally for antiinflammatory activity by the carrageenin-induced rat foot edema method,[11] and the results are recorded in Table I. The acids generally exhibited higher activity than the corresponding esters. The most effective compound, **22**, had a minimal effective dose of approximately 50 mg/kg (30% inhibition of edema), with an oral LD_{50} of 1782 mg/kg in mice. By comparison, N-(3-trifluoromethylphenyl)anthranilic acid and N-(2,6-dichloro-3-methylphenyl)anthranilic acid showed 39 and 52% inhibition of edema, respectively, at doses of 128 mg/kg.

All of the compounds were examined at oral doses of 150 mg/kg for analgetic activity in mice by a modified phenylquinone test.[12] Only **13**, a close analog of the analgetic N-(2,3-dimethylphenyl)anthranilic acid, showed activity, with a minimal effective dose of 75 mg/kg.

In summary, it can be said that the carboxyl-substituted benzene ring of the N-phenylanthranilic acids and esters can be replaced by the pyrimidine ring with the retention of antiinflammatory and analgetic activities. The most effective compounds in both series have identical substitution patterns in the common benzene ring.

Experimental Section[13]

Starting Materials.—5-Carbethoxy-4-chloropyrimidine[14] and 5-carbethoxy-4-chloro-2-methylpyrimidine[15] were prepared by known procedures. 5-Carbethoxy-4-chloro-2-phenylpyrimidine was prepared by the method of Partyka.[16] 2,6-Dichloro-3-methylaniline[17] and 3-methylsulfonylaniline[18] were prepared by known procedures. All other anilines were obtained from commercial sources.

General Procedure for 4-Anilino-5-carbethoxypyrimidines (1–4 and 6–17).—The esters were prepared by a method similar to that described for 4-anilino-5-carbethoxypyrimidine (**1**) by Bredereck, *et al.*[9] A solution of a 5-carbethoxy-4-chloropyrimidine and 2 equiv of an aniline in benzene was heated under reflux until the reaction was complete (0.5–1 hr). The precipitated aniline hydrochloride was removed by filtration and the filtrate was reduced to dryness. The residual anilino ester was recrystallized from solvents indicated in Table I.

General Procedure for 4-Anilino-5-pyrimidinecarboxylic Acids (18–31, 34, and 35).—Most of the pyrimidine esters were heated under reflux in 5–10% aqueous KOH for 0.5–2 hr. The cooled reaction solutions were acidified to pH 2 with concentrated HCl, and the precipitated acids were purified as indicated in Table I.

Ethanol was added to the aqueous KOH to increase the hydrolysis rates of esters **15** and **17**. The potassium salt **31** separated from the cooled reaction mixture.

5-Carbomethoxy-4-(3-trifluoromethylanilino)pyrimidine (5).—An ethereal solution of excess diazomethane was added to a stirred suspension of 3 g of 4-(3-trifluoromethylanilino)pyrimidine-5-carboxylic acid (**22**) in ether (60 ml). The resulting solution was filtered and the filtrate was reduced to dryness on a steam bath to leave 2.1 g (66.6%) of **5**.

N-(2,6-Dichloro-3-methylanilino)pyrimidine-5-carboxylic Acid (32). Method A.—A solution of 2,6-dichloro-3-methylaniline[17] (10.3 g, 0.0585 mole) in dry DMF (40 ml) was added rapidly to a stirred suspension of sodium hydride (2.4 g of a 58.6% NaH dispersion in mineral oil, 0.0585 mole of NaH) in DMF (30 ml). The mixture was heated to 60° and kept at this temperature until H_2 evolution ceased. The temperature of the mixture was then raised to 120°, when a solution of 5-carbethoxy-4-chloropyrimidine[14] (10.9 g, 0.0585 mole) in DMF (40 ml) was added dropwise. The mixture was heated at 120° for 3 hr. The DMF was removed from the cooled reaction mixture in a rotary evaporator. A suspension of the oily residue in a solution of water (70 ml), ethanol (30 ml), and KOH (15 g) was heated under reflux for 2.5 hr. Most of the ethanol was then removed in a rotary evaporator and water (150 ml) was added to the residue. The aqueous mixture was washed with three 100-ml portions of $CHCl_3$. The resulting aqueous solution was treated at its boiling point with decolorizing carbon and filtered while hot. The cooled filtrate was acidified to pH 2 with concentrated HCl to precipitate **32** (2.1 g, 12%) as a light brown solid, mp 266–268° dec. The product crystallized from methanol (decolorizing carbon) as colorless crystals.

Method B.—The sodium salt of 4-ethoxypyrimidine-5-carboxylic acid[16] was prepared by warming a solution of the acid

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(13) Melting points were determined in a Mel-Temp apparatus and are uncorrected.

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(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.

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

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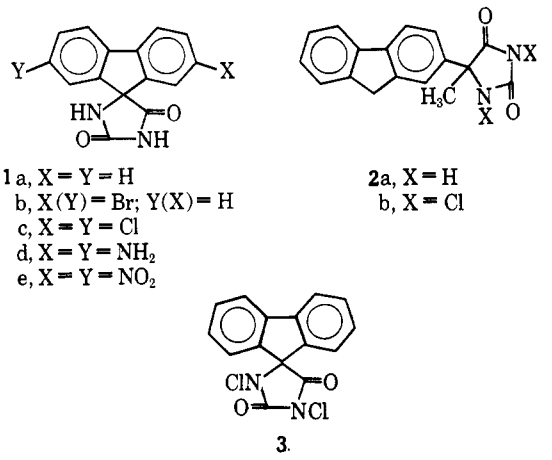
Because of the biological activity of certain imidazolidinediones,[2,3] we are synthesizing a number of such compounds incorporating variously substituted fluorene nuclei, connected through their 9 positions (spirohydantoins), and through their 2 positions (4-fluorenyl-4-methylimidazolidinediones). This 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.

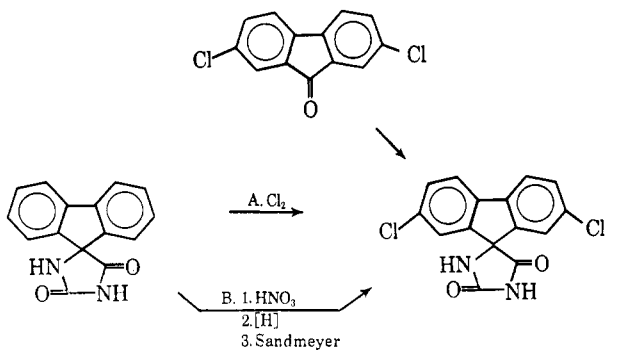


1 a, X = Y = H
b, X(Y) = Br; Y(X) = H
c, X = Y = Cl
d, X = Y = NH_2
e, X = Y = NO_2

2 a, 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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