# Experimental Antiulcer Drugs. 1. Indole-1-alkanamides and Pyrrole-1-alkanamides

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The synthesis and gastric antisecretory activity of a series of indole-1-alkanamides and pyrrole-1-alkanamides are presented. A marked elevation of the pH of the gastric secretions of the rat was observed after oral administration of 100 mg/kg of 2,3-dimethylindole-1-acetamide (**2**), -1-propionamide (**8**), and -1-butyramide (**13**). Replacement of either methyl group by a hydrogen atom or an ethyl radical resulted in greatly diminished activity. In the acetamide and propionamide series the 3-hydroxymethyl-2-methyl (**14** and **15**) derivatives exhibited activity but only when administered by the subcutaneous route. 2,3-Dimethylindole (**18**) was active and 2,3,4,5-tetramethylpyrrole-1-acetamide was moderately active. A number of the active compounds were tested in the mouse mydriasis test for anticholinergic activity and found to be inactive. They were also found to be inactive in blocking histamine-induced acid secretion in the dog.

During the investigation of the gastric irritation potential of a group of arylalkanoic acids and their derivatives in the rat one of us (J.B.) discovered that oral administration of 2,3-dimethylindole-1-acetamide (**2**, Table II) resulted in the elevation of the pH of gastric fluids. Evaluation of the compound in the Shay rat[1] revealed that the drug inhibited gastric acid secretion in a dose-related manner (Table I). The data also indicated that the drug was long acting and that it must be absorbed in order to be effective, i.e., the observed effect is not the result of a topical action on the gastric mucosa. The fact that the drug did not appear to exhibit anticholinergic properties and the fact that its structure is unrelated to known experimental nonanticholinergic antiulcer drugs[2,3] provided incentive for further investigation of its pharmacology and the evaluation of related compounds.

The drug did not inhibit histamine-stimulated gastric acid secretion in the dog. We, therefore, have little basis for projecting that it would inhibit gastric acid secretion in man. At the very least, a candidate antiulcer drug should have a demonstrable effect in both the rat and the dog.[3] It should also inhibit gastric acid secretion and ulcer formation induced by a number of secretagogues and ulcer-inducing agents. Furthermore, the indole **2** was emetic in the dog, an obvious disadvantage when projected for use in the human ulcer condition.

We report here the synthesis and evaluation of a number of close relatives of **2** in a search for compounds which display activity in the rat and the dog and which exhibit little or no potential for inducing emesis in the dog.

**Chemistry.** The indoles **2**, **4**, **6**, and **7** (Table II) were prepared by alkylation of the sodium salt of the parent indole with ethyl bromoacetate, saponification of the resulting ester to the carboxylic acid, and conversion to the amide by a mixed anhydride procedure (method A). The derivatives **8**–**12** resulted from cyanoethylation of the required indole followed by acid hydrolysis to the amide (method B). Compounds **3** and **5** as well as the aldehyde precursor to **14** were synthesized by alkylation of the corresponding sodioindole with chloroacetamide. The 1-carbamylindole **1** arose from the reaction of 2,3-dimethylindole and chlorosulfonyl isocyanate followed by hydrolysis of the intermediate chlorosulfonyl derivative.

The butyramide **13** was synthesized by alkylation of the sodium salt of 2-methylindole-3-carboxaldehyde with 4-bromobutyronitrile, hydrolysis to the amide, Wolff–Kishner reduction to 2,3-dimethylindole-1-butyric acid, followed by conversion to the amide. Condensation of 3-aminopropionitrile with 2,5-hexanedione yielded the nitrile precursors to the pyrroles **25** and **27**. Condensation of glycinamide with 3,4-dimethyl-2,5-hexanedione afforded directly the pyrroles **24** and **26**. The hydroxymethyl derivatives **15**–**18** were prepared by sodium borohydride reduction or catalytic hydrogenation of the corresponding aldehydes.

Table I. Effect of 2,3-Dimethylindole-1-acetamide on Gastric Acid Secretion in the Shay Rat

| Dose, mg/kg po[a] | pH ± SE | % inhibition Vol | % inhibition Total acid output |
|---|---|---|---|
| 0 | 1.1 ± 0.03 | 0 | 0 |
| 25 | 2.6 ± 0.71 | 26 | 47 |
| 50 | 3.0 ± 0.22 | 39 | 69 |
| 100 | 6.0 ± 0.76 | 27 | 85 |
| 200 | 6.7 ± 0.32 | 56 | 88 |
| 100[b] | 3.2 ± 0.53 | 44 | 69 |
| 100[c] | 1.5 ± 0.09 | 32 | 52 |
| Atropine, 6.25 | 1.5 ± 0.13 | 43 | 58 |
| Cimetidine,[d] 100 | 2.1 ± 0.55 | 14 | 37 |

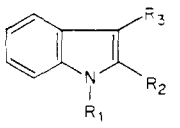
[a] Drugs were administered 1 h prior to pyloric ligation unless otherwise noted. Four to nine rats were used at each dose level. [b] Drug administered 24 h prior to pyloric ligation. [c] Drug administered at the time of pyloric ligation. [d] Reference 6.

## Discussion

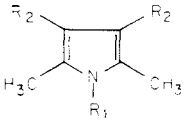
Substitution of either one or both methyl groups of 2,3-dimethylindole-1-acetamide (**2**) by a hydrogen atom resulted in the complete loss of antisecretory activity at screening doses (**3**, **4**, and **5**, Table II). The change of either methyl group to an ethyl radical resulted in greatly diminished antisecretory activity (**6** and **7**). Both the propionamide **8** and butyramide **13** were as active as the acetamide **2**. Replacement of either methyl group of the propionamide **8** by a hydrogen atom led to inactive compounds (**9** and **10**). Exchange of either methyl group of the propionamide **8** for ethyl radicals resulted in derivatives (**11** and **12**) with greatly diminished activity.

The apparent requirement for methyl groups at C-2 and C-3 suggested the synthesis of the tetramethylpyrroles, **23** and **24**. These compounds were not potent antisecretory drugs but this maneuver served to illustrate the extent to which the indole nucleus may be modified with retention of key structural features and still retain significant antisecretory activity. Replacement of the methyl groups at

Table II. Gastric Antisecretory Activity in the Rat. Screening Results



1-22



23-26

| Compd | $R_1$ | $R_2$ | $R_3$ | pH[a] | Formula[b] |
|---|---|---|---|---|---|
| 1 | $CONH_2$ | $CH_3$ | $CH_3$ | 1.2 | $C_{11}H_{12}N_2O$ |
| 2 | $CH_2CONH_2$ | $CH_3$ | $CH_3$ | 6.0 | $C_{12}H_{14}N_2O$ |
| 3 | $CH_2CONH_2$ | H | $CH_3$ | 2.3 | $C_{11}H_{12}N_2O$ |
| 4 | $CH_2CONH_2$ | $CH_3$ | H | 1.2 | $C_{11}H_{12}N_2O$ |
| 5 | $CH_2CONH_2$ | H | H | 1.2 | $C_{10}H_{10}N_2O$ |
| 6 | $CH_2CONH_2$ | $C_2H_5$ | $CH_3$ | 2.8 | $C_{13}H_{16}N_2O$ |
| 7 | $CH_2CONH_2$ | $CH_3$ | $C_2H_5$ | 2.8 | $C_{13}H_{16}N_2O$ |
| 8 | $(CH_2)_2CONH_2$ | $CH_3$ | $CH_3$ | 5.3 | $C_{13}H_{16}N_2O$ |
| 9 | $(CH_2)_2CONH_2$ | H | $CH_3$ | 1.1 | $C_{12}H_{14}N_2O$ |
| 10 | $(CH_2)_2CONH_2$ | $CH_3$ | H | 1.4 | $C_{12}H_{14}N_2O$ |
| 11 | $(CH_2)_2CONH_2$ | $C_2H_5$ | $CH_3$ | 4.1 | $C_{14}H_{18}N_2O$ |
| 12 | $(CH_2)_2CONH_2$ | $CH_3$ | $C_2H_5$ | 3.4 | $C_{14}H_{18}N_2O$ |
| 13 | $(CH_2)_3CONH_2$ | $CH_3$ | $CH_3$ | 6.2 | $C_{14}H_{18}N_2O$ |
| 14 | $CH_2CONH_2$ | $CH_3$ | $CH_2OH$ | 1.5 (sc 6.9) | $C_{12}H_{14}N_2O_2$[c] |
| 15 | $(CH_2)_2CONH_2$ | $CH_3$ | $CH_2OH$ | 1.9 (sc 6.7) | $C_{13}H_{16}N_2O_2$ |
| 16 | $(CH_2)_3CONH_2$ | $CH_3$ | $CH_2OH$ | 1.3 (sc 1.2) | $C_{14}H_{18}N_2O_2$ |
| 17 | $(CH_2)_2CONH_2$ | $CH_2OH$ | $CH_3$ | 1.3 (ip 1.7) | $C_{13}H_{16}N_2O_2$[d] |
| 18 | H | $CH_3$ | $CH_3$ | 4.2 | *e* |
| 19 | $CH_3$ | $CH_3$ | H | 1.3 | *e* |
| 20 | H | $CH_3$ | H | 1.2 | *e* |
| 21 | H | H | $CH_3$ | 2.5 | *e* |
| 22 | H | H | H | 1.9 | *e* |
| 23 | $CH_2CONH_2$ | $CH_3$ | | 3.6 | $C_{10}H_{16}N_2O$ |
| 24 | $(CH_2)_2CONH_2$ | $CH_3$ | | 2.4 | $C_{11}H_{18}N_2O$ |
| 25 | $CH_2CONH_2$ | H | | 1.7 | $C_8H_{12}N_2O$ |
| 26 | $(CH_2)_2CONH_2$ | H | | 1.1 | $C_9H_{14}N_2O$ |

[a] pH of gastric contents after administration of the drug at 100 mg/kg po 1 h prior to 5-h pyloric ligation period. [b] Elemental analyses for C, H, and N were within 0.4% of the calculated values unless otherwise noted. [c] Calcd: C, 68.44; H, 7.58; N, 11.55. Found: C, 66.03; H, 6.47; N, 12.89. [d] Calcd: C, 67.22; N, 12.06. Found: C, 66.64; N, 11.59. [e] Commercially available samples were tested.

C-3 and C-4 by hydrogen atoms led to complete loss of activity or greatly diminished activity (**25** and **26**).

The results of testing numerous compounds, not reported here, in which the substituents at C-2 and C-3 of the indole nucleus were modified, emphasized the need for methyl groups at these positions in order to achieve high activity. This observation suggested that the activity of these compounds may be mediated wholly or in part by metabolites since a methyl group attached to an aromatic nucleus is a candidate for metabolic transformation. The corresponding hydroxymethyl derivatives appeared to be likely possibilities and four of them, compounds **14–17**, are reported here. The derivatives **14** and **15** proved to be very active when administered by the subcutaneous route but they exhibited no activity when administered by the oral route. 3-Hydroxymethylindoles are known[4] to be acid sensitive. The failure of **14** and **15** to exhibit oral activity may be the result of transformation in the acidic environment of the rat stomach to inactive compounds. The inactivity of the hydroxymethyl compounds **16** and **17** is not explained by this hypothesis.

An intriguing observation is the fact that the acetamide **2**, the propionamide **8**, and the butyramide **13** were all highly active. A possible explanation is that the activity of all three compounds is mediated by 2,3-dimethylindole (**18**), a theoretical metabolite of all three amides.[5] Indeed, **18** did display moderate activity in the rat, a fact which would tend to support the hypothesis. The compound could not be detected in urine of rats which had been medicated with **2** but may, itself, have been extensively metabolized. It is of interest that again both methyl groups were required for good activity (**20–22**). The isomeric 1,2-dimethylindole **19** was inactive.

Compounds **2**, **18**, and **23** did not induce mydriasis when administered to mice and are therefore assumed to lack anticholinergic activity. They were also evaluated in vitro for their effect on the histamine response of guinea pig atria and were found to be inactive. In this respect, therefore, they contrast with the $H_2$-receptor antagonists.[6]

A number of the amides were evaluated in the dog for inhibition of histamine-induced gastric acid secretion. None of them were active and all of them were emetic. 2,3-Dimethylindole did display some oral activity in the dog but it was also emetic. Thus, our objective of finding a structural modification of **2** which is not emetic in the dog and which has antisecretory activity in this species was not achieved by the structural variations reported in Table I.

Nevertheless, by more extensive modification of the structure of this class of compounds, it has been possible to produce derivatives which exhibit gastric antisecretory inhibitory activity in both rats and dogs. These results will be reported in the next paper in this series along with the results of more extensive pharmacological studies.

## Experimental Section

NMR spectra, supplemented by MS and IR spectra, were used to aid in the characterization of all the new compounds. Where

analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

**1-Carbamoyl-2,3-dimethylindole (1).** A solution of 29 g (0.2 mol) of 2,3-dimethylindole in 300 mL of $CH_2Cl_2$ was treated with 14.1 g of chlorosulfonyl isocyanate (0.2 mol) in portions with external cooling. The reaction mixture was diluted with 400 mL of pentane and the crude chlorosulfonyl derivative collected. It was dissolved in 200 mL of acetone. Water (20 mL) was added, slowly at first (exothermic reaction). After a few minutes, the mixture was diluted with 100 mL of $CH_3OH$; the product was collected and recrystallized from $CH_3OH$. The yield from two runs was 18 g (23%), mp 185.5–187 °C.

**Method A. Amides 2, 4, 6, and 7. 2,3-Dimethylindole-1-acetamide (2).** A solution of the sodium salt of 2,3-dimethylindole was prepared from 42 g (0.29 mol) of 2,3-dimethylindole and 11.5 g (0.29 mol) of a 60.1% NaH dispersion in 700 mL of DMF at room temperature. Ethyl bromoacetate (32 mL, 0.30 mol) was added dropwise to the stirred 0 °C solution over 15 min. The mixture was stirred at room temperature for 2 h and poured into 2.5 L of ice $H_2O$, and the crystalline ester was collected. Saponification of the ester was accomplished by boiling for a few minutes with aqueous methanolic KOH. The crude **2,3-dimethylindole-1-acetic acid** weighed 35 g. Recrystallization of 13 g from $C_6H_6$ gave 9 g, mp 186–188 °C (sealed, evacuated capillary). Anal. ($C_{12}H_{12}NO_2$) C, H, N. This carboxylic acid (22 g, 0.108 mol) in 500 mL of $CH_2Cl_2$ and 15 mL of $Et_3N$ (0.108 mol) at 0 °C was converted to the mixed anhydride by addition of 11.7 g (0.108 mol) of ethyl chloroformate. After 30 min, 300 mL of $CH_2Cl_2$ saturated with dry $NH_3$ was added and the mixture stirred at room temperature for 1 h. The reaction mixture was washed with $NaHCO_3$ solution and saturated NaCl solution, dried ($Na_2SO_4$), and concentrated to 25 mL, and the product was crystallized by addition of hexane: 6.8 g (31%); mp 197–199 °C (EtOAc).

Amide **4**, 68% (from the carboxylic acid), mp 135–136 °C (*i*-PrOH); **6**, 37%, mp 161–162 °C ($C_6H_6$); **7**, 22%, mp 169 °C ($C_6H_6$).

**3-Methylindole-1-acetamide (3).** A suspension of 26.4 g (0.615 mol) of a 56% NaH dispersion and 78 g (0.6 mol) of 3-methylindole was stirred in 300 mL of DMF with external cooling. When the reaction was complete, a solution of 60 g (0.64 mol) of chloroacetamide in 150 mL of DMF was added during 10 min. The temperature was held at 40 °C by external cooling and then kept at 70 °C for 2 h. Upon dilution with $H_2O$ and recrystallization of the precipitate from *i*-PrOH, there was obtained 20 g (16%), mp 174–175 °C (lit.[7] 169–170 °C).

**Indole-1-acetamide (5)** was prepared from indole in the same manner as **3**: 13% yield; mp 179.5–180.5 °C (EtOH).

**Method B. Amides 8–12. 2,3-Dimethylindole-1-propionamide (8).** A solution of 29.4 g (0.2 mol) of 2,3-dimethylindole in 200 mL of dioxane containing 14 mL (0.213 mol) of acrylonitrile and 11 mL of 35% Triton B was left at room temperature for 20 h and poured into $H_2O$, and the mixture was acidified with dilute HCl. The precipitate was recrystallized from *i*-PrOH to give 28 g, mp 84–85 °C (lit.[8] 80 °C), of **2,3-dimethylindole-1-propionitrile**. The nitrile (11 g) was kept in 17 mL of 91% $H_2SO_4$ on the steam bath for 10 min. The mixture was poured into water and the product extracted with $CHCl_3$. The extracts were washed with dilute $NH_4OH$ and $H_2O$, dried ($MgSO_4$), and concentrated to give 11.5 g of a gum. Two crystallizations from $C_6H_6$ yielded 9.5 g (81%), mp 106–107 °C.

Amide **9**, 40% (from the nitrile), mp 97–101 °C ($Et_2O$); **10**, 46%, mp 118–119 °C ($C_6H_6$); **11**, 43%, mp 110–111 °C ($C_6H_6$); **12**, 57%, mp 90–91 °C ($C_6H_6$–$C_6H_{12}$).

**2,3-Dimethylindole-1-butyramide (13).** 2-Methylindole-3-carboxaldehyde[9] (113 g, 0.71 mol) and 37.5 g (0.89 mol) of a 57% NaH dispersion were stirred in 1 L of DMF until $H_2$ evolution was complete. This mixture was stirred and kept at −10 °C during the addition of 158 g of 4-bromobutyronitrile in 100 mL of DMF. After completion of the addition the mixture was stirred at 0 °C for 1 h and then left at room temperature overnight. The mixture was poured into ice $H_2O$ and extracted with EtOAc, the extracts were washed with $H_2O$ and saturated NaCl solution, dried ($Na_2SO_4$), and concentrated, and the residue was recrystallized from $C_6H_6$ to give 120 g (74%) of 3-formyl-2-methylindole-1-butyronitrile, mp 104–106.5 °C.

The nitrile was converted to **3-formyl-2-methylindole-1-butyramide** in 91% $H_2SO_4$ as described in method B: 59% yield; mp 178.5–180.5 °C (EtOH). Anal. ($C_{14}H_{16}N_2O$) C, H, N.

By means of the Huang–Minlon modification of the Wolff–Kishner reduction procedure, the above aldehyde amide yielded **2,3-dimethylindole-1-butyric acid** in essentially quantitative yield: mp 102–104 °C ($CCl_4$). The acid was converted to the amide by the mixed anhydride procedure (method A): 70% yield; mp 132–134 °C (EtOAc).

**3-Hydroxymethyl-2-methylindole-1-acetamide (14). 3-Formyl-2-methylindole-1-acetamide** was prepared in the same manner as **3** in 56% yield: mp 256–257 °C. Anal. ($C_{12}H_{12}N_2O_2$) C, H, N. To this aldehyde (21.6 g, 0.1 mol) in 1500 mL of boiling absolute EtOH was added 14.4 g (0.3 mol) of $NaBH_4$ in portions during a few minutes. On completion of the addition the mixture was filtered, concentrated in vacuo to about 200 mL, and added to 400 mL of 3% aqueous NaOH. The suspension was stored at 0 °C for 16 h, and the product was collected, dried, and recrystallized from $CH_3OH$ to give the unstable **14**: 8.6 g (39%); mp 181–182 °C dec.

**3-Hydroxymethyl-2-methylindole-1-propionamide (15). 3-Formyl-2-methylindole-1-propionamide** was prepared by method A, mp 201–202 °C (MeOH). Anal. ($C_{13}H_{14}N_2O$) C, H, N. This compound (46 g, 0.2 mol) and 26 g (0.6 mol) of $NaBH_4$ in 3 L of absolute EtOH was refluxed for 30 min, filtered, and concentrated in vacuo to 600 mL. The product crystallized slowly upon addition of 1 L of 3% NaOH: yield 22 g (47%); mp 155 °C (EtOH).

**3-Hydroxymethyl-2-methylindole-1-butyramide (16)** was prepared by $NaBH_4$ reduction of the corresponding aldehyde (for preparation see **13**) in the same manner as **15**: 37% yield; mp 110–112.5 °C (EtOAc).

**2-Hydroxymethyl-3-methylindole-1-propionamide (17). 3-Methylindole-1-propionitrile**[10] (method B), 60 g (0.307 mol), and $POCl_3$ (33 g, 0.359 mol) in 96 mL of DMF were heated at 80 °C until TLC indicated the reaction was complete (~20 min). The cooled reaction mixture was poured into 600 mL of ice $H_2O$. Addition of 62 g of NaOH in 360 mL of $H_2O$ followed by recrystallization of the product from $CH_3OH$ afforded 50 g (72%) of 2-formyl-3-methylindole-1-propionitrile, mp 104–105 °C, which was converted (method B) to **2-formyl-3-methylindole-1-propionamide**: 34% yield; mp 97–101 °C. Anal. ($C_{12}H_{14}N_2O$) C, H, N. After shaking 16 g of this aldehyde in 1.8 L of absolute EtOH with 2 g of 10% Pd/C at 50 °C for 18 h, there was isolated 1.4 g (9%) of **17**, mp 180–181 °C dec. When the reduction was carried out with $NaBH_4$ in hot EtOH, 3-methylindole-1-propionamide (**9**) was isolated in good yield.

**2,3,4,5-Tetramethylpyrrole-1-acetamide (23).** A solution of 8.8 g (0.0618 mol) of 3,4-dimethyl-2,5-hexanedione,[11] 6.8 g (0.062 mol) of glycinamide hydrochloride, and 5.1 g (0.062 mol) of NaOAc in 60 mL of HOAc was boiled for 30 min. The reaction mixture was poured into $H_2O$ and the crude product collected and washed thoroughly with $H_2O$. This material was dissolved in EtOAc and the dried ($Na_2SO_4$) solution concentrated to give white crystals which darkened on exposure to air. Two recrystallizations from EtOAc yielded 2 g (18%) of product, mp 204–205 °C (sealed, evacuated capillary).

**2,3,4,5-Tetramethylpyrrole-1-propionamide (24).** A solution of 34 g (0.239 mol) of 3,4-dimethyl-2,5-hexanedione, 30.6 g (0.239 mol) of 3-aminopropionitrile fumarate, and 19.6 g (0.239 mol) of NaOAc in 150 mL of AcOH was refluxed for 1 h and poured into $H_2O$ and the crude nitrile (29 g, 69%) collected. This sample was converted (method B) to 15 g of crude amide which failed to crystallize. Chromatography on Florisil with 30% EtOAc–$C_6H_6$ yielded 8 g of solid product which upon recrystallization from hot degassed EtOAc gave 5 g (16%), mp 153–154.5 °C (sealed, evacuated capillary).

**2,5-Dimethylpyrrole-1-acetamide (25)** was prepared in the same manner as **23** from 2,4-hexanedione: 36% yield; mp 172–174 °C (EtOAc).

**2,5-Dimethylpyrrole-1-propionamide (26)** was prepared in the same manner as **24** from 2,4-hexanedione: 51% yield; mp 123–125 °C ($C_6H_6$).

**Biological Methods.** A modification of the method of Shay et al.[1] was used to evaluate the effect of drugs on gastric secretion

in pyloric ligated rats. Male, albino rats weighing approximately 140–150 g were housed in individual cages and fasted for 48 h but allowed water ad libitum. The test compounds were administered either po stomach tube or sc as a suspension in 1% gum tragacanth in a volume of 1.0 ml/100 g of body weight. Drugs were administered as a single dose either 24 or 1 h prior to pyloric ligation or immediately following ligation. Five hours after pyloric ligation, the rats were sacrificed. Acidity of the stomach contents was determined by titration with 0.1 N NaOH to a phenolphthalein end point (pH 7.8). Gastric pH was determined on a Beckman zeromatic pH meter.

Anticholinergic activity was assessed by means of the mouse mydriasis test. Test compounds were administered po in 1% gum tragacanth. Pupillary diameter was measured 1, 3, 5, and 24 h after medication with a microscope. Atropine at a dose 10 mg/kg sc was used as a positive control. Compounds **2**, **18**, and **23** were tested at 100 mg/kg and were found to be inactive.[12]

The effect of test compounds on the rate of beating of guinea pig right atria which had been stimulated with histamine was measured in vitro in an oxygenated Krebs–Henseleit solution at 35 °C. Compounds **2**, 18, and **23** were dissolved in $Me_2SO$–$H_2O$ and evaluated at concentrations of $10^{-5}$ and $5 \times 10^{-5}$ M. The tissue was exposed to the drugs for 5 min. They were found to be without effect on the histamine dose–response curve. Metiamide[13] was used as a positive control. At concentrations of $10^{-5}$ and $5 \times 10^{-5}$ M this drug caused an 11-fold and 38-fold shift in the histamine dose–response curve.[14]

Evaluation of the gastric antisecretory inhibitory activity in the dog was carried out in the following manner. Nonanesthetized beagle dogs weighing 9–13 kg with intact stomachs containing chronic gastric fistulas (Thomas cannula) and trained to Pavlov stands were used. The dogs were medicated via the cannula at a dose of 50 mg/kg in 1% gt. Two hours later, they were placed in the Pavlov stands and their stomach contents removed under slight vacuum for 10–15 min. The dogs then received 0.04 mg of base/kg of histamine dihydrochloride im in a volume of 0.05 mL of $H_2O$/kg. Aspiration of the stomach contents continued under slight vacuum and total secretions were collected at 15-min intervals. Analyses of secretions were carried out as described in the Shay rat preparation.

## References and Notes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# 11,12-Secoprostaglandins. 3. 8-Alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic Acids and Related Compounds


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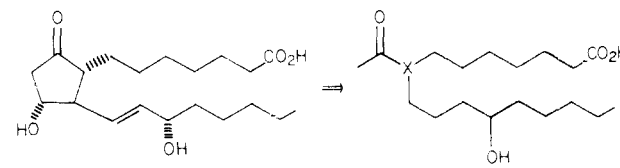
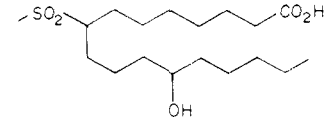
*Received August 30, 1976*


A series of 8-alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic acids which embody structural features of 11,12-secoprostaglandins was synthesized and evaluated for their ability to mimic the E series prostaglandins in stimulating cAMP formation in the mouse ovary and in binding to the rat lipocyte prostaglandin receptor. A key member of the series, 8-methylsulfonyl-12-hydroxyheptadecanoic acid, markedly stimulates cAMP formation at reasonable pharmacological concentrations, shows significant affinity for a prostaglandin receptor, and effectively inhibits antigen-induced lymphocyte transformation. In contrast, this compound is not a substrate for 15-hydroxyprostaglandin dehydrogenase, the major prostaglandin-metabolizing enzyme.


Recent publications from these laboratories have described our approach to the design of structurally unique compounds displaying desirable prostaglandin-like activity, satisfactory metabolic stability, oral efficacy, and selective tissue specificity involving 11,12-secoprostaglandins typified by Ia and Ib.[1,2] The interesting in vitro and in vivo prostaglandin-like activity of certain compounds (e.g., Ia and Ib) prompted the synthesis and biological examination of a series of 8-alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic acids (e.g., **3b**) which constitute the subject of this manuscript. Furthermore, application of the concept of carbonyl surrogation via isosteric substitution of carbon by sulfur appeared to be especially attractive to investigate at this point in our studies.[3]




3b

**Chemistry.** The sulfur-containing hydroxyalkanoic acids that were prepared are tabulated in Table I. Compounds **2a,b** and **3a–c** are diastereomeric mixtures and were synthesized as shown in Scheme I. Ethyl 8-carboxy-12-acetoxyheptadecanoate[1] was converted to the bromo derivative **1** with bromine-red mercuric oxide. The latter reacted smoothly with the appropriate mercaptide to give, after saponification, thioethers **2a,b**. Oxidation of **2a** with sodium metaperiodate provided sulfoxide **3a** whereas treatment of **2a** with 30% hydrogen peroxide in the presence of ammonium molybdate afforded sulfone **3b**. Likewise, oxidation of **2b** with the latter reagent gave sulfone **3c**.