(Acylaryloxy)acetic Acid Diuretics. 4. Indeno[5,4-*b*]furan-2-carboxylic Acids[1]

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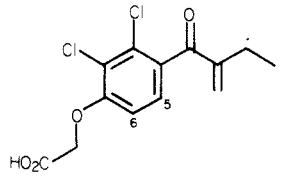
Investigation of the chemistry of the potent new uricosuric diuretic indacrinone (MK-196) led to a class of novel annulated derivatives, indeno[5,4-*b*]furan-2-carboxylic acids. The structural requirements for optimal diuretic and uricosuric activity of the tricyclic analogues differed from those of their (indanyloxy)acetic acids counterparts. Most notably, the tricyclic analogues were two to four times more natriuretic than the corresponding (indanyloxy)acetic acids when administered orally to rats, and in chimpanzees, uricosuria was observed only in those indenofurans having a nuclear aryl substituent.

The structure–activity relationships developed for the (aryloxy)acetic acid class of diuretics, such as ethacrynic acid (1), suggest that optimal diuretic activity requires the



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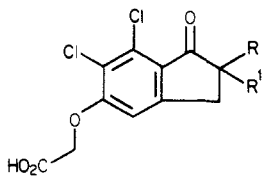
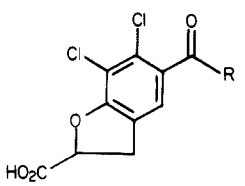


2a (MK-196), R = CH_3; R^1 = C_6H_5
b (MK-473), R = CH_3; R^1 = c-C_5H_9
c, R + R^1 = -$(CH_2)_4$-



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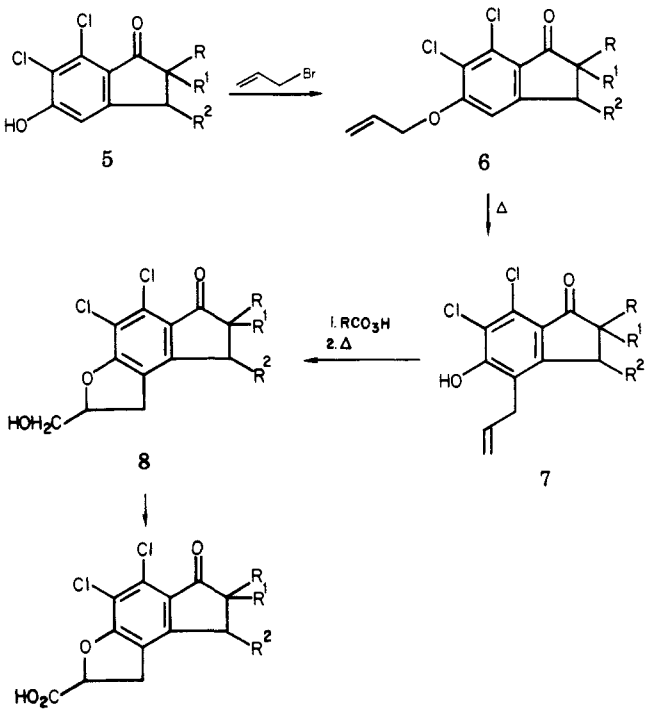
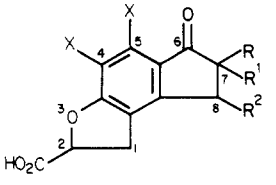
absence of substituents in positions 5 and/or 6 of the aromatic ring. Recently, this suggestion was shown to be incorrect with the discovery of the potent diuretic and uricosuric properties of [(6,7-dichloro-2-methyl-1-oxo-2-phenyl-5-indanyl)oxy]acetic acid (**2a**, MK-196) and its congeners.[2,3] These results indicate that annulation of the α,β-unsaturated ketone side chain to position 5 is not only accompanied by retention of diuretic activity but also results in the introduction of uricosuric properties. Furthermore, annulation of the oxyacetic acid moiety to the 6 position to afford benzofurans (e.g., **3** where R = 2-thienyl) also provided biologically active compounds.[4-7]

The preceding observations encouraged us to synthesize and evaluate a series of indeno[5,4-*b*]furan-2-carboxylic acids (**4**),[8,9] structures formally derived by annulation at

Scheme I



both positions 5 and 6. Herein we describe the syntheses and SARs developed for novel tricyclic structures **4**, some of which, when administered orally, are the most potent diuretics ever evaluated in these laboratories.



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Chemistry. Two synthetic routes to tricyclic compounds **4** were employed. Compounds **4** bearing chloro substituents were prepared by the synthetic route depicted in Scheme I. This route utilized the hydroxyindanone precursors **5** available from our earlier research on the (indanyloxy)acetic acids.[2,3] Alkylation of the phenolic group in **5** with allyl bromide, followed by thermally induced Claisen rearrangement of the allyl ethers **6**, gave intermediates **7**. Peracid oxidation of **7** provided the carbinols **8** through an epoxide intermediate.[6] Oxidation of the carbinol moiety in structures **8** afforded the target tetrahydroindeno[5,4-*b*]furancarboxylic acids **4**.

(1) This paper has been presented in part. See "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, April, 1979; American Chemical Society: Washington, DC, 1979; Abstr MEDI 66.
(2) Woltersdorf, O. W., Jr.; deSolms, S. J.; Schultz, E. M.; Cragoe, E. J., Jr. *J. Med. Chem.* **1977**, *20*, 1400.
(3) deSolms, S. J.; Woltersdorf, O. W., Jr.; Cargoe, E. J., Jr.; Watson, L. S.; Fanelli, G. M., Jr. *J. Med. Chem.* **1978**, *21*, 437.
(4) Zergenyi, J.; Habicht, E. U.S. Patent 3 676 560, 1972.
(5) Habicht, E.; Livis, J. U.S. Patent 3 761 494, 1973.
(6) Kraetz, J.; Criscione, L.; Hedwall, P. *Arch. Pharmacol.* **1978**, 302, Suppl. R42.
(7) Hoffman, W. F.; Woltersdorf, O. W., Jr.; Novello, F. C.; Cragoe, E. J., Jr.; Springer, J. P.; Watson, L. S.; Fanelli, G. M., Jr. *J. Med. Chem.*, preceding paper in this issue.
(8) Cragoe, E. J., Jr.; Woltersdorf, O. W., Jr. U.S. Patent 3 931 239, 1976.
(9) Cragoe, E. J., Jr.; Woltersdorf, O. W., Jr. U.S. Patent 3 984 552, 1976.

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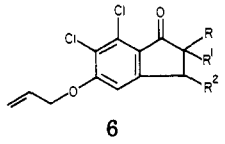
Table I



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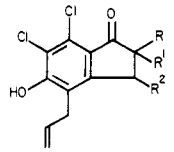

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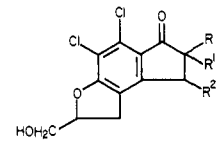

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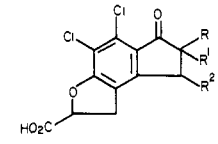

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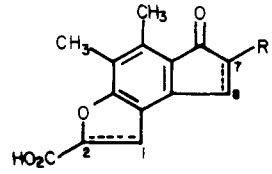
no.	R	R^1	R^2	% yield	recrystn solvent	mp, °C	emp formula	anal.
6a	C_6H_5	CH_3	H	74	C_6H_{12}	105	$C_{19}H_{16}Cl_2O_2$	CH
6b	c-C_5H_9	CH_3	H	77	hexane	92	$C_{18}H_{20}Cl_2O_2$	CH
6c	-$(CH_2)_4$-		H	97	C_6H_{12}	110-112	$C_{16}H_{16}Cl_2O_2$	CH
6d	C_2H_5	H	C_6H_5	67	EtOH	115	$C_{20}H_{18}Cl_2O_2$	CH
7a	C_6H_5	CH_3	H	66	BuCl	125	$C_{19}H_{16}Cl_2O_2$	CH
7b	c-C_5H_9	CH_3	H	62	hexane	95	$C_{18}H_{20}Cl_2O_2$	CH
7c	-$(CH_2)_4$-		H	57	BuCl-hexane	103	$C_{16}H_{16}Cl_2O_2$	CH
7d	C_2H_5	H	C_6H_5	37	BuCl-hexane	129	$C_{20}H_{18}Cl_2O_2$	CH
8a	C_6H_5	CH_3	H	NP[a]				
8b	c-C_5H_9	CH_3	H	95	oil			
8c	-$(CH_2)_4$-		H	64	Et_2O	123-125	$C_{16}H_{16}Cl_2O_3$	CH
8d	C_2H_5	H	C_6H_5	50	BuCl	169-170	$C_{20}H_{18}Cl_2O_3$	CH
4a (α)	C_6H_5	CH_3	H	8.2	AcOH	242-244	$C_{19}H_{14}Cl_2O_4$	CH
4b (β)	C_6H_5	CH_3	H	8.9	AcOH	163-166	$C_{19}H_{14}Cl_2O_4$	CH
4c	c-C_5H_9	CH_3	H	50	NaOH-HCl	85	$C_{18}H_{18}Cl_2O_4$	CH
4d	-$(CH_2)_4$-		H	20	toluene	195	$C_{16}H_{14}Cl_2O_4$	CH
4e	C_2H_5	H	C_6H_5	40	toluene	222	$C_{20}H_{16}Cl_2O_4$	CH

[a] NP = not purified.

Table II



no.	R	1,2 dbl bond	7,8 dbl bond	recrystn solvent	mp, °C	emp formula	anal.
14	$(CH_2)_2CH_3$	no	no	BuCl	161	$C_{17}H_{20}O_4$	CH
12	$(CH_2)_2CH_3$	yes	no	AcOH	287	$C_{17}H_{18}O_4$	CH
16a	$(CH_2)_2CH_3$	yes	yes	CH_3NO_2	242	$C_{17}H_{16}O_4$	CH
17a	$=CHCH_2CH_3$	yes	no	EtOH	301	$C_{17}H_{16}O_4$	CH
16b	$(CH_2)_2CH_3$	no	yes	CH_3NO_2	212	$C_{17}H_{18}O_4$	CH
17b	$=CHCH_2CH_3$	no	no	EtOH	229	$C_{17}H_{18}O_4$	CH

In the second synthetic route (Scheme II), the benzofuran nucleus of the starting material **9** was elaborated from the requisite halocoumarin via a Perkin rearrangement. Acylation of **9** under Friedel–Crafts conditions gave ketone **10**. In a standard Mannich reaction, **10** was treated with paraformaldehyde and dimethylamine hydrochloride and the product was deaminated with sodium acetate in acetic acid to provide the α,β-unsaturated ketone **11**. Cyclialkylation of the latter compound afforded dihydroindeno[5,4-*b*]furan-2-carboxylic acid **12**.

Reduction of the 1,2 double bond of **12** with sodium amalgam (Scheme III) resulted in concomitant reduction of the carbonyl moiety at position 6 to give **13**. Subsequent oxidation of hydroxy acid **13** with chromium trioxide provided keto acid **14**. Both the 7-substituted dihydroindenofurans **12** and their tetrahydro analogues **14** were brominated in acetic acid to give the corresponding 7-bromo derivatives **15**. The 7,8 double bond was introduced by dehydrobromination of **15** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in Me_2SO to give compounds **16**. Dehydrobromination of **15** with lithium bromide in DMF provided the exocyclic unsaturated compounds **17**.

The indeno[5,4-*b*]furan-2-carboxylic acids bearing asymmetric centers at positions 7 (or 8) and 2 consist of two diastereomeric isomer pairs, since the cyclization of intermediates **7** to **8** is nonstereospecific. With one exception (**4a,b** wherein R = C_6H_5 and R^1 = CH_3), no attempt was made to separate the diastereomeric isomer pairs. Accordingly, the biological results reflect the activities determined on a mixture of four stereoisomers in all instances except that one cited. Diastereomeric isomer pairs **4a** and **4b** were separated by fractional crystallization and their purities were established by glass capillary GC. The higher melting racemate **4a** is arbitrarily designated α and the lower melting racemate **4b** is designated β.

Structure–Activity Relationships. The amount of urine, Na^+, K^+, and Cl^- excreted was measured in experiments conducted in rats and chimpanzees, but for brevity only the Na^+ excretion is reported here. The relative amount of urine volume, K^+, and Cl^- excreted generally paralleled that of Na^+ excretion; thus, any one of these can be used for relative potency comparisons. Insufficient sample size precluded the evaluation of four compounds (**16a,b** and **17a,b**) in the two diuretic protocols. However, these compounds were evaluated in the SH rat antihypertensive assay and found to be inactive.

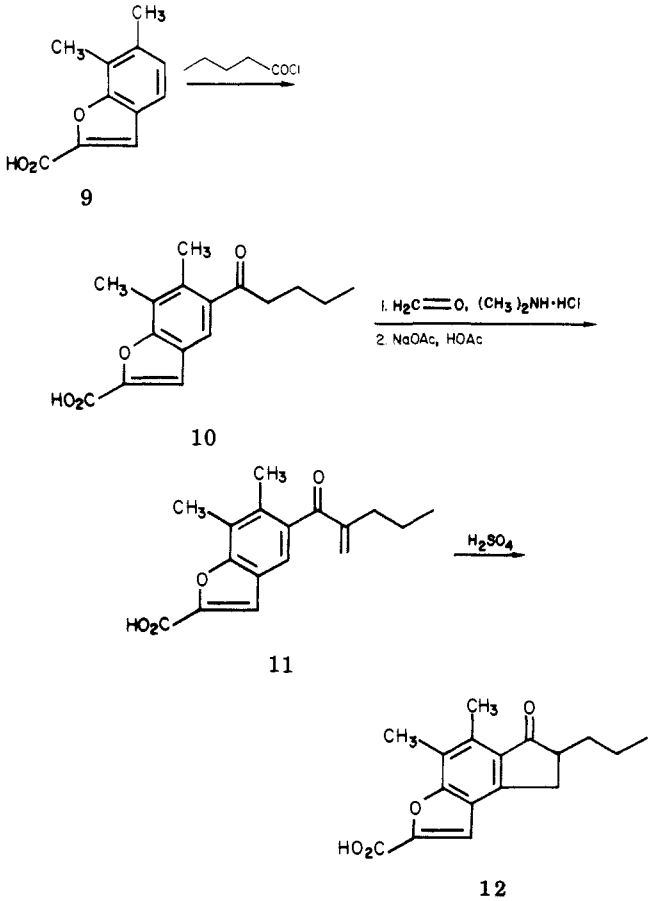
Rat Data. The oral natriuretic activity of the indeno[5,4-*b*]furans (determined at four doses) is recorded in Table III. The most potent of the six compounds evaluated was the spirocyclopentyl compound **4d**. In every

Table III. Oral Activity

compd	rat,[a] mequiv of $Na^+ \times 100$/cage at each dose				chimpanzee,[b] 5 mg/kg	
	3 mg/kg	9 mg/kg	27 mg/kg	81 mg/kg	μequiv of Na^+/min	$\Delta C_{urate}/\Delta C_{inulin}$
4a	141	174	217	[c]	395[d]	0.14[d]
4b	189	267	281	388	1305[e]	0.09[e]
4c	127	223	279	340	437	−0.04
4d	224	323	349	432	1500	0.00
4e	94	109	82	87	820	0.16
12	15	16	32	28	0	0.01
14	[c]	[c]	[c]	[c]	252	0.01
2a	86	97	129	189	409	0.38
furosemide	[c]	7	125	244	1035	−0.02
hydrochlorothiazide	123	112	131	128	144	−0.02
placebo	8					

[a] Female rats (Charles River, 150–170 g) were maintained overnight on a sugar diet with water ad libitum. The test substance was dissolved in pure DMF and subsequently diluted with water (which contained 3 drops of Tween 80 per 100 mL) such that the final vehicle was 4% DMF. At the time of the test, animals were given the vehicle (as placebo) or test substance suspended in a final volume of 5.0 mL po. Rats were housed in groups of three in metabolism cages. Urine was collected for the 0- to 5-h interval in graduated cylinders and was analyzed for sodium, potassium, and chloride content. Animals that received placebo were run concurrently. Results are reported as milliequivalents × 100 per cage and are the geometric means of three cages per dose level. Standard methodology was used for determination of electrolyte levels. [b] Fasted male chimpanzees weighing 21–77 kg were immobilized with phencyclidine (which was shown not to affect the results) (1.0–1.5 mg/kg im plus 0.25 mg/kg iv as needed) and were prepared by catheterization for standard renal clearance studies using routine clinical asceptic procedures. Pyrogen-free inulin (iv) was used to measure the glomerular filtration rate (GFR). Clearance of inulin, urate, and the excretion rates of Na^+, K^+, and Cl^- was determined by standard Auto Analyzer techniques. (Inulin and urate in chimpanzee plasma are freely filterable.) Average control clearances were calculated from three 20-min consecutive periods. Drug-response values were derived as the average of eight 15–20 min clearance periods after oral administration of an aqueous solution of the compound through an indwelling nasal catheter. All data are reported as the difference between (average) treatment and control values obtained from single experiments. [c] Not tested at this dose. [d] 1 mg/kg. [e] 0.1 mg/kg.

Scheme II



instance in which natriuretic activity could be compared, the indeno[5,4-*b*]furan was two to four times more potent than the corresponding indanone.[2,3]

Chimpanzee Data (Table III). These data are generally derived from a single experiment. Unlike the (indanyloxy)acetic acid diuretics, all of which were uricosuric, uricosuria was observed only in those indenofurans where R^1 or R^2 is an aryl substituent, i.e., **4a,b,e**.

It is of interest to compare the activity in chimpanzees of several of the indeno[5,4-*b*]furans to that of their corresponding indanones (Table IV). Compound **4c** is equinatriuretic to MK-473; however, **4d** is nearly five times as potent as its corresponding indanone. Neither of these indeno[5,4-*b*]furans is uricosuric. At one-fifth the dose, **4a** is equinatriuretic to MK-196. At one-fiftieth the dose (0.1 mg/kg), **4b** is three times as potent as MK-196, making it one of the most potent orally administered diuretics ever evaluated in these laboratories.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained are within 0.4% of the theoretical values. Detailed experimental procedures are given only for selected compounds, which will serve to illustrate the general synthetic methods employed.

5-(Allyloxy)-6,7-dichloro-2-methyl-2-phenyl-1-indanone (6a). A stirred mixture of 2-methyl-2-phenyl-5-hydroxy-6,7-dichloro-1-indanone (15 g, 0.049 mol), K_2CO_3 (7.4 g, 0.053 mol), and allyl bromide (6.58 g, 0.054 mol) in DMF (80 mL) was heated at 55 °C for 1 h and then poured into H_2O (0.4 L) to give **6a**. Compounds **6b–d** were prepared in this manner.

4-Allyl-6,7-dichloro-5-hydroxy-2-methyl-2-phenyl-1-indanone (7a). A solution of **6a** (12.5 g, 0.036 mol) in *N,N*-diethylaniline (120 mL) was heated at reflux for 1.5 h. The reaction mixture was poured into cold, dilute HCl (excess) and extracted with Et_2O. The ethereal extract was washed with H_2O, dried ($MgSO_4$), and evaporated to give **7a**. Compounds **7b–d** were prepared in this manner.

4,5-Dichloro-2-(hydroxymethyl)-7-methyl-6-oxo-7-phenyl-1,2,7,8-tetrahydro-6H-indeno[5,4-*b*]furan (8a). A solution of **7a** (6.94 g, 0.02 mol) in CH_2Cl_2 (60 mL) was treated with NaOAc (110 mg) and 40% AcOOH (4.4 mL). The reaction was stirred at 25 °C for 5 days. The CH_2Cl_2 solution was washed (H_2O, $NaHCO_3$, brine), dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate gave a frothy residue. After heating

Scheme III

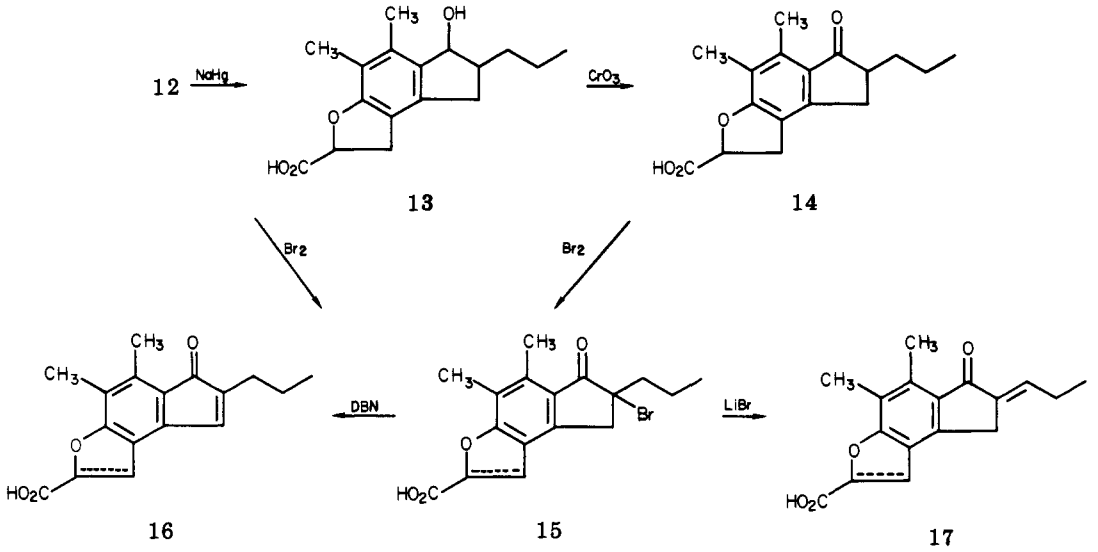


Table IV. Comparison of Indans with Indeno[5,4-b]furans for Oral Diuretic Activity in Chimpanzees

compd	dose, mg/kg	$\Delta C_{urate}/\Delta C_{inulin}$	μequiv of Na^+/min	μequiv of K^+/min	μequiv of Cl^-/min
2a	5	0.38	409	108	539
4a	1	0.14	395	47	509
4b	0.1	0.09	1305	88	1532
2b	5	0.20	425	64	367
4c	5	−0.04	437	63	614
2c	5	0.14	321	42	399
4d	5	0	1500	274	1990
hydrochlorothiazide	5	−0.02	144	73	198
probenecid	5	0.05			

at 120 °C for 15 min, there was obtained 6.5 g of solvated **8a** which was used without further purification.

4,5-Dichloro-7-methyl-6-oxo-7-phenyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (4a and 4b). To a solution of **8a** (6.5 g, 0.018 mol) in Me_2CO (200 mL) was added dropwise a solution of Jones reagent (34 mL) in 8-h intervals with stirring at room temperature over 48 h. The Me_2CO solution was decanted from precipitated salts and filtered into H_2O (500 mL). The aqueous mixture was extracted with Et_2O, washed with H_2O, and extracted with aqueous $NaHCO_3$. The basic layer was added to dilute aqueous HCl, whereupon an oil was liberated. The oily mixture was extracted with Et_2O, washed with H_2O, and dried ($MgSO_4$). On concentrating the Et_2O layer to dryness and triturating the oily residue with toluene, there was obtained **4a** plus **4b**, a mixture of diastereomeric pairs. Fractional crystallization from AcOH gave 560 mg (8.2%) of the α-isomer **4a** (93.3% pure GC) and 600 mg (8.9%) of the β-isomer **4b** (82% pure GC).

4,5-Dichloro-7-methyl-6-oxo-7-phenyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (β-Isomer, 4b). To a solution of **7a** (1.73 g, 0.005 mol) in CH_2Cl_2 (30 mL) was added *m*-chloroperoxybenzoic acid (1.03 g, 6 mmol) and 4,4′-thiobis(6-*tert*-butylphenol) (10 mg). The reaction was heated at reflux for 5 h, cooled, and filtered, the filtrate was washed (H_2O, $NaHCO_3$, and brine), the CH_2Cl_2 was evaporated, and the residual oil was heated at 120 °C for 20 min. The crude 4,5-dichloro-2-(hydroxymethyl)-6-oxo-7-methyl-7-phenyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan (β isomer) thus obtained was dissolved in Me_2CO (60 mL) and heated with a solution of CrO_3 (1.4 g) dissolved in H_2O (10 mL) and concentrated H_2SO_4 (1.24 mL). After stirring for 18 h at 25 °C, the Me_2CO solution was decanted from precipitated salts into H_2O (60 mL), extracted with Et_2O, washed with H_2O, and dried ($MgSO_4$), and the Et_2O was evaporated to give **4b**.

4,5-Dimethyl-6-oxo-7-propyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (14) Step A. 4,5-Dimethyl-6-pentanoylbenzofuran-2-carboxylic Acid (10). A stirred suspension of 4,5-dimethylbenzofuran-2-carboxylic acid (18 g 0.094 mol) and pentanoyl chloride (15 g 0.12 mol) in CH_2Cl_2 (0.3 L) was cooled to 5 °C and treated with $AlCl_3$ (40 g, 0.30 mol) in portions during a 0.5-h period, during which time the suspended reactant dissolved. The reaction mixture was stirred at ambient temperature for 48 h and then poured into ice H_2O (0.5 L) and HCl (50 mL) to give **10**, mp 188–189 °C ($EtOH-H_2O$). Anal. ($C_{16}H_{18}O_4$)C, H.

Step B. 4,5-Dimethyl-6-(2-methylenepentanoyl)benzofuran-2-carboxylic Acid (11). A mixture of **10** (15 g, 0.05 mol), paraformaldehyde (3.5 g, 0.117 mol), and dimethylamine hydrochloride (7 g, 0.085 mol) in *p*-dioxane (100 mL) was heated at reflux for 8 h and then cooled. The 4,5-dimethyl-6-[2-[(dimethylamino)methyl]pentanoyl]benzofuran-2-carboxylic acid hydrochloride which precipitated was collected, then dissolved in AcOH (200 mL) containing NaOAc (25 g), heated at reflux for 2 h, and poured into H_2O (200 mL) containing HCl (25 mL) to afford **11**, mp 172 °C (BuCl). Anal. ($C_{17}H_{18}O_4$) C, H.

Step C. 4,5-Dimethyl-6-oxo-7-propyl-7,8-dihydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (12). A solution of **11** (6 g, 0.021 mol) in concentrated H_2SO_4 (80 mL) was stirred at 25 °C for 18 h and then poured into ice–H_2O (0.5 L) to give **12**, mp 287 °C (AcOH). Anal. ($C_{17}H_{18}O_4$) C, H.

Step D. 4,5-Dimethyl-6-hydroxy-7-propyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (13). A solution of **12** (2.0 g, 0.007 mol) in aqueous $NaHCO_3$ (40 mL) was treated with 1% NaHg (120 g) and then stirred at 25 °C for 18 h. The Hg was separated and the aqueous phase acidified with HCl to give **13**, mp 161 °C (CH_3NO_2). Anal. ($C_{17}H_{22}O_4$) C, H.

Step E. 4,5-Dimethyl-6-oxo-7-propyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (14). A stirred suspension of **13** (5.0 g, 0.017 mol) in Me_2CO (250 mL) was heated over a 10-min period with a solution of CrO_3 in H_2O (18 mL) and concentrated H_2SO_4 (2.2 mL). The Me_2CO solution was decanted from the precipitated salts and poured into H_2O (0.7 L) to give **14**, mp 161 °C (BuCl). Anal. ($C_{17}H_{20}O_4$) C, H.

4,5-Dimethyl-6-oxo-7-bromo-7-propyl-7,8-dihydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (15a). A stirred solution of **12** (2.86 g, 0.01 mol) in THF (75 mL) was treated during a 0.5-h period with a solution of pyrrolidone hydrotribromide (4.96 g, 0.01

mol) in THF. Addition of H_2O (500 mL) to the reaction gave **15a**, mp 233 °C (toluene). Anal. ($C_{17}H_{17}BrO_4$) H; C: calcd, 55.90; found, 56.75.

4,5-Dimethyl-6-oxo-7-propyl-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (16a). A solution of **15a** (1.2 g, 0.0033 mol) and DBN (0.8 mL) in Me_2SO (8 mL) was stirred at 25 °C for 1 h and then treated with H_2O (30 mL), HCl (5 mL), and EtOH (20 mL) to give **16a** as a red solid: mp 242 °C (CH_3NO_2); ^1H NMR (Me_2SO) δ 0.90 (t, 3, propyl C_3 H), 1.30–1.70 (m, 2, propyl C_2 H), 2.20 (s, 3, C_4 CH_3), 2.30 (s, 3, C_5 CH_3), 2.0–2.7 (m, 2, propyl C_1 H), 7.30 (s, 1, C_8 H), 7.68 (s, 1, C_1 H). Anal. ($C_{17}H_{16}O_4$) C, H.

4,5-Dimethyl-6-oxo-7-propylidene-7,8-dihydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (17a). A stirred solution of **15a** (0.8 g, 0.0022 mol) and anhydrous LiBr (0.49 g, 0.0056 mol) in DMF (10 mL) was heated at 95 °C under N_2 for 1 h and then poured into H_2O (100 mL) to give **17a**: mp 301 °C (EtOH); ^1H NMR (Me_2SO) δ 1.12 (t, 3, propylidene C_3 H), 2.35 (s, 3, C_4 CH_3), 2.50 (s, 3, C_5 CH_3), 2.70–3.40 (m, 2, propylidene C_2 H), 3.65 (s, 2, C_8 H), 6.70 (t, 1, propylidene C_1 H), 7.75 (s, 1, C_1 H).

4,5-Dimethyl-6-oxo-7-bromo-7-propyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (15b). A stirred suspension of **14** (1.4 g, 0.005 mol) in AcOH (15 mL) was treated with Br_2 (0.8 g, 0.005 mol) in AcOH (5 mL) over a 3-min period, poured into H_2O (100 mL) containing $NaHSO_3$ (1 g), extracted with Et_2O, washed with H_2O, and dried ($MgSO_4$), and the Et_2O was evaporated to give **15b** as a white solid, mp 78 °C.

4,5-Dimethyl-6-oxo-7-propyl-1,2-dihydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (16b). A solution of **15b** (0.7 g, 0.0019 mol) and DBN (0.5 mL) in Me_2SO (5 mL) was stirred at 25 °C for 1.5 h, poured into H_2O, acidified with HCl, extracted into Et_2O, washed with H_2O, and dried ($MgSO_4$), and the Et_2O was evaporated to give **16b**: mp 212 °C (CH_3NO_2); ^1H NMR (Me_2SO-d_6) δ 0.85 (t, 3, propyl C_3 H), 1.20–1.80 (m, 2, propyl C_2 H), 2.00 (s, 3, C_4 CH_3), 2.06 (s, 3, C_5 CH_3), 3.20–3.60 (m, 4, C_1 H and propyl C_1 H), 5.25 (m, 1, C_2 H), 7.48 (s, 1, C_8 H). Anal. ($C_{17}H_{18}O_4$) C, H.

4,5-Dimethyl-6-oxo-7-propylidene-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (17b). A stirred solution of **15b** (0.7 g, 0.0019 mol) and LiBr (0.5 g, 0.0057 mol) in DMF (10 mL) was heated at 95 °C under N_2 for 1 h and then poured into H_2O (50 mL) to give **17b**: mp 229 °C (EtOH); ^1H NMR (Me_2SO-d_6) δ 1.02 (t, 3, propylidene C_3 H), 2.00–2.60 (m, 2, propylidene C_2 H), 2.20 (s, 6, $ArCH_3$), 3.40 (s, 2, C_8 H), 3.25–3.80 (m, 2, C_1 H), 5.25 (m, 1, C_2 H), 6.55 (t, 1, propylidene C_1H). Anal. ($C_{17}H_{18}O_4$) C, H.

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Notes

Synthesis and Antiallergy Activity of 4-Oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines[1]

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A series of 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines with substitutions in the 2, 3, and 7 positions was prepared. The compounds were evaluated in the rat passive cutaneous anaphylaxis test for antiallergy activity. Several compounds had potent oral activity and were found to be superior to disodium cromoglycate and doxantrazole. Structure–activity relationships are discussed.

Allergic reactions and bronchial asthma in particular are thought to be the result of an antigen–antibody combination on the mast cell with subsequent release of the mediators of immediate hypersensitivity which include histamine, leukotrienes, and various kinins.[2] The clinical manifestations of the allergic reaction are elicited by the subsequent interaction of the mediators with the end organ smooth muscle or mucous membranes. Traditionally, symptomatic treatment of allergies and bronchial asthma has been provided by β-sympathomimetic agents, methylxanthines, corticosteroids, and anticholinergics. The introduction of disodium cromoglycate (DSCG) in 1967 provided an agent which inhibited the release of mediators of anaphylaxis from sensitized mast cells and thus provided a prophylactic treatment for allergies and bronchial asthma.[3] The major disadvantages of DSCG are that it is not orally effective and that it must be used as an insufflated powder.

A great deal of research has gone into developing orally active antiallergy agents.[4] Recent papers have described the antiallergy activity of the 3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylates[5] and the pyrido[2,1-*b*]quinazolinecarboxylic acids.[6]

In this paper, we describe the synthesis of some novel 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines which exhibit oral antiallergy activity.

(1) F. J. Tinney, W. A. Cetenko, J. J. Kerbleski, D. T. Connor, R. J. Sorenson, and D. J. Herzig, "Abstracts of Papers", 180th National Meeting of the American Chemical Society, Las Vegas, NV, Aug 24–29, 1980, American Chemical Society, Washington, DC, 1980, Abstr MEDI 60.
(2) A. S. Rebuck, *Drugs*, 7, 344 (1974).
(3) J. S. G. Cox, *Nature (London)*, 216, 1328 (1967).
(4) S. C. Bell and R. J. Capetola, *Annu. Rep. Med. Chem.*, 14, 51 (1979).
(5) D. L. Temple, J. P. Yevich, R. R. Covington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey, and M. J. Bartek, *J. Med. Chem.*, 22, 505 (1979).
(6) J. W. Tilley, R. A. Le Mahieu, M. Carson, R. W. Kierstead, H. W. Baruth, and B. Yaremko, *J. Med. Chem.*, 23, 92 (1980).

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