was refluxed for 1 hr. Most of the solvent was removed from the reaction mixt, and the residue was treated with Et_2O. The pptd crude product was recrystd from MeOH–Et_2O to yield 0.63 g (60%) of the MeI salt **46**. *Anal.* ($C_8H_{18}INO$) C, H, I, N.

(±)-*trans*-2-Acetoxymethylcyclobutyltrimethylammonium Iodide (11). Compd **46** (0.45 g, 0.00166 mole) was treated with 5 g (0.049 mole) of Ac_2O as described for **10**. The product was recrystd from EtOH–Et_2O to yield 0.3 g (58%) of material, mp 104–105°. *Anal.* ($C_{10}H_{20}INO_2$) C, H, I, N.

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dl-α-[4-Cycloalkyl(cyclohexen-1-yl)]alkanoic Acids and Derivatives as Antiinflammatory and Antiarthritic Compounds

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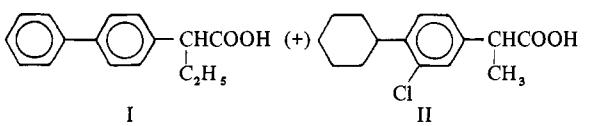
The Reformatsky reaction followed by dehydration gave 6 esters of the title compounds. These esters furnished a total of 16 corresponding acids, amides, and hydroxamic acids which were submitted to antiinflammatory assays. *dl*-α-[(4-Cyclohexyl)cyclohexen-1-yl]propionic acid was a potent adjuvant arthritis inhibitor and was selected for toxicological studies before clinical trials.

A large number of analgetic-antiinflammatory arylacetic acids have been reported. Among them, *p*-butoxyphenylacethydroxamic acid,[1] 4-allyloxy-3-chlorophenylacetic acid,[2] and α-(4-isobutylphenyl)acetic and -propionic acids[3] have been selected for a clinical use after extensive pharmacological studies. Moreover, α-(4-biphenylyl)butyric acid (I) is an active antiartherosclerotic drug,[4] and its dimethylaminoethanol salt is a good analgetic.[5] The most active antiinflammatory agents in these series were prepared by Shen, *et al.*[6,7] After an extensive synthetic and pharmacological study, the *d* isomer of 2-(*p*-cyclohexyl-*m*-chlorophenyl)propionic acid (II) appeared as unsurpassed by any other nonsteroidal agent in the granuloma assay and in the carrageenin edema assay.



I II

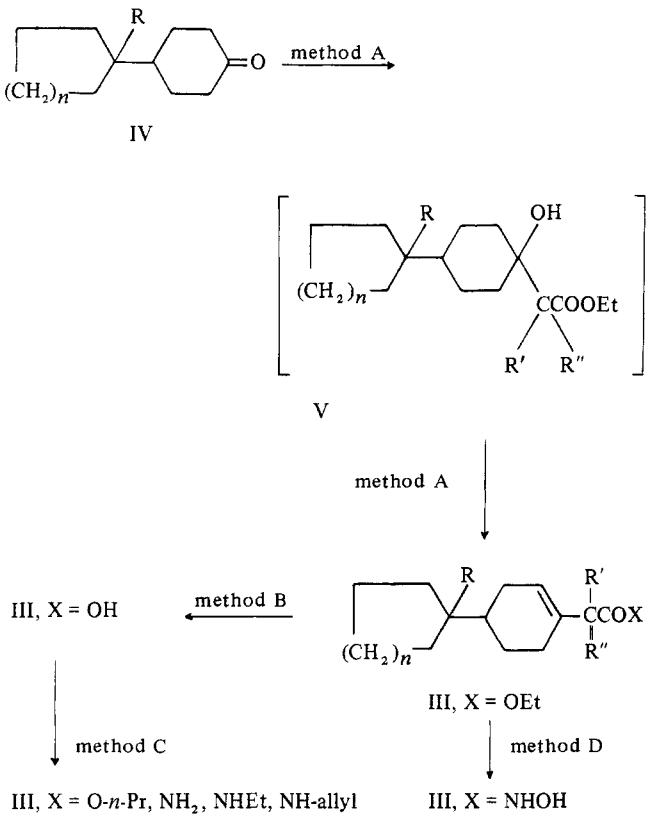
We have found that several *dl*-α-[4-cycloalkyl(cyclohexen-1-yl)]alkanoic acids and derivatives (III) retained an interesting and above all antiarthritic activity, although one of their rings was completely, and the other one was partially saturated.

The compounds III were prepared following Scheme I. A 4-cycloalkylcyclohexanone (IV) was treated by the Reformatsky reaction with an α-bromo ester. The crude cis-trans mixture of hydroxy esters (V) so obtained was dehydrated with P_2O_5,[8] providing a β-unsaturated ester (III, X = OEt) (method A). This last derivative was either saponified (method B), furnishing an acid (III, X = OH), or treated with $HONH_2$ (method D), thus producing an hydroxamic acid (III, X = NHOH). Several compounds of structure III were prepared from III (X = OH) by condensing its acid chloride (III, X = Cl) with an alcohol or an amine (method C).

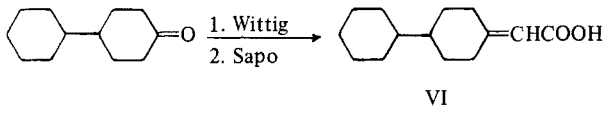
In structure III, the position of the double bond was ambiguous, because the dehydration of V could produce either an α- or a β-unsaturated ester. Therefore, the β-unsaturated nonconjugated structure of all derivatives III was ascertained by ir and uv spectrophotometry.[9] We also confirmed these results in one case, by synthesizing the conjugated α-unsaturated derivative VI in an unambiguous way, and by comparing it with its β-unsaturated isomer **7** (see Experimental Section).

The stereochemistry of the compounds III was ambiguous but has not been studied yet. The homogeneity of all the tested compounds was established by glc and tlc. The intermediates (III, X = OEt) and the test compounds (III) are listed in Tables I and II, respectively.

Scheme I



Biological Activity. The antiinflammatory activity of the compds was assessed by determining their ability to inhibit the rat hind paw carrageenin[10] edema and to delay the development of erythema induced by skin exposure to uv



radiation in guinea pigs.[11] The criteria by which compds were selected for further examination were: (a) a mean inhibition of at least 30% as compared with a control group in the rat paw edema test, and (b) a protection of about 35% in the erythema assay. Phenylbutazone was selected for comparison. The results are presented in Table II. Compds **9** and **16** were examined for inhibition of granuloma formation induced in rats by sc implantation of cotton pellets,[12] and for reduction of abscess formation in rats after the sc injection of a carrageenin solution.[13] As can be seen in Table II, some compds had considerable antiinflammatory activity in the preliminary acute screening test, although none of them seemed to be better than phenylbutazone in potency. Compds **9** and **16** presented also a weak inhibitory activity against the cotton granuloma formation. Compd **9** was equivalent to phenylbutazone in the carrageenin abscess test.

Compds **9** and **16** were also tested as potential adjuvant-induced arthritis inhibitors in rats. Arthritis was induced by injecting 0.6 mg of heat-killed tubercle bacilli in 0.1 ml of paraffin oil into the plantar surface of the right hind foot. Drugs were administered by intubation of suspensions in a 10% gum Tragacanth soln (10 ml/kg). Control rats received vehicle only. The development of the disease was observed daily for 23 days. Grading from 0 to 4 was used, according to inflammation. Each digit was graded separately and the metatarsus, metacarpus, tarsus, carpus, and tail were each graded as individual units. Total score was 108/rat.[14] Male rats (Charles River CD strain) weighing 250 g were used and dosed orally with the compds, the treatment beginning the day before the injection of Freund's adjuvant, and going on until the 23rd day. A mean arthritis score was calcd each day for the untreated control group and for the treated groups after the evaluation of the individual score. All groups consisted of 12 rats.

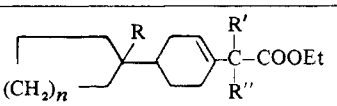
Figures 1 and 2 exhibit the effects of **9** and **16**, respectively, on the development of adjuvant arthritis. As can be seen, **9** strongly inhibits the development of the disease, particularly the secondary lesions, the activity being dose related. Compd **16** was moderately active. Indomethacin and phenylbutazone were employed as standards in these experiences. The LD_{50} of **9** after an 8 days' delay was 1170 mg/kg po in the rat.

The results of chronic studies on **9** suggest a good antiinflammatory activity and also a better therapeutic index than with the standards used. As **9** appears to be a potent adjuvant's arthritis inhibitor, a useful antirheumatic activity may be expected.

Experimental Section

Method A. One third of a soln contg ethyl α-bromoalkanoate (0.09 mole), 4-substituted cyclohexanone (IV, 0.09 mole), and anhyd C_6H_6 (150 ml) was added to Zn cuttings (0.09 g-atom) in the presence of some $HgCl_2$ and a crystal of I_2. The Reformatsky reaction was started with slight heating and the remainder of the soln was dropped into the reaction mixt maintd at the bp. Heating under reflux was contd for 3 hr after the completion of the addn, then the reaction mixt was cooled to room temp and poured on cracked ice

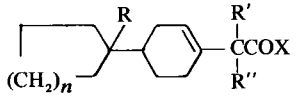
Table I



Compound	n	R	R'	R''	Bp (mm), °C	Formula[a]	Bp (mm), °C intermediate V
1	2	H	H	H	124-128 (0.05)	$C_{16}H_{26}O_2$	132-135 (0.35)
2	2	H	H	C_2H_5	120-124 (0.03)	$C_{18}H_{30}O_2$	148-150 (0.1)
3	2	H	CH_3	CH_3	120-122 (0.05)	$C_{18}H_{30}O_2$	128-132 (0.05)
4	2	H	H	C_3H_7	134-136 (0.15)	$C_{19}H_{32}O_2$[b]	160-164 (0.1)
5	2	CH_3	H	CH_3	129-130 (0.07)	$C_{18}H_{30}O_2$	132-134 (0.02)
6	1	CH_3	H	CH_3	120-122 (0.07)	$C_{17}H_{28}O_2$	120-124 (0.05)

[a] Anal. results obtained for C, H, and N if present, were within ±0.4% of the theoretical values. [b] C: Calcd, 78.03; found, 78.91. H: Calcd, 11.02; found, 10.59. The product contains some C_6H_6 (glc) but was not further purified before saponification.

Table II



Compd	n	R	R′	R″	X	Method	Solvent	Formula[a]	Mp, and/or bp (mm), °C	Carrageenin edema: Dose, mg/kg po	Carrageenin edema: % edema inhib, 3 hrs after carrageenin injection	Uv erythema: Dose, mg/kg po	Uv erythema: % erythema inhib, 5 hr
7	2	H	H	H	OH	B	Pentane	$C_{14}H_{22}O_2$	100–101	100	17.8	75	13.3
8	2	H	H	H	NHOH	D	EtOH–H_2O	$C_{14}H_{23}NO_2$	180–181	40	17	75	17.9
										80	35		
9	2	H	H	CH_3	OH	B		$C_{15}H_{24}O_2$	61–62	40	29	50	33.3
										80	46	75	42.5
									148–150 (0.04)	120	48	100	52.03
10	2	H	H	CH_3	OEt	A		$C_{17}H_{28}O_2$	126–128 (0.1)[b]	40	24.6	75	28.7
										80	45.9	150	37.6
11	2	H	H	CH_3	O-*n*-Pr	C		$C_{18}H_{30}O_2$	122–123 (0.02)	80	27.7	75	14.5
12	2	H	H	CH_3	$OCH_2CHOHCH_2OH$	C[c]	Pentane	$C_{18}H_{30}O_4$	72–74	*d*	*d*	*d*	*d*
13	2	H	H	CH_3	NH_2	C	Cyclohexane	$C_{15}H_{25}NO$	140–141	40	21.3	75	35.0
										80	27.8		
14	2	H	H	CH_3	NHEt	C	Pentane–cyclohexane	$C_{17}H_{29}NO$	101–102	80	4.0	*d*	*d*
15	2	H	H	CH_3	$NHCH_2CH{=}CH_2$	C	Cyclohexane	$C_{18}H_{29}NO$	82–84	80	0.0	*d*	*d*
16	2	H	H	CH_3	NHOH	D	C_6H_6	$C_{15}H_{25}NO_2$	150–153	75	21.3	75	35.7
										150	28.3	150	56.6
17	2	H	H	C_2H_5	OH	B	Pentane	$C_{16}H_{26}O_2$	83–85	80	19.6	75	36.2
												150	56.0
18	2	H	H	C_2H_5	NHOH	D	Pentane	$C_{16}H_{27}NO_2$	122–125	80	19.1	*d*	*d*
19	2	H	CH_3	CH_3	OH	B	Pentane	$C_{16}H_{26}O_2$	141–142	80	5.0	*d*	*d*
20	2	H	H	*i*-C_3H_7	OH	B	Cyclohexane	$C_{17}H_{28}O_2$	132–134	80	16.6	*d*	*d*
21	2	CH_3	H	CH_3	OH	B	Pentane	$C_{16}H_{26}O_2$	70–74	40	16.9	50	21.2
										80	30.0	75	37.8
22	1	CH_3	H	CH_3	OH	B	Pentane	$C_{15}H_{24}O_2$	68–70	80	36.3	50	27.1
Phenylbutazone										15	16	10	14.8
										30	44	20	42.5
										60	51	40	46.3

[a] See footnote *a*, Table I. [b] Bp of the crude hydroxylated intermediate V: 126–128° (0.1 mm). [c] See Experimental Section. [d] Insufficient data to state potency.

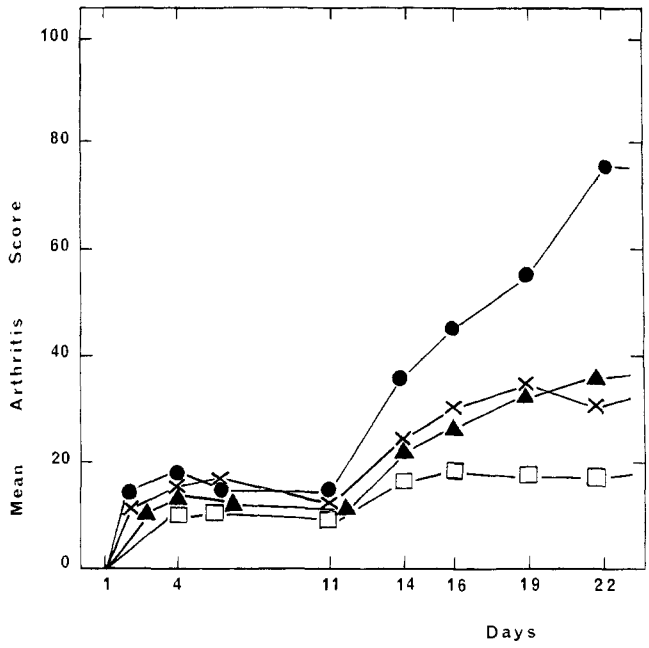


Figure 1. Development of adjuvant arthritis in rats. The animals were given daily oral doses for 23 days of: ▲–▲, indomethacin (2.0 mg/kg); X–X, compound 9 (40.0 mg/kg); □–□, compound 9 (80.0 mg/kg); ●–●, control group. Each group consisted of twelve rats.

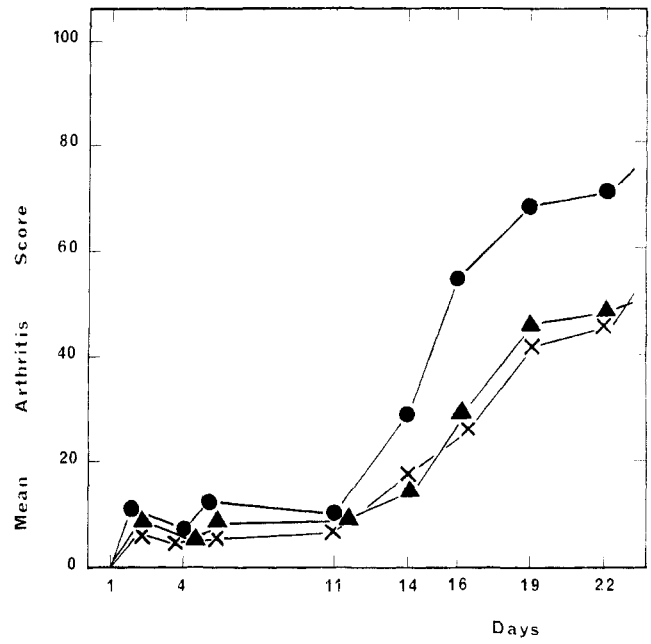


Figure 2. Development of adjuvant arthritis in rats. The animals were given daily oral doses for 23 days of: ▲–▲, phenylbutazone (50.0 mg/kg); X–X, compound 16 (80.0 mg/kg); ●–●, control group. Each group consisted of twelve rats.

(50–100 g) and AcOH (50 ml). The C_6H_6 layer was washed with an aq soln of $NaHCO_3$, then with distd H_2O until neutral. After drying ($CaSO_4$) and filtration the soln was concd to dryness and the residue distd under vacuum. A mixt comprising the crude cis-trans mixt of hydroxy ester V (0.05–0.09 mole), C_6H_6 (55 ml), and P_2O_5 (0.0625–0.112 mole) was stirred at reflux for 4 hr. After pouring off, the C_6H_6 layer was concd to dryness and the residual crude VI distd under reduced pressure.

Method B. A soln of ester III (X = OEt) (0.04 mole) in 1 *N* NaOH soln (45 ml) and EtOH (160 ml) was heated at reflux for 4 hr. After concn to dryness, the residue was dissolved into distd H_2O and the unsaponifiable products were extd with pentane. The H_2O layer was acidified until pH 2.5 with 5 *N* HCl and the pptg acid was extd with Et_2O. The Et_2O soln was washed with distd H_2O, dried ($CaSO_4$), filtered, and concd to dryness. The residue was crystd from the appropriate solvent or distd under vacuum.

Method C. $SOCl_2$ (0.1 mole) was dropped slowly into a soln cooled to 0–5° and contg the acid (III, X = OH) (0.1 mole), Et_3N (0.1 mole), and Et_2O (200 ml). The pptg $Et_3NH^+ Cl^-$ was filtered, and the soln contg the crude acid chloride was dropped at room temp into another soln contg an amine (0.2 mole) or an alcohol (0.1 mole). The mixt was heated at reflux for 2 hr, cooled, and washed successively with H_2O, aq $NaHCO_3$, and again with H_2O until neutral. After drying, the Et_2O soln was concd to dryness and the residue was crystd from the appropriate solvent or distd under vacuum.

Method D. An NH_2OH soln was prepd from $NH_2OH \cdot HCl$ (0.018 mole) and Na (0.018 g-atom) in EtOH (15 ml). The NaCl formed was filtered. To the filtrate were added successively an ester (III, X = OEt) (0.012 mole) and a soln of EtONa prepd from Na (0.012 g-atom) and EtOH (10 ml). During the addn, the temp was maintd at 0–2°. The mixt was stirred for 5 hr, allowed to stand overnight at room temp, and concd to dryness under reduced pressure. The residue was suspended in H_2O, acidified with HCl to pH 1, and the pptg acid was extd with Et_2O. The Et_2O soln was washed with H_2O, dried ($CaSO_4$), filtered, and concd to dryness (10 mm). The residue was crystd from the appropriate solvent.

Compound VI. To NaH (0.102 mole) suspended in 1,2-dimethoxyethane (120 ml) was added dropwise and with stirring ethyl diethylphosphonoacetate (0.106 mole) over a period of 1.5 hr and at 26–29°. The resulting soln was stirred for an addl 1.5 hr and then 4-cyclohexylcyclohexanone (0.0975 mole) was added dropwise and with stirring over a 1-hr period. The resulting suspension was stirred for 0.5 hr and then dild with H_2O and extd with Et_2O. The ethereal ext was dried ($CaSO_4$), filtered, and concd. Fractional distn of the residue sep the conjugated Et ester (0.064 mole) of VI: bp 130–138° (0.2 mm); ir absorption 1720 (conjugated ester) and 1.650 cm^{-1} (conjugated C=C). *Anal.* ($C_{16}H_{26}O_2$) H; C: calcd 76.75, found 77.07. A soln comprising NaOH (0.0864 mole), the preceding conjugated Et ester (0.04 mole), H_2O (13 ml), and EtOH (54 ml) was stirred at room temp for 4 days. After concn to 50 ml at room temp under vacuum, the aq suspension of Na salts so obtd was extd with pentane, then neutralized to pH 4 (aq HCl), and extd with Et_2O. This Et_2O ext was dried ($CaSO_4$), filtered, and concd to dryness. The residue was crystd from pentane, leaving VI (0.025 mole).

Table III. Physical Data of VI and 7

	VI	7
Mp, °C	115–116	100–101°
Mmp, °C	50–70	50–70°
Ir absorption (CCl_4), cm^{-1} (ϵ)	conjugated C=C, 1640 (475)	No absorption
	conjugated C=O, 1685 (325)	Nonconjugated C=O, 1705 (470)
Uv absorption (EtOH), nm (ϵ)	C=CC=O, 218 (15.400)	No absorption

The data for the isomers, VI and 7 are compared in Table III.

Compd 12. Following method C, the acid chloride (0.045 mole) of 9 was treated with glycerol acetonide (0.045 mole), and the resulting ester (0.022 mole) was distd: bp 170–172° (0.01 mm). *Anal.* ($C_{21}H_{34}O_4$) Calcd: C, 71.96; H, 9.78. Found: C, 72.47; H, 10.28. A mixt of this ester (0.019 mole) and 2 *N* HCl (48 ml) was stirred and heated at reflux over 0.5 hr. The oily layer was extd with Et_2O, washed with aq $NaHCO_3$, then with H_2O to neutrality, dried ($CaSO_4$), filtered, and concd to dryness. The residue was distd, and the fraction of bp 184–195° (0.2 mm) crystd from pentane, furnishing **12.**

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Aminobenzoic Acid Diuretics. 3.[1] 4-Substituted 5-Sulfamylanthranilic Acid Derivatives

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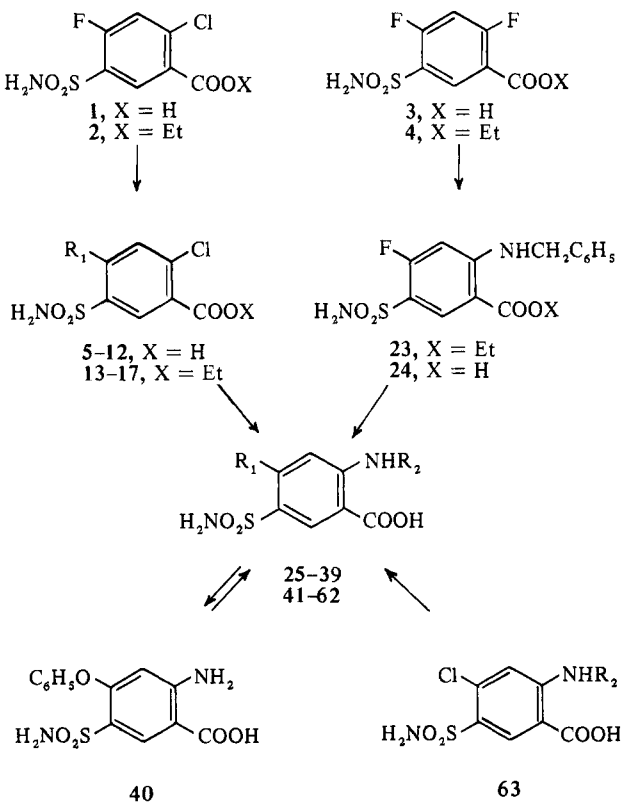
The synthesis of 37 N-alkylated 4-substituted 5-sulfamylanthranilic acids by partial and successive replacement reactions of the halogens in the 2,4-dihalogeno-5-sulfamylbenzoic acids is described. Reasons for the interest in these new anthranilic acid derivatives are discussed. Diuretic screening results for some of the compounds are summarized and compared with those of 3 selected 4-chloro-5-sulfamylanthranilic acid derivatives. The data have revealed that many of the new 4-R_1-*N*-R_2-5-sulfamylanthranilic acids are much more potent diuretics than the corresponding 4-Cl compounds. **55** (R_1 = OC_6H_5; R_2 = 2-furylmethyl) was the most potent compound having a level of activity and diuretic profile similar to that of bumetanide, recently described as a "high-ceiling" diuretic. *N*-*n*-Butyl-4-phenoxy-3-sulfamylanthranilic acid (**70**) prepared as a representative of the third isomeric aminosulfamylbenzoic acid series was devoid of diuretic activity.

In the preceding paper[1] of this series the synthesis of several 4-substituted 3-amino-5-sulfamylbenzoic acid derivatives and their diuretic properties were reported. Certain of these compounds were shown to be much more potent than the corresponding N-substituted 3-amino-4-chloro-5-sulfamylbenzoic acid diuretics.†[2] In the course of investigating the structure-activity relationship of high-ceiling diuretics we became concerned over the question of whether an analogous alteration of the 4-substituent in 4-chloro-*N*-(2-furylmethyl)-5-sulfamylanthranilic acid[3,4] (furosemide) and the related 4-chloroanthranilic acid diuretics[4] would increase their potency.

Furthermore it seemed justified to synthesize the *N*-*n*-butyl-4-phenoxy-3-sulfamylanthranilic acid (**70**) as a representative of the third possible isomeric 4-substituted aminosulfamylbenzoic acid derivatives in which the sulfonamide group still remains in the meta position to the carboxyl. Our choice of phenoxy to be the 4 substituent was prompted by the unusual potency and efficacy afforded by this substituent in both the 3-amino-5-sulfamylbenzoic acid derivatives[1] and the 5-sulfamylanthranilic acid series described in the present paper.

Chemistry. Different synthetic approaches (Scheme I) were used for the preparation of the 4-substituted *N*-R_2-5-sulfamylanthranilic acids[5] listed in Table III. The routes are based mainly on partial and successive replacement reactions of the halogens in various 2,4-dihalogeno-5-sulfamylbenzoic acids and are an extension of the described reactions of 2,4-dichloro- and 2-chloro-4-fluoro-5-sulfamylbenzoic acid (**1**) with different amines.[4] The most attractive route from the known 4-chloro-5-sulfamylanthranilic acid diuretics **63** was found to be only of limited application as the reactivity of the halogen atom is diminished by the aminofunction in the 2 position. It was therefore more advantageous to use 2-chloro-4-fluoro-5-sulfamylbenzoic acid (**1**) or its Et ester **2** as starting material. After reaction of the intermediate 4-R_1-2-chloro-5-sulfamylbenzoic acids (**5–12**) and esters (**13–17**) (Table I) with different amines the 4-R_1-*N*-R_2-5-sulfamyl-

Scheme I



†In ref 2 the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout.