dild with H_2O (4 ml), stirred for 30 min at room temp, and evapd to dryness at less than 45°. A soln of the residue in $CHCl_3$ (50 ml) was washed 3 times with satd $NaHCO_3$ soln (50 ml), 2 times with H_2O (50 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue crystd from EtOAc: yield 335 mg (37%). The analytical sample was obtd by recrystn from EtOAc. It was dried at 100° (0.07 mm) over P_2O_5 for 20 hr: mp 203–204°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 242 (9.80), 308 (14.2), pH 7, 248 (16.2), 297 (9.40), 0.1 *N* NaOH, 275 (9.74), 303 (sh) (4.35); $\bar{\nu}_{max}$ (cm^{-1}): 3400 (broad) (OH), 3320 (NH), 2965, 2930, 2875 (CH), 1730, 1720, 1655 (C=O), 1605, 1580, 1480 (C=C, C=N); δ in ppm: 0.9 (m, CH_3), 1.6 and 2.4 (m, CH_2 of butyryl), 4.3 (m, $C_2'H$, $C_4'H$, and $C_5'H_2$), 5.0 (t, $C_3'H$), 6.0 and 6.1 (overlapping d, $C_2'OH$ and $C_1'H$), 7.2 and 7.9 (AB pair, C_5H and C_6H), 10.8 (s, NH). These assignments were verified by spin decoupling. *Anal.* ($C_{21}H_{31}N_3O_8$) C, H, N.

1-(3,5-Di-*O*-butyryl-β-D-arabinofuranosyl)cytosine (VII). A soln of 1-(3,5-di-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (1.18 g, 2.51 mmoles) and picric acid (1.18 g, 5.10 mmoles) in MeOH (100 ml) was refluxed for 1 hr and stirred with enough Dowex 1-X8 (carbonate) ion-exchange resin to give a colorless soln. Evapn of the soln to dryness gave a white glass. A $CHCl_3$ soln of the glass was washed with H_2O, dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue crystd from EtOAc: yield 640 mg (66%); mp 166–167°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 212 (9.55), 278 (13.2); pH 7, 230 (sh) (7.83), 270 (9.18); 0.1 *N* NaOH, 230 (sh) (7.83), 273 (9.53); $\bar{\nu}_{max}$ (cm^{-1}): 3420, 3345, 3230, 3115 (NH), 2965, 2935, 2905, 2875 (CH), 1735, 1660, 1640 (C=O), 1620, 1605, 1525, 1485 (C=C, C=N). *Anal.* ($C_{17}H_{25}N_3O_7$) C, H, N.

1-(2,3,5-Tri-*O*-butyryl-β-D-arabinofuranosyl)cytosine (VIII). A soln of 1-(2,3,5-tri-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (4.84 g, 9.25 mmoles) and picric acid (4.84 g, 11.1 mmoles) in MeOH (200 ml) was refluxed for 1 hr and evapd to dryness *in vacuo*. A soln of the yellow residue in 95% aq Me_2CO (100 ml) was stirred with enough Dowex 1-X8 (carbonate) ion-exchange resin to give a colorless soln. Evapn of the soln to dryness gave a syrup that crystd from Et_2O. A soln of the cryst product in $CHCl_3$ (100 ml) was washed with 0.1 *N* H_2SO_4 (100 ml), satd $NaHCO_3$ soln (100 ml), and then H_2O (100 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue crystd from Et_2O: yield, 3.20 g (76%); mp 127–129°. The analytical sample was obtd from a previous run by recrystn from Et_2O and dried at 78° (0.07 mm) over P_2O_5 for 8 hr: mp 126–127°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 277 (13.2); pH 7, 233 (7.67), 269 (8.88); 0.1 *N* NaOH, 274 (10.0); $\bar{\nu}_{max}$ (cm^{-1}): 3445, 3320, 3265, 3125 (NH), 2965, 2935, 2875 (CH), 1760, 1735, 1655 (C=O), 1605, 1525, 1495, 1475 (C=C, C=N). *Anal.* ($C_{21}H_{31}N_3O_8$) C, H, N.

1-(2,3,5-Tri-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (IX). A soln of 1-β-D-arabinofuranosylcytosine hydrochloride (3.00 g, 10.8 mmoles) in pyridine (300 ml) contg butyric anhydride (7.86 ml, 47.7 mmoles) was heated at 80–85° for 2 hr. Another 1.86 ml of butyric anhydride was added and heating continued for 1 hr. The soln was then evapd to 60 ml and poured into ice water (300 ml). The resulting mixt was extd 3 times with $CHCl_3$ (200 ml). The $CHCl_3$ ext was extd 2 times with satd $NaHCO_3$ soln (300 ml), then H_2O (300 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. Crystn of the residue from Et_2O–petr ether gave a white solid: yield 4.85 g (86%); mp 91–93°. The analytical sample was obtd from a previous run by recrystn from Et_2O–petr ether. It was dried at 78° (0.07 mm) over P_2O_5 for 20 hr: mp 91–93°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 248 (12.3), 301 (8.85); pH 7, 249 (15.9), 297 (8.26); 0.1 *N* NaOH, 274 (9.73), 305 (sh) (3.51); $\bar{\nu}_{max}$ (cm^{-1}): 3230 (NH), 2965, 2930, 2875 (CH), 1730, 1665 (C=O), 1610, 1550, 1480 (C=C, C=N). *Anal.* ($C_{25}H_{37}N_3O_9$) C, H, N.

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Antibacterial Activity of *o*-Amino-*N*-hydroxybenzenesulfonamides†

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Several reports in the chemical literature have demonstrated the potentiating effect of an NOH moiety on the antibacterial properties of an arylsulfonamide. For example, *N*-hydroxybenzenesulfonamide is more potent against *Mycobacterium tuberculosis* than is benzenesulfonamide[1] and several N^4-acyl-N^1-hydroxybenzenesulfonamides are more effective against β-hemolytic streptococci in mice than is sulfanilamide itself.[2] Furthermore, the SO_2NHOH grouping is well known as a chelator of metal ions[3,4] a property which might be expected to be reflected in enhanced antibacterial effects.[5] However, N^1-hydroxysulfanilamide appears less active than the nor-OH counterpart *in vitro* but of equivalent activity *in vivo* by virtue of a metabolic conversion of sulfanilamide.[6] Tests against *Escherichia coli*[7] and other microorganisms[8] have shown that *o*- and *m*-aminobenzenesulfonamides, lacking the NOH on the sulfonamide group, do not inhibit bacterial growth.

Thus, our observation of significant antibacterial potency in several *o*-amino-*N*-hydroxysulfonamides, appears as a striking example of the activity promoting effects of an NOH function. We have prepared these materials (**1**, **2**, **4**, **5**, **6**) through the intermediacy of the *o*-aminobenzenesulfonyl chlorides and their subsequent reaction with hydroxylamines (H_2NOR) to yield both *N*-OH and *N*-OMe systems. Employing a cyclization method previously applied to ortho substituted carboxamides and dimethyl acetylenedicarboxylate,[9,10] the 1,2,4-benzothiadiazine (**7**) was prepared. Methylation of this heterocyclic with aq Me_2SO_4 yielded **3**. By a technique described by Wei, *et al.*[11] for condensation of aldehydes with *o*-amino-*N*-hydroxybenzenesulfonamides, *p*-nitrobenzaldehyde and the 2-amino-4,5-dichloro-*N*-hydroxybenzenesulfonamide (**1**) gave the 1,2,4-benzothiadiazine (**8**) in 90% yield.

Biological Activity. Compounds were applied to penicillin assay disks (Schleicher and Schuell Co., 12 mm diam) as either solution or suspension in 95% EtOH to achieve a concn of 4 mg/disk of test substance. The disks were then air-dried and placed on the surface of brain heart infusion agar medium (Difco) which had been seeded with the test organism. The assay plates were incubated at 37° and inhibition zones were measured after 24 and 48 hr (see Table I).

A free *o*-NH_2 and an SO_2NHOR appear to be essential for inhibitory activity since neither the heterocyclics, **7** and **8**, nor the *N*,*N*-Me_2N analog, **3**, displayed any measurable

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Table I[a]

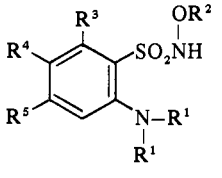
Compd	*Mycobacterium smegmatis*	*Mycobacterium sp.* (Rutgers strain 607R)	*E. coli*	*S. aureus*	*Pseudomonas fluorescens*
1	12	7	4	4	7[d]
2	15	9	2	3	9[d]
3	c	c	c	c	3[d]
4[b]	7	7	2	3	2[d]
5	c	c	c	c	c
6	c	c	c	c	c
7	c	c	c	c	1
8	c	c	c	c	3
SA[e]	12[d]	18[d]	5[d]	c	10[d]

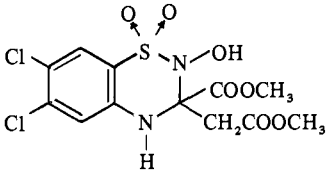
[a]Inhibition zones were measured in millimeters from the edge of the assay disk to the edge of growth surrounding the clear area after 48 hr. [b]Prepared as described in ref 11. [c]No inhibition. [d]Incomplete inhibition or inhibition followed by overgrowth after 24 hr. [e]SA = sulfanilamide.

activity. Methylation of the sulfonamido OH (compare **1** and **2**) has no appreciable influence on antibacterial effects indicating that the OH is probably not directly involved in binding. Replacing Cl by CH_3 at C-5 diminishes activity but a similar substitution of CH_3 for Cl at C-4 totally abolishes any growth inhibition (compare **1**, **4**, and **5**). The decrease in activity of the Me analogs is probably not solely electronic in origin, although it might be argued that in proceeding from **1** to **4** to **5** the "acidity" of the sulfonyl NH is being reduced. However, an adjacent NO_2, such as in **6**, would surely be expected to cancel any acidity-diminishing influence imparted by the CH_3 and yet this NO_2 compd is equally inactive. A steric argument seems implicated.

The 2 most potent compounds, **1** and **2**, were tested along with sulfanilamide against *Mycobacterium marinum*, ATCC 927, a slow growing pigmented strain. Both **1** and **2** strongly inhibited *M. marinum* (11 mm complete inhibition zones) but sulfanilamide was completely ineffective.

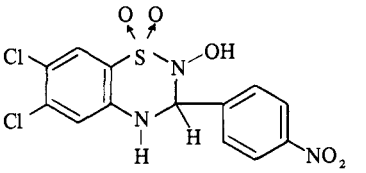
Since nonhydroxylated *o*-aminobenzenesulfonamides were proven ineffective against bacteria which are competitively (PABA) inhibited by the *p*-amino analogs,[7,8] it appears unlikely that our active *o*-amino-*N*-hydroxybenzenesulfonamides inhibited at the *p*-aminobenzoic acid incorporation stage. It is still possible, however, that they interfere with either the synthesis or function of folate. Furthermore, the history of the SO_2NHOH moiety as an ion binder,[3,4] and the structure-activity relationships observed herein, might also support a chelation type inhibition for these compounds.





7

1, $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Cl$
2, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = R^5 = Cl$
3, $R^1 = R^2 = CH_3$; $R^3 = H$; $R^4 = R^5 = Cl$
4, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$; $R^5 = Cl$
5, $R^1 = R^2 = R^3 = H$; $R^4 = Cl$; $R^5 = CH_3$
6, $R^1 = R^2 = R^4 = H$; $R^3 = NO_2$; $R^5 = CH_3$



8

Experimental Section

Combustion analyses were provided by Dr. G. I. Robertson, Florham Park, N. J. Only analytical samples were tested. Analytical values were within ±0.4% of calcd values for all elements indicated.

2-Amino-4,5-dichlorobenzenesulfonyl Chloride. 3,4-Dichloroaniline (66.0 g, 0.41 mole) was added in small portions to 200 ml of chilled, well-stirred $ClSO_3H$. During the addn the temp was held below 50° but then was raised to 125–130° for 1 hr and cooled to room temp, and 66 ml of $SOCl_2$ was added dropwise. The entire mixt was heated on a steam bath for 30 min and then poured over chopped ice. The greenish solid was collected, washed with cold water, air-dried, and dissolved in PhH. A small quantity of insol solid was filtered off, and the PhH phase was treated with decolorizing C and $MgSO_4$. Evapn of the filtered PhH gave 74.3 g of greenish yellow solid which after a second recrystn from 2:1 cyclohexane–PhH gave 59.5 g, 56%, of analytical material, mp 130.5–131.0°.‡ *Anal.* ($C_6H_4Cl_3NO_2S$) C, H, N.

2-Amino-4,5-dichloro-*N*-hydroxybenzenesulfonamide (1). A soln of 2-amino-4,5-dichlorobenzenesulfonyl chloride (73 mmoles) in 110 ml of 1,4-dioxane was added dropwise to a chilled soln of 10.2 g of $NH_2OH \cdot HCl$, 16 g of Et_3N, and 30 ml of H_2O. After being allowed to stand at ambient temp for 24 hr the reaction medium was concd *in vacuo* and dild with H_2O to ppt the product. Recrystn from 1:2 EtOH–H_2O gave 16.0 g, 73%, of **1** as a hemidioxane solvate, mp 170–171°. Combustion and integrated nmr analysis (CH_2's at 3.55 ppm δ) confirmed the presence of a 0.5 molar quantity of dioxane. *Anal.* [$C_6H_6Cl_2N_2O_3S \cdot 0.5(C_4H_8O_2)$] C, H, N. The dioxane can be removed by subsequent recrystn from PhH or by drying the solvate at 80° (0.4 mm) for 1 week. The solvent-free material also melted at 170–171°. *Anal.* ($C_6H_6Cl_2N_2O_3S$) C, H, N.

2-Amino-4,5-dichloro-*N*-methoxybenzenesulfonamide (2). A soln of 1.6 g, 6.16 mmoles, of the sulfonyl chloride in 16 ml of dimethoxyethane was added to 6 ml of 50% aq dimethoxyethane contg 0.6 g of $NH_2OMe \cdot HCl$. Et_3N (1.48 g) was added, and the mixt was stirred mechanically at room temp for 24 hr. The org layer was sepd and concd *in vacuo*, and the crude crystals were recrystd from H_2O to yield 0.70 g, 42%, of white **2**, mp 103.5–104.5°. *Anal.* ($C_7H_8Cl_2N_2O_3S$) C, H, N.

2-Hydroxy-3-carbomethoxy-3-carbomethoxymethyl-6,7-dichloro-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (7). A soln of equimolar amt (7.0 mmoles) of dimethyl acetylenedicarboxylate and 2-amino-4,5-dichloro-*N*-hydroxybenzenesulfonamide in 100 ml of MeOH was refluxed for 48 hr and concd *in vacuo*, and the product was removed by filtration. Recrystn from PhH gave 1.24 g, 45%, of **7**; a subsequent PhH recrystn yielded the analytical sample, mp 201.0–201.5°. *Anal.* ($C_{12}H_{12}Cl_2N_2O_7S$) C, H, N.

2-(*N,N*-Dimethylamino)-4,5-dichloro-*N*-methoxybenzenesulfonamide (3). Me_2SO_4 (0.5 ml) was added dropwise to a well-stirred soln of 1.25 mmoles of **7**, 25 ml of Me_2CO, 35 ml of H_2O, and 0.5 g of NaOH. After being stirred for 1 hr, the soln was freed of Me_2CO by gentle heating and the resultant aq medium extd with four 25-ml portions of PhH. The PhH phase was washed with H_2O, dried ($MgSO_4$), and evapd. The product was recrystd from MeOH with the aid of charcoal to give 0.13 g, 35%, of **3**. The analytical sample, mp 122.5–123.5°, was prepd by a second MeOH recrystn. *Anal.* ($C_9H_{12}Cl_2N_2O_3S$) C, H, N.

2-Hydroxy-3-(*p*-nitrophenyl)-6,7-dichloro-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (8). A soln of equimolar amt (3.33 mmoles) of *p*-nitrobenzaldehyde and 2-amino-4,5-dichloro-*N*-hydroxybenzenesulfonamide in 50 ml of MeOH was refluxed for 20 hr and evapd, and the solid residue was recrystd from 1:1 EtOH–H_2O to yield 1.18 g (89%) of pure **8**, mp 251–254°. *Anal.* ($C_{13}H_9Cl_2N_3O_5S$) C, H, N.

‡A synthesis of this compd has been published[12] but with insufficient experimental details to duplicate it. We gratefully acknowledge the assistance of Dr. Scott Childress, Wyeth Laboratories, for providing us with the two previously unpublished experimental methods for generating *o*-aminobenzenesulfonyl chlorides which we are utilizing herein.

2-Amino-4-methyl-5-chloro-*N*-hydroxybenzenesulfonamide (5). Potassium 2-amino-4-methyl-5-chlorobenzenesulfonate (82.0 mmoles) and 40 ml of $ClSO_3H$ were mixed, heated on a steam bath for 2 hr, cooled to room temp, and treated with 20 ml of $SOCl_2$. This soln was heated for 2 hr and poured over chopped ice. The crude sulfonyl chloride was filtered, dissolved in 200 ml of PhH, and dried ($MgSO_4$). Concn of PhH pptd 8.42 g, 43%, of the chloride, mp 95–97°. This chloride (5.0 g, 21 mmoles) was dissolved in 30 ml of dioxane and added dropwise to a chilled soln of 3.0 g of $NH_2OH \cdot HCl$, 5.0 g of Et_3N, and 15 ml of H_2O. After 12 hr, vacuum concn and diln with H_2O pptd the product. Recrystn from 50% aq EtOH gave 4.31 g, 87%, of mp 182–185°. *Anal.* ($C_7H_9ClN_2O_3S$) C, H, N.

2-Amino-4-methyl-6-nitrobenzenesulfonyl Chloride. By the above technique, potassium 2-amino-4-methyl-6-nitrobenzenesulfonate (70 mmoles), 40 ml of $ClSO_3H$, and 20 ml of $SOCl_2$ were allowed to react to yield 10.9 g (62%) of the chloride. Two recrystns from PhH produced analytical material, mp 119–121°. *Anal.* ($C_7H_7ClN_2O_4S$) C, H, N.

2-Amino-4-methyl-6-nitro-*N*-hydroxybenzenesulfonamide (6). A chilled soln of 0.04 mole of Et_3N, 0.025 mole of $H_2NOH \cdot HCl$, and 12 ml of H_2O was treated by dropwise addn, with stirring, of 0.02 mole of the sulfonyl chloride in 30 ml of dioxane. After 12 hr, the mixt was concd *in vacuo* and dild with H_2O, and the ppt was collected the washed with cold H_2O. The solid was recrystd (twice from EtOH) to give 3.71 g, 75%, of yellow powder, mp 134–136°. *Anal.* ($C_7H_9N_3O_5S$) C, H, N.

Acknowledgment. We acknowledge the technical assistance of Mrs. J. Trimble Gallagher for the microbiological screening results.

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5-Cyclohexyl-1-hydroxyacetylindans as Potential Antiinflammatory Agents

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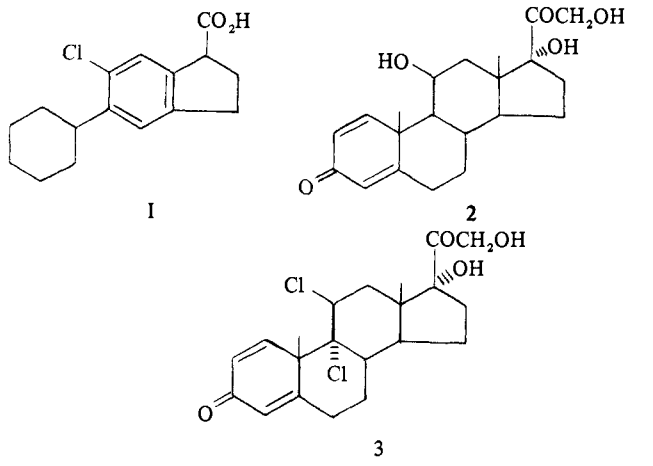
We recently reported[1] some indan-1-carboxylic acids with antiinflammatory activity. Subsequently, Noguchi, *et al.* confirmed[2] the activity of 6-chloro-5-cyclohexylindan-1-carboxylic acid (**1**) and suggested that a structural analogy between 1 and the antiinflammatory corticosteroids such as 2 and 3 might account for this activity.

We also had considered this analogy, and so prepared two racemic 1-hydroxyacetylindans (**9** and **11**) which bear an even closer resemblance to the steroid molecules.

Chemistry. Both **9** and **11** were prepared from the corresponding indan-1-carboxylic acids 4 and **10**. The route[3] outlined in Scheme I for **9** is representative.



Scheme I

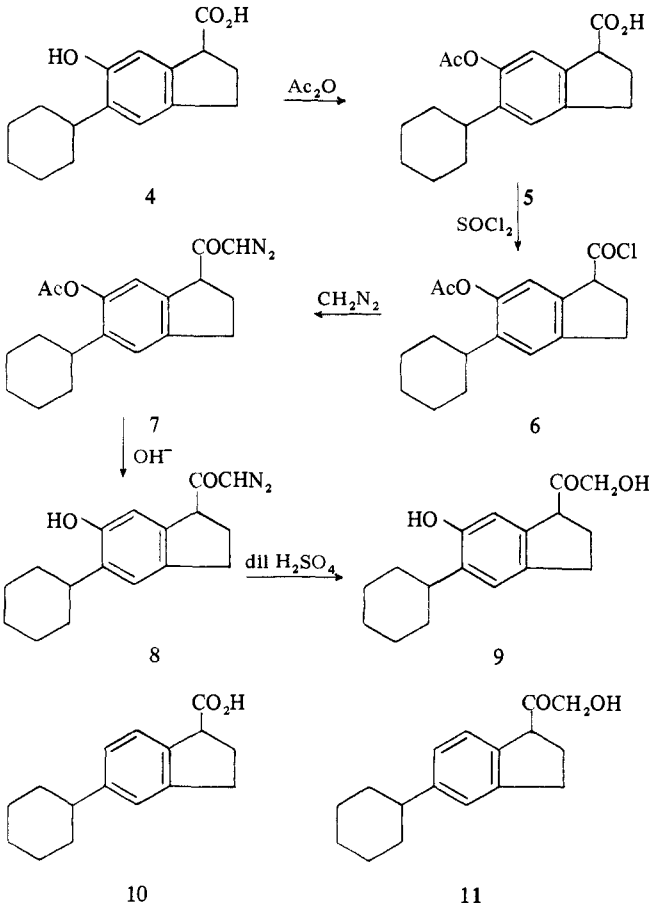


Table I.

Compound	Antiinflammatory activity, ED_{30}, mg/kg
4	6.2
10	3.7
9	128
11	16

Structure-Activity Relationships. Compds 4 and **9–11** were tested orally for antiinflammatory activity using the carrageenin-induced foot edema method in the fasted rat.[4] The results, expressed as the doses which inhibited 30% of the edema (ED_{30}), are recorded in Table I.

It is apparent that the 1-hydroxyacetyl compds **9** and **11** are considerably less active than the corresponding carboxy