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.

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5-Cyclohexyl-1-hydroxyacetylindans as Potential Antiinflammatory Agents

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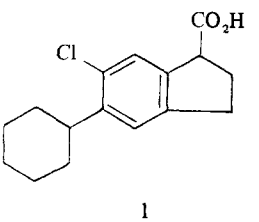
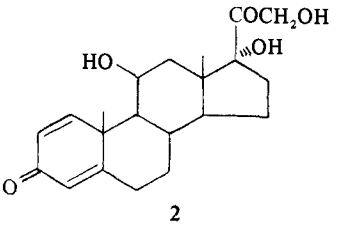
We recently reported[1] some indan-1-carboxylic acids with antiinflammatory activity. Subsequently, Noguchi, *et al.* confirmed[2] the activity of 6-chloro-5-cyclohexylindan-1-carboxylic acid (**1**) and suggested that a structural analogy between **1** and the antiinflammatory corticosteroids such as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

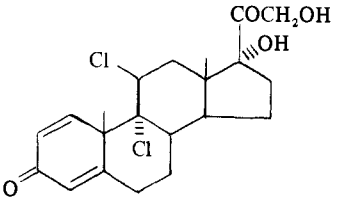
Chemistry. Both **9** and **11** were prepared from the corresponding indan-1-carboxylic acids **4** and **10**. The route[3] outlined in Scheme I for **9** is representative.



1



2



3

Scheme I

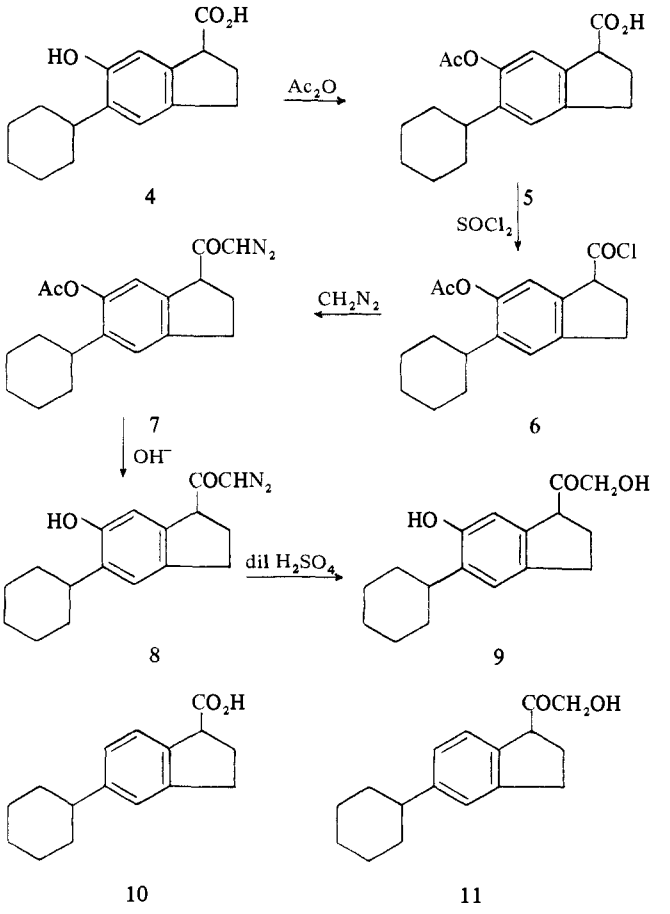


Table I.

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

compds **4** and **10**. These results do not support the idea that the antiinflammatory activity of the indan-1-carboxylic acids is due to a steroid-like mechanism.

Experimental Section†

(±)-6-Acetoxy-5-cyclohexylindan-1-carboxylic Acid (5). Ac_2O (3.8 ml, 0.0401 mole) was added to a cooled (ice-H_2O), stirred soln of (±)-5-cyclohexyl-6-hydroxyindan-1-carboxylic acid[1] (**4**, 7.79 g, 0.0299 mole) in 5 *N* NaOH (14.9 ml, 0.0745 mole) and H_2O (20 ml) contg ice (50 g). After 3 min the soln was acidified with concd HCl. The ppt was collected, washed (H_2O), and dried. The product was recrystd from cyclohexane to give **5** (6.6 g, 73%) as colorless crystals: mp 188–190°. *Anal.* ($C_{18}H_{22}O_4$) C, H.

(±)-5-Cyclohexyl-6-hydroxy-1-hydroxyacetylindan (9). A soln of **5** (5.54 g, 0.0183 mole), $SOCl_2$ (2.74 g, 0.023 mole), and DMF (5 drops) in CH_2Cl_2 (85 ml) was refluxed for 2 hr. The cooled soln was concd and then treated twice with C_6H_6 (55 ml), concg after each addn. A soln of the residue in Et_2O (20 ml) was added to a soln of CH_2N_2 (0.111 mole) in Et_2O (200 ml). The soln was kept in an ice bath for 1 hr and then concd to half vol. The soln was filtered and concd to yield 7 as a yellow oil: ir (film) 1639 (C=O) and 2110 cm^{-1} ($CH=N^+=N^-$).

A mixt of this crude diazo ketone 7 and KOH (2.33 g) in CH_3OH (55 ml) and H_2O (2.5 ml) was stirred at 25° for 1 hr. A gummy solid was pptd with AcOH. The solid was extd into Et_2O. The Et_2O soln was washed (H_2O), dried (Na_2SO_4), and concd to give **8** as a viscous gum (5.2 g). A soln of crude **8** in a mixt of dioxane (85 ml) and 2.5 *N* H_2SO_4 (33 ml) was heated at 50° for 10 min. The mixt was dild with H_2O and extd with Et_2O. The Et_2O soln was washed (H_2O, aq $NaHCO_3$, satd aq NaCl), dried (Na_2SO_4), and concd to yield a red gum (4.56 g). The gum was chromatogd over silicic acid (Mallinckrodt, CC-7, 100–200 mesh) with PhMe–Me_2CO (10:1) to give a solid which was recrystd from C_6H_6–Skellysolve B (charcoal) to yield 9 (1.5 g, 30% based on **5**) as brown crystals: mp 136–138°. Recrystn from MeOH–H_2O gave pale yellow crystals: mp 135.5–137°; ir (KBr) 1715 (ketone C=O) and 3395 cm^{-1} (OH, broad). *Anal.* ($C_{17}H_{22}O_3$) C, H.

(±)-5-Cyclohexyl-1-hydroxyacetylindan (11). A soln of (±)-5-cyclohexylindan-1-carboxylic acid[1] (**10**, 5.0 g, 0.0205 mole), $SOCl_2$ (1.6 ml, 0.0215 mole), and DMF (2 drops) in CH_2Cl_2 (50 ml) was refluxed for 1.25 hr. The cooled soln was concd and then treated twice with C_6H_6 (25 ml), concg after each addn. A soln of the residue in Et_2O (15 ml) was added to a cold soln of CH_2N_2 (0.0667 mole) in Et_2O (125 ml). The soln was kept in an ice bath for 4 hr and was then allowed to stand at 25° for 16 hr. The soln was filtered and concd to give the diazo ketone (5.3 g) as yellow crystals: mp 75–79° dec; ir (CH_2Cl_2) 1639 (C=O) and 2110 cm^{-1} ($CH=N^+=N^-$).

A soln of the diazo ketone in dioxane (100 ml) and 2 *N* H_2SO_4 (65 ml) was heated on a steam bath for 30 min and then refluxed for 2 min. The cooled soln was dild with H_2O and extd with Et_2O. The Et_2O soln was washed (H_2O, satd aq $NaHCO_3$, H_2O), dried (Na_2SO_4), and concd. The residue was recrystd from pentane (charcoal) to give 11 (2.7 g, 51% based on 10): mp 84–86°. Recrystn from petr ether (bp 37–47°) gave pale yellow crystals: mp 85.5–86.5°; ir (KBr) 1722 (ketone C=O), 3440, and 3460 cm^{-1} (O–H). *Anal.* ($C_{17}H_{22}O_2$) C, H.

†Where analyses are indicated only by symbols of the elements, results obtained for these elements were within ±0.4% of the theoretical values. Melting points are uncorrected.

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New Compounds

Synthesis of Some 6-Hydroxymethyluracil Derivatives

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As part of a program for the synthesis of pyrimidines for biological evaluation,[1] the preparation of certain derivatives of 6-hydroxymethyluracil (I) was undertaken. It was thought that these compounds could be transformed into benzylium type species (uracil-6-methylenium ions) which in turn might react with other molecules and bring about biochemically significant reactions.

Experimental Section

The purity of the compounds was determined by paper chromatog: solvent A, *n*-BuOH–AcOH–H_2O, 4:1:5, descending; solvent B, *n*-BuOH–H_2O, 86:14, ascending. All evapns were carried out *in vacuo* at 40°.

6-Hydroxymethyluracil[2] (I). A soln of *n*-butyl orotate[3] (2.0 g, 9.4 mmoles) in dry THF (50 ml) was added dropwise to a suspension of LAH (0.7 g) in 100 ml of THF over a period of 90 min. After the addn was complete, the mixt was stirred at room temp for 8 hr. The excess hydride was decompd by the slow addn of H_2O, and the whole was concd to dryness. The residual solid was extd with H_2O (3 × 50 ml) at 50°. The combined aq soln was concd under reduced pressure to 40 ml and acidified with dil HCl to pH 3–4. The product sepd on cooling and was crystd from H_2O: yield, 0.60 g (52%); mp 254° dec; R_f A, 0.45; B, 0.32; uv 0.1 *N* HCl, λ_{max} 262 nm (ϵ 10,880), 0.1 *N* NaOH, λ_{max} 284 nm (ϵ 10,280). *Anal.* ($C_5H_6N_2O_2$) C, H, N.

6-Acetoxymethyluracil (II). A mixt of I (710 mg, 5 mmoles) and Ac_2O (3 ml) in pyridine (15 ml) was stirred for 2 hr under anhyd condns. The mixt was treated with 50% EtOH and evapd. The residual white solid was crystd from H_2O to yield 725 mg (78%) of II: mp 240–242°; R_f A, 0.65; B, 0.49; uv 0.1 *N* HCl, λ_{max} 261 nm (ϵ 11,100), 0.1 *N* NaOH, λ_{max} 282 nm (ϵ 10,785). *Anal.* ($C_7H_8N_2O_4$) C, H, N.

6-Acetoxymethyl-4-thiouracil (III). A mixt of II (1.16 g, 6.3 mmoles) and P_2S_5[4] (0.70 g, 3.15 mmoles) was refluxed in dry pyridine (40 ml) with exclusion of moisture for 5 hr. The dark-brown soln was evapd to dryness. H_2O (20 ml) was added to the residue and the whole cooled at 4°. The brown solids were collected, washed thoroughly with cold H_2O and crystd twice from hot H_2O: yield, 487 mg (41%); mp 206–208°; R_f A, 0.82; B, 0.69; uv 0.1 *N* HCl, λ_{max} 330 nm (ϵ 18,500) 0.1 *N* NaOH, λ_{max} 327 nm (ϵ 12,700), 333 nm inflection (ϵ 10,700). *Anal.* ($C_7H_8N_2O_3S$) C, H, N.

6-Hydroxymethyl-4-thiouracil (IV). Compd III (600 mg, 3 mmoles) was dissolved in 2.1 ml of concd HCl and heated on a steam bath for 2 hr. The soln was cooled in an ice bath, and the sepd brown solid was collected, washed with cold H_2O, and crystd from H_2O: yield, 366 mg (61%); mp 226–227°; R_f A, 0.61; B, 0.55; uv 0.1 *N* HCl, λ_{max} 327 nm (ϵ 17,930), 0.1 *N* NaOH, λ_{max} 317 nm

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