

## The Synthesis and Diuretic Properties of Some N-Alkylaminocarbonyl- and N-Pyrrolylcarbonylanthranilic Acid Derivatives

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The preparation of a new series of substituted N-pyrrolylcarbonylanthranilic acids (VII, IVa-d) and N-alkylaminocarbonylanthranilic acids (IIIa-j) is reported. In the first series, N-pyrrolylcarbonyl-4-chloro-5-sulfamoylanthranilic acid (IVd) was the most active compound in our diuretic screen. N-Indolylcarbonyl-4-chloro-5-sulfamoylanthranilic acid (VII) showed somewhat diminished diuretic activity. In the second series of compounds, N-pyrrolidinylcarbonyl-4-chloro-5-sulfamoylanthranilic acid (IIIj) was the most active diuretic. The mode of action of these compounds was shown to be similar to that of hydrochlorothiazide.

In an attempt to find diuretic drugs with a mechanism of action differing from those already in use we synthesized a number of derivatives of substituted anthranilic acids. These compounds were evaluated pharmacologically and compared with hydrochlorothiazide and furosemide.

Cleavage reactions of isatoic anhydride are known to occur with a variety of nucleophiles by two competing mechanisms.<sup>1-3</sup> The intermediacy of an isocyanate (II) for path a reactions (Scheme I) was proposed<sup>2,3</sup> and later confirmed by Iwakura.<sup>4</sup> The successful reaction of phenyl isocyanate with pyrrolylpotassium to give l-pyrrolylcarboxanilide<sup>5,6</sup> encouraged us to treat isatoic anhydrides with metal derivatives of pyrrole and indole. We successfully prepared a new series of N-pyrrolylcarbonyl- (IVa-d) and N-indolylcarbonylanthranilic acids (VII) (see Table I). The diuretic activity of these compounds prompted us to synthesize another series of N-alkylaminocarbonyl-4-chloro-5-sulfamoylanthranilic acids (IIIa-j) (Table II). Only the parent compound (IIIa) has been reported<sup>7,8</sup> in this series. The starting material, 4-chloro-5-sulfamoylisatoic anhydride (Id), was best prepared by the procedure of Gadekar and Ross<sup>9</sup> from the corresponding anthranilic acid.<sup>10</sup>

The ureas (VII, IVa-d), the related esters (V, VI), and the series of N-alkylaminocarbonyl-4-chloro-5-sulfamoylanthranilic acids (IIIa-j) were all screened for their diuretic activity.

**Biological Results.**—The most active compound in this study was N-pyrrolylcarbonyl-4-chloro-5-sulfamoylanthranilic acid (IVd) (Table III). It was about 75% as active as furosemide (Table IV). In the dog it was equal to that of hydrochlorothiazide (Table V). Since IVd did not produce any additive diuretic response in the hydrochlorothiazide-loaded animal (Table VIII) this suggested a mechanism of action similar to that of the thiazides.<sup>11</sup>

Table III summarizes the diuretic response observed in the adx (DOCA) rat for the N-pyrrolylcarbonyl-

anthranilic acids and N-indolylcarbonyl-4-chloro-5-sulfamoylanthranilic acid (VII) in order of decreasing activity. Replacement of the free CO<sub>2</sub>H in IVd by the methyl ester (V) showed a moderate decrease in diuretic activity. Removal of the sulfamoyl group (IVc) or both the chloro and sulfamoyl groups (IVa) further diminished the diuretic activity. Moreover, IVa was inactive in the saline-loaded rat (Table IV) and in the nembutalized dog (Table V) where IVd showed some activity.

Table VI summarizes the diuretic activity in the adx (DOCA) rat for the N-alkylaminocarbonylanthranilic acids in order of decreasing activity. The most active compound in this series was IIIi (the tetrahydro analog of IVd). The least active in the series was the parent compound IIIa. In the pentobarbitalized dog IIIi produced a diuresis which appeared to be somewhat less than that of hydrochlorothiazide (Table VII). It is interesting to note that although IIIi had very little diuretic activity, the corresponding ethyl ester IIIe produced a comparatively large increase in sodium excretion. IIIi also exhibited less diuretic activity than IIIi. The diuretic activity of the di-N-alkylated derivative IIib was about equal to IIIi.

In the hydrochlorothiazide-loaded dog IIIi did not produce any additive diuretic effects (Table VIII) suggesting, as with IVd, a hydrochlorothiazide-like action in the kidney.

### Experimental Section

#### Biological Methods. Adrenalectomized DOCA-Treated Rat.

—Testing for diuretic activity in adrenalectomized (adx) deoxycorticosterone acetate (DOCA) treated male rats (Charles River) was based on a modified method of Marcus, *et al.*<sup>12</sup> The animals were deprived of food and water for 2.5 hr prior to test time and were injected subcutaneously with 12  $\mu$ g of DOCA and with 0.1 or 1.0 mg/rat of the test compound. A 5-hr pooled urine sample obtained at each dose from three pairs of rats was compared to controls receiving 1.0 mg/rat of furosemide subcutaneously. Volumes were recorded and samples were analyzed for Na, K, and Cl. The ratios represent the mean urine and electrolyte values from the test group (TG) compared to furosemide (F)-treated controls.

The DOCA inhibitory factor (DIF) was calculated using the formula  $DIF = (X_t - X_d)/(X_p - X_d)$  where X represents the Na/K ratio of test drug (t), DOCA controls (d), and placebo group (p). A value of 1.0 represents a complete inhibition of DOCA response, while a minus value suggests a DOCA-like activity.

While diuretic activity in this preparation may reflect DOCA

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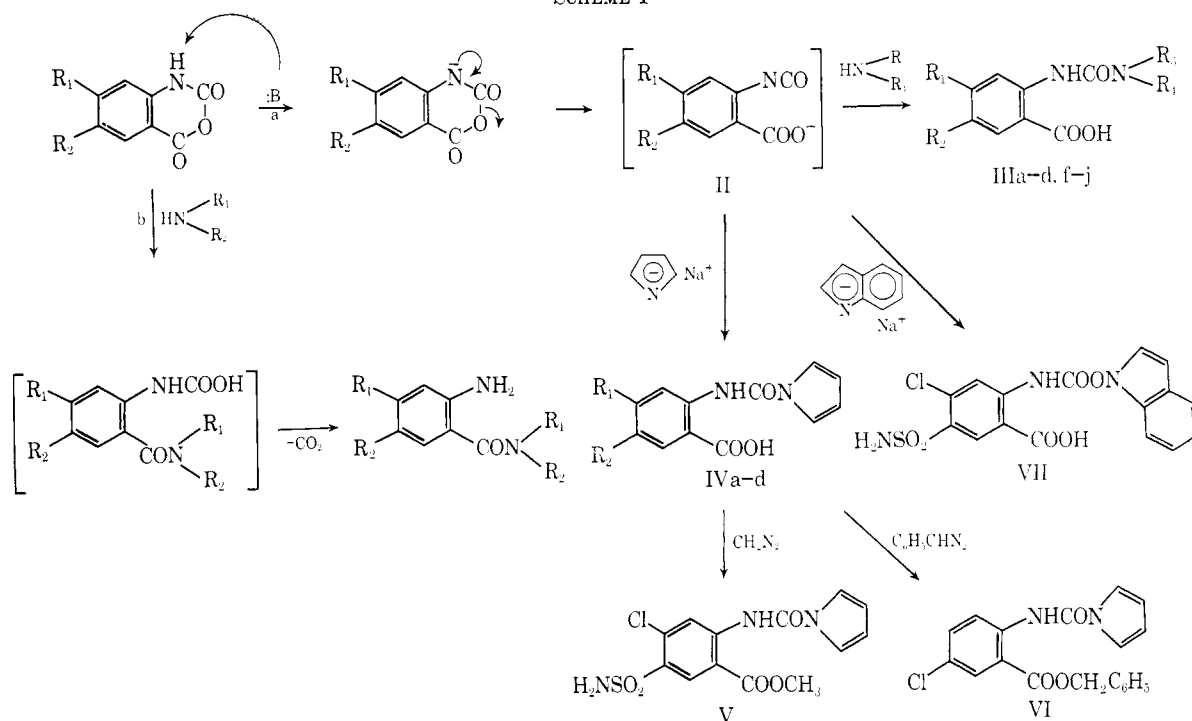
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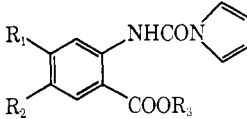
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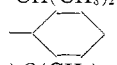
SCHEME I

TABLE I  
N-PYRROLYLCARBONYL- AND N-INDOLYLCARBONYLANTHRANILIC ACID DERIVATIVES

Compd				Crystd from <sup>a</sup>	Yield, %	Mp, °C	Formula <sup>b</sup>
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>				
IVa	H	H	H	A-B	37	202-204	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>
IVb	H	Cl	H	A-B	18 <sup>c</sup>	220-222	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>3</sub>
IVc	Cl	H	H	A-B	56	216-222	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>3</sub>
IVd	Cl	H <sub>2</sub> NSO <sub>2</sub>	H	A-B	20	263-265	C <sub>12</sub> H <sub>10</sub> ClN <sub>2</sub> O <sub>3</sub> S
V	Cl	H <sub>2</sub> NSO <sub>2</sub>	CH <sub>3</sub>	C-B	25	275-280	C <sub>13</sub> H <sub>12</sub> ClN <sub>2</sub> O <sub>3</sub> S
VI	H	Cl	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	A	53	108-109	C <sub>19</sub> H <sub>18</sub> ClN <sub>2</sub> O <sub>3</sub>
VII	Cl	H <sub>2</sub> NSO <sub>2</sub>	H	THF-B	29	298 dec	C <sub>16</sub> H <sub>12</sub> ClN <sub>2</sub> O <sub>3</sub> S

<sup>a</sup> A = EtOH, B = H<sub>2</sub>O, C = DMF. <sup>b</sup> Satisfactory analyses were obtained for C, H, N. <sup>c</sup> This reaction was carried out in the usual way using pyrrolyllithium.

TABLE II  
N-ALKYLAMINOCARBONYL-4-CHLORO-5-SULFAMOYLANTHRANILIC ACID DERIVATIVES

Compd				Crystd from <sup>a</sup>	Yield, %	Mp, °C	Formula <sup>b</sup>
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>				
IIIa	H	H	H	A-B	48	225-227	C <sub>8</sub> H <sub>8</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIIb	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	C-B	47	215-220	C <sub>12</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIIc	H	CH(CH <sub>3</sub> )C <sub>2</sub> H <sub>5</sub>	H	C-B	19	185-190	C <sub>12</sub> H <sub>16</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIId	H	CH(CH <sub>3</sub> ) <sub>2</sub>	H	D-B	19	150-154	C <sub>11</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIIe	H	CH(CH <sub>3</sub> ) <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	C-B	34	238-240	C <sub>13</sub> H <sub>18</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIIf	H		H	C-B	32	205-209	C <sub>14</sub> H <sub>18</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIIg	-(CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	H	H	E-C-B	44	204-207	C <sub>12</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>6</sub> S
IIIh	-(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> -	H	H	A-D	28	196-201	C <sub>13</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>3</sub> S
IIIi	-(CH <sub>2</sub> ) <sub>4</sub> -	H	H	C-B	14	125-216	C <sub>12</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> S
IIIj	-(CH <sub>2</sub> ) <sub>5</sub> -	H	H	C-B	29	192-197	C <sub>13</sub> H <sub>16</sub> ClN <sub>2</sub> O <sub>3</sub> S

<sup>a</sup> A = DMF, B = H<sub>2</sub>O, C = EtOH, D = MeOH, E = THF. <sup>b</sup> Satisfactory analyses were obtained for C, H, N.

TABLE III  
SUBSTITUENT EFFECT OF N-PYRROLYLCARBONYL-  
AND N-INDOLYLCARBONYLANTHRANILIC ACIDS ON  
ADRENALCTOMIZED DOCA-TREATED RATS

Compd	Dose, mg/rat sc	DIF <sup>a</sup>	TG/F <sup>b</sup>		
			Vol	Na	Na/K
IVd	1.0	3.145	0.615	0.903	1.031
V	0.1	1.564	0.249	0.417	0.932
VII	1.0	1.555	0.690	0.989	0.930
IVc	0.1	0.694	0.352	0.541	0.685
IVa	0.1	0.610	0.264	0.246	0.661

<sup>a</sup> DIF refers to DOCA inhibitory factor (see biological methods).

<sup>b</sup> Ratios represent the mean urine and sodium value from the test group (TG) compared to furosemide (F)-treated controls (see biological methods). The mean control values for 29 pairs of furosemide-treated rats equals urine volume  $9.1 \pm 0.5$ , Na  $1.045 \pm 0.067$ , and K  $0.937 \pm 0.063$ ; for 69 pairs of DOCA-treated rats urine volume equals  $2.7 \pm 0.2$ , Na  $0.339 \pm 0.033$ , and K  $0.645 \pm 0.037$ . The volume is expressed as ml/5 hr and electrolytes as mequiv/5 hr.

TABLE IV  
SUBSTITUENT EFFECT OF N-PYRROLYLCARBONYL-  
AND N-INDOLYLCARBONYLANTHRANILIC ACIDS ON  
NORMAL SALINE LOADED RATS

Compd	Dose, mg/kg po	TG/F <sup>a</sup>			
		Vol	Na	Cl	Na/K
IVa	10	0.28	0.36	0.35	0.52
	20	0.21	0.30	0.33	0.43
	40	0.21	0.26	0.32	0.40
IVd	10	0.02	0.44	0.34	0.64
	20	0.36	0.65	0.59	0.66
	40	0.45	0.74	0.64	0.67

<sup>a</sup> Ratios represent the mean urine and electrolyte value from test group (TG) compared to furosemide (F)-treated controls (see biological methods). The mean control values for 12 pairs of furosemide-treated (10 mg/kg) normal saline loaded rats equals urine volume  $8.57 \pm 1.30$ ; Na  $1.585 \pm 0.185$ , K  $1.024 \pm 0.102$ ; for 3 pairs at 20 mg/kg urine volume equals  $22.3 \pm 3.5$ , Na  $3.340 \pm 0.446$ , K  $1.588 \pm 0.148$ ; and for 3 pairs at 40 mg/kg urine volume equals  $48.5 \pm 1.50$ , Na  $6.729 \pm 0.294$ , K  $2.140 \pm 0.330$ ; for 41 pairs of placebo-treated rats urine volume equals  $6.47 \pm 0.40$ , Na  $0.95 \pm 0.05$ , and K  $1.02 \pm 0.04$ .

TABLE V  
SUBSTITUENT EFFECT OF N-PYRROLYLCARBONYL-  
AND N-INDOLYLCARBONYLANTHRANILIC ACIDS ON  
ANESTHETIZED DOGS

Compd	Dog no.	Time, min	Urine, ml/min	Uv electrolytes <sup>a</sup> μequiv/min			Na/K
				Na	K	Cl	
IVd	106 <sup>b</sup>	-30	5.3	240	69	154	3.48
		-15	5.1	212	68	126	3.12
		0					
		15	5.0	390	90	310	4.33
		30	5.3	384	69	309	5.57
IVa	105 <sup>b</sup>	-30	4.8	50	36	13	1.39
		-15	4.1	36	34	12	1.06
		0					
		15	3.3	41	39	10	1.05
		30	3.7	56	37	11	1.51

<sup>a</sup> Uv represents the excretion of electrolytes. <sup>b</sup> 5 mg/kg iv.

antagonism, other renal mechanisms cannot be ruled out on the basis of this test.

**Saline-Loaded Rat.**—All food and water was removed 2 hr prior to test time from adult male Charles River rats. At test time, a 0.9% saline load was administered intraperitoneally at 30 ml/kg. Each compound, at various doses, was administered *per os*, to three separate pairs of rats. A pooled urine sample was obtained from each pair and the mean values for urine and electrolytes were compared to similarly treated furosemide controls. The results are expressed as ratios as previously cited.

**Anesthetized Dog.**<sup>13</sup>—Female mongrel dogs were fasted for 18 hr and permitted water *ad libitum*. The animals were prepared surgically for diuretic assay.<sup>11,14</sup> During the equilibration period and just prior to drug administration, two 15-min urine control specimens were obtained and were used as a comparison for the 30-min postdrug effect.

Animals received hydrochlorothiazide as an intravenous priming dose and as a sustaining infusion to maintain a maximal diuresis during the testing period. Compounds were evaluated on the basis of producing an additive diuretic effect during a sustained hydrochlorothiazide infusion.<sup>11</sup>

**Chemical Methods.**—All melting points were determined microscopically on a hot stage and are corrected. Ir spectra were determined on a Beckman IR-9 spectrophotometer, nmr spectra with a Varian A-60 instrument. Tlc was done on plates prepared with silica gel G. DMF and THF were dried over Woelm grade I neutral alumina and used directly. The structures of all compounds were assigned on the basis of compatible ir and nmr spectra and on satisfactory analyses.

**4-Chloro-5-sulfamoylisatoic Anhydride (Id).**—COCl<sub>2</sub> was bubbled through 12.3 g (0.049 mol) of 2-amino-4-chloro-5-sulfamoylbenzoic acid<sup>10</sup> dissolved in a solution of 6.08 g (0.049 mol) of

TABLE VI  
SUBSTITUENT EFFECT OF  
N-ALKYLAMINOCARBONYLANTHRANILIC ACIDS ON  
ADRENALCTOMIZED DOCA-TREATED RATS

Compd	Dose, mg/rat sc	DIF <sup>a</sup>	TG/F <sup>b</sup>		
			Vol	Na	Na/K
IIIi	0.1	1.236	0.651	1.033	0.803
IIIe	1.0	1.050	0.517	0.322	0.507
IIIg	0.1	0.957	0.406	0.492	0.759
IIIf	1.0	0.901	0.487	0.740	0.744
IIIj	1.0	0.858	0.452	0.672	0.733
IIIb	0.1	0.818	0.270	0.433	0.720
IIIc	1.0	0.581	0.360	0.396	0.654
IIIh	0.1	0.543	0.176	0.252	0.641
IIId	0.1	0.482	0.318	0.425	0.625
IIIa	1.0	0.431	0.203	0.267	0.610

<sup>a</sup> DIF refers to DOCA inhibitory factor (see biological methods).

<sup>b</sup> Ratios represent the mean urine and Na<sup>+</sup> value from test group (TG) compared to furosemide (F)-treated controls (see biological methods). Volume is expressed as ml/5 hr and electrolytes as mequiv/5 hr.

TABLE VII  
SUBSTITUENT EFFECT OF N-ALKYLAMINOCARBONYLANTHRANILIC  
ACIDS ON ANESTHETIZED DOGS

Compd	Dog no.	Time, min	Urine, ml/min	Uv electrolytes <sup>a</sup> μequiv/min			Na/K
				Na	K	Cl	
IIIb	132 <sup>b</sup>	-30	4.7	93	70	21	1.33
		-15	5.3	91	80	21	1.38
		0					
		15	4.5	195	104	140	1.88
		30	4.5	183	89	112	2.06
IIIi	155 <sup>b</sup>	-30	5.6	106	44	45	2.41
		-15	5.7	103	40	37	2.57
		0					
		15	5.5	182	54	111	3.37
		30	5.3	144	45	59	3.20
IIId	183 <sup>b</sup>	-30	2.0	8.2	18.1	4.12	0.45
		-15	2.3	7.8	19.8	4.6	0.39
		0					
		15	3.2	102.4	48.0	92.8	2.14
		30	3.1	58.1	33.6	36.7	1.73

<sup>a</sup> Uv represents the excretion of electrolytes. <sup>b</sup> 5 mg/kg iv.

(13) L. B. Czyzewski, complete details to be published.

(14) K. H. Beyer, J. E. Baer, J. K. Michaelson, and H. F. Russo, *ibid.*, 147, 1 (1965).

TABLE VIII  
DIURETIC ACTIVITY OF COMPOUNDS IIIb AND IVd DURING  
CONTINUOUS INFUSION OF HYDROCHLOROTHIAZIDE  
IN THE ANESTHETIZED DOG

Compd	Dog no.	Time, min	Urine, ml/min	Uv electrolytes, <sup>a</sup> μequiv/min			Na/K
				Na	K	Cl	
IIIb <sup>c</sup>	133	-75	3.6	110	45	30	2.44
		HCT <sup>b</sup> prime 5 mg/kg iv plus 5 mg/kg/hr infused					
		-60	3.8	148	34	125	4.35
		-15	3.8	171	34	148	5.03
		-10	4.2	185	40	164	4.62
		-5	4.0	172	40	144	4.30
		0					
		5	4.0	172	42	140	4.10
		10	4.0	188	48	148	3.92
		15	3.8	175	42	141	4.17
IVd <sup>c</sup>	122	20	4.2	193	42	151	4.60
		25	3.4	156	34	122	4.59
		30	4.0	172	40	136	4.30
		-15	4.6	258	60	193	4.30
		-10	3.8	217	49	163	4.43
		-5	4.0	220	56	152	3.93
		0					
		5	2.4	113	46	70	2.46
		10	3.2	160	42	93	3.81
		15	3.8	228	61	141	3.74
		20	4.2	239	55	143	4.35
		25	3.6	212	50	137	4.24
		30	4.4	255	66	145	3.86

<sup>a</sup> Uv represents the excretion of electrolytes. <sup>b</sup> Hydrochlorothiazide. <sup>c</sup> 5 mg/kg iv.

Na<sub>2</sub>CO<sub>3</sub>·H<sub>2</sub>O in 140 ml of H<sub>2</sub>O and 140 ml of THF. After 15 min, the reaction mixture was immersed in an ice bath and phosgenation continued for an additional 2 hr. N<sub>2</sub> was bubbled through the mixture to rid the system of COCl<sub>2</sub> and filtration afforded 5.1 g (63% based on unrecovered starting material) of Id as white prisms, mp 282–290° dec, lit.<sup>7</sup> mp 293° dec. The mother liquor afforded 4.9 g of starting material.

**General Method for the Preparation of N-Alkylaminocarbonyl-4-chloro-5-sulfamoylanthranilic Acids (IIIa–j).**—To a solution of 0.2 mol of the amine in 100 ml of H<sub>2</sub>O was added 0.02 mol of Id portionwise with stirring. Stirring continued for 30 min at 25°. The reaction mixture was worked up by the addition of 250 ml of H<sub>2</sub>O followed by acidification with 4 N H<sub>2</sub>SO<sub>4</sub>. The mixture was cooled to 0° and filtered. Recrystallization from the appropriate solvent gave pure products (Table II).

**N-Isopropylaminocarbonyl-4-chloro-5-sulfamoylanthranilic Acid Ethyl Ester (IIIe).**—A mixture of 1.0 g (0.003 mol) of N-isopropylaminocarbonyl-4-chloro-5-sulfamoylanthranilic acid (IIIId) in 75 ml of C<sub>6</sub>H<sub>6</sub> was treated with 10 ml of SOCl<sub>2</sub> and heated under reflux for 14 hr. The resultant yellow homogeneous

solution was evaporated to dryness and taken up in 25 ml of EtOH, and 100 ml of H<sub>2</sub>O was added. The mixture was cooled to 0° and filtered. Recrystallization of the product from an EtOH–H<sub>2</sub>O mixture gave 0.4 g (34%) of IIIe as white rods, mp 238–240°.

**General Method for the Preparation of N-Pyrrolylcarbonyl-anthranilic Acids (IVa–d).**—A solution of 1.37 g (0.02 mol) of pyrrole in 55 ml of DMF was treated portionwise with 0.8 g (0.02 mol) of NaH (60% dispersion in mineral oil). The reaction mixture was stirred at 25° for 2 hr under N<sub>2</sub> and then the isatoic anhydride (Ia–d) (0.01 mole) was added portionwise with stirring over 30 min. The reaction mixture was stirred at 25° overnight was then treated with 300 ml of H<sub>2</sub>O, filtered through Norit, acidified with 2 M HCl, cooled to 0°, and filtered. Recrystallization of the product from EtOH–H<sub>2</sub>O gave the pure products (Table I).

**Methyl N-Pyrrolylcarbonyl-4-chloro-5-sulfamoylanthranilate (V).**—A solution of 3.44 g (0.01 mol) of N-pyrrolylcarbonyl-4-chloro-5-sulfamoylanthranilic acid (IVd) in 150 ml of MeOH was treated portionwise with a solution of CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O.<sup>15</sup> [A total volume of 300 ml of nonstandardized CH<sub>2</sub>N<sub>2</sub> solution was required to consume all of the carboxylic acid as shown by tlc (5:1 CHCl<sub>3</sub>–EtOH).] The reaction mixture was allowed to stand at 0° overnight. The crude tan solid obtained by filtration was recrystallized from DMF–H<sub>2</sub>O to give 0.9 g (25%) of V as white prisms.

**N-Pyrrolylcarbonyl-5-chloroanthranilic Acid Benzyl Ester (VI).**—A solution of 1.7 g (0.0064 mol) of N-pyrrolylcarbonyl-5-chloroanthranilic acid (IVb) in 200 ml of Et<sub>2</sub>O was treated with a solution of phenyldiazomethane in Et<sub>2</sub>O.<sup>16</sup> (A total volume of 150 ml of nonstandardized PhCHN<sub>2</sub> solution was required to consume all the carboxylic acid as shown by tlc.) The Et<sub>2</sub>O solution was extracted with saturated aqueous NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), filtered, and evaporated to dryness. Crystallization of the residue from EtOH afforded 1.2 g (53%) of VI as white prisms, mp 108–109°.

**N-Indolylcarbonyl-4-chloro-5-sulfamoylanthranilic Acid (VII).**—A solution of 11.1 g (0.095 mol) of indole in 100 ml of DMF was treated with 3.75 g (0.095 mol) of NaH (60% dispersion in mineral oil). The reaction mixture stirred at 25° for 2.5 hr under N<sub>2</sub>. To this was added 7.35 g (0.0265 mol) of 4-chloro-5-sulfamoylisatoic anhydride (IVd) portionwise, and the resulting mixture was stirred at 25° overnight. The reaction mixture was treated with 250 ml of H<sub>2</sub>O, filtered through Norit, acidified with 2 N HCl, cooled to 0°, and filtered to give 3 g (29%) of VII. Recrystallization from THF–H<sub>2</sub>O gave the pure material as white prisms.

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