88413-03-0; IV (A = B = CH_2CH_3), 88413-04-1; IV [A, B = $(CH_2)_5$], 88413-05-2; IV (A = H; B = CH_3), 88413-07-4; IV [A = H; B = $(CH_2)_2CH_3$], 88413-14-3; IV [A = H; B = $(CH_2)_3CH_3$], 88413-15-4; IV (A = H, B = $(CH_2)_5CH_3$), 88413-16-5; IV (A = H; B = $(CH_2)_6CH_3$), 88413-17-6; IV [A = H; B = $CH_2CH(OH)CH_2OH$], 88413-18-7; IV (A = H; B = c-C_6H_{12}), 88413-19-8; IV (A = B = CH_3), 88413-20-1; IV [A, B = $(CH_2)_4$], 88413-21-2; IV [A, B = $(CH_2)_2O(CH_2)_2$], 88413-22-3; V (A = B = CH_2CH_3), 88413-23-4; V [A, B = $(CH_2)_5$], 13272-12-3; V (A = H, B = CH_3), 88413-26-7; VI (A = B = CH_2CH_3), 88413-24-5; VI (A = H; B = CH_3), 88413-27-8; *N*-[3-(methylamino)-4-nitrophenyl]ethanesulfonamide, 88413-06-3; *N*-[3-(methylamino)-4-nitrophenyl]propanesulfonamide, 88413-08-5; *N*-[3-(methylamino)-4-nitrophenyl]butanesulfonamide, 88413-09-6; *N*-[3-(methylamino)-4-nitrophenyl]-pentanesulfonamide, 88413-10-9; *N*-[3-(methylamino)-4-nitrophenyl]hexanesulfonamide, 88413-11-0; *N*-[3-(methylamino)-4-nitrophenyl]heptanesulfonamide, 88413-12-1; *N*-[3-(methylamino]-4-nitrophenyl]octanesulfonamide, 88413-13-2; 9-chloroacridine, 1207-69-8; 3-(1-piperidinyl)-4-aminoacetanilide, 88413-25-6; methanesulfonyl chloride, 124-63-0; *N*-methylethanolamine, 109-83-1; diethylamine, 109-89-7; piperidine, 110-89-4; methylamine, 74-89-5; ethanesulfonyl chloride, 594-44-5.

Dibenz[*b*,*e*]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 4. Synthesis and Evaluation of 4-(4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)butanol and -butyric Acid and Related Derivatives

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4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid (**6**) was previously reported as a potent antiinflammatory–analgesic agent characterized by an impressive therapeutic ratio in comparison with indomethacin. With the goal of finding compounds that might display even more favorable therapeutic ratios and/or enhanced antiinflammatory/analgesic properties in comparison to **6**, we synthesized 4-(4,10-dihydro-10-oxothieno[3,2-*c*][1]-benzoxepin-8-yl)butanol (**4b**) and -butyric acid (**5a**) and a series of related derivatives. All compounds were evaluated for potential analgesic activity in the phenylquinone-induced writhing (PQW) assay, for antiinflammatory activity in the carrageenan-induced paw edema (CPE) model and, where warranted, for gastric irritation (GI) liability. Of the compounds investigated, **4b** (HP 573) displays moderate analgesic-like activity in PQW, is approximately half as potent as indomethacin or **6** as an antiinflammatory agent in the CPE, and is characterized by an extremely low propensity to induce GI as reflected by comparison of the therapeutic ratios (GI ED_{50}/CPE ED_{50}: **4b** > 46, **6** = 9.9, indomethacin = 0.4). Compound **4b** was selected for clinical evaluation.

We previously reported the synthesis and biological evaluation of dihydro-10-oxofuro- and -thieno[3,2-*c*][1]-benzoxepin-8-acetic acids.[1-3] From this work, 4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid (**6**) emerged as a potent antiinflammatory–analgesic agent that is characterized by an impressive therapeutic ratio in comparison with indomethacin.[2] The fact that nonsteroidal antiinflammatory agents may exhibit gastric irritation (GI) on oral or parenteral administration is established, and the reduction of GI by molecular modification to minimize a high localization of the active drug in the gastrointestinal mucosa has been discussed by Stella.[4] With the goal of finding compounds that might display even more favorable therapeutic ratios and/or enhanced antiinflammatory/analgesic properties in comparison to **6**, we synthesized 4-(4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)butanol (**4b**) and -butyric acid (**5a**) and a series of related derivatives. On oral administration we hoped that these compounds would be absorbed without significant gastric irritation due to a local effect and then be converted to **6** as the, a priori, biologically active species. Support for **6** as possibly being the biologically active species is derived from analogy to the recently established biotransformation of the antiinflammatory agent fenbufen to 4-biphenylacetic acid, which was inferred to be the biologically active moiety based on in vitro and in vivo studies of fenbufen and its metabolities.[5] The synthesis of the acetoxyacetate derivative **7** was prompted by a report that enhanced antiinflammatory activity is associated with the acetoxyacetic acid analogue of indomethacin.[6] The oxazoline **11**, prepared for C-alkylation studies, also represents a masked form of **6**, and both **7** and **11** are reversible derivatives of **6**, at least in a chemical sense.

Chemistry. The synthesis of the various analogues is outlined in Schemes I and II, and the properties of the compounds are summarized in Table I. Condensation of methyl 3-(bromomethyl)-2-thiophenecarboxylate (**1**) with 4-(4-hydroxyphenyl)butanol (**2a**) or ethyl 4-(4-hydroxyphenyl)butyrate (**2b**) and hydrolysis afforded the intermediates **3a** and **3b**, respectively. Cyclization of **3a** with trifluoroacetic anhydride gave the trifluoroacetyl ester **4a** which after acid-catalyzed hydrolysis and esterification afforded the butanol analogue **4b** and the acetyl ester **4c**, respectively. Similar cyclization of **3b** gave the butyric acid derivative **5a** from which esters **5b–e** were prepared by standard methods.

Ester derivatives of **6** were previously reported.[7] The acetoxyacetate analogue **7** was prepared by condensation of **6** under mildly alkaline conditions with methyl bromoacetate. Selective borane–methyl sulfide reduction of **6**

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(1) Aultz, D. E.; Helsley, G. C.; Hoffman, D.; McFadden, A. R., Lassman, H. B.; Wilker, J. C. *J. Med. Chem.* **1977**, *20*, 66.
(2) Aultz, D. E.; McFadden, A. R.; Lassman, H. B. *J. Med. Chem.* **1977**, *20*, 456.
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(4) Stella, V. In "Pro-drugs as Novel Drug Delivery Systems" (*ACS Symp. Ser. no. 14*); Higuchi, T.; Stella, V., Eds.; American Chemical Society: Washington, DC, 1975; Chapter 1.
(5) Sloboda, A. E.; Tolman, E. L.; Osterberg, A. C.; Panagides, J. *Arzneim.-Forsch.* **1980**, *30*, 716.
(6) Boltze, K.H.; Brendler, O.; Jacobi, H.; Opitz, W.; Raddatz, S.; Seidel, P. R.; Vollbrecht, D. *Arzneim.-Forsch.* **1980**, *30*, 1314.
(7) McFadden, A. R.; Aultz, D. E. U.S. Patent 4025640, 1977.

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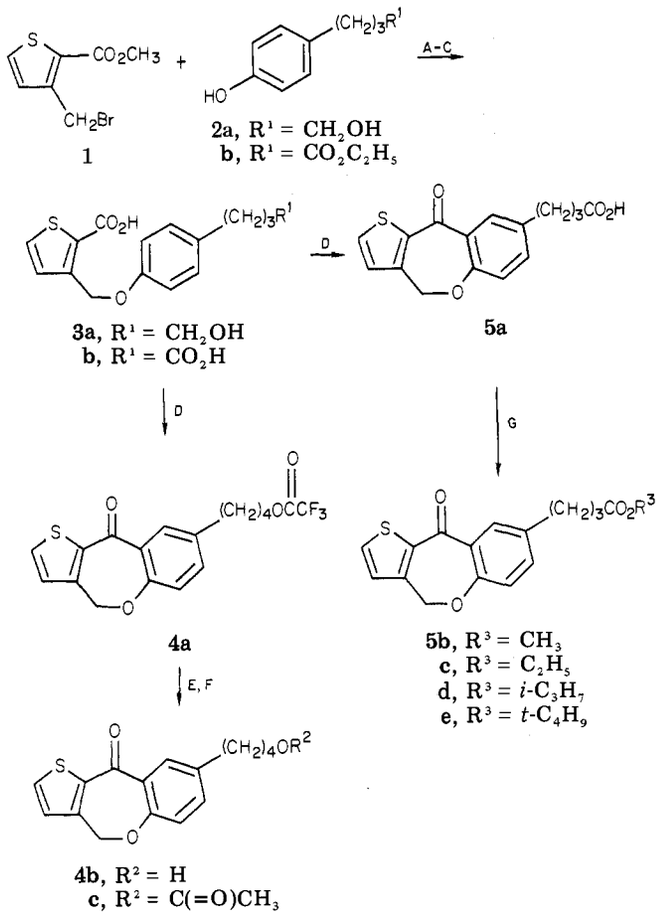
Scheme I[a]



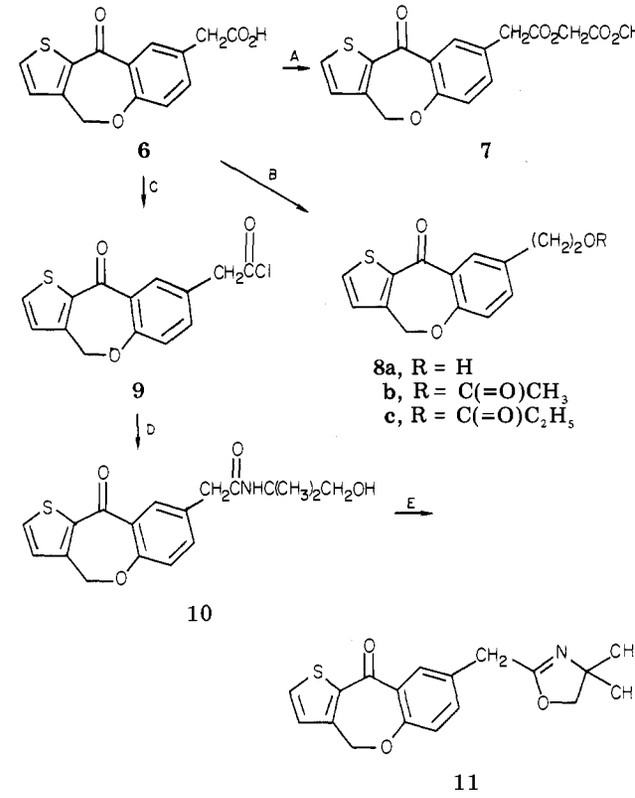
[a] A = 2-butanone/K_2CO_3/KI; B = KOH/H_2O/C_2H_5OH; C = HCl; D = $(CF_3CO)_2O$; E = HCl/acetone; F = $(CH_3CO)_2O$/pyridine; G = R^3OH/H_2SO_4 (R^3 = CH_3, C_2H_5, i-C_3H_7) or $SOCl_2$ and $LiOC(CH_3)_3$ (R^3 = t-C_4H_9).

gave the ethanol derivative **8a**, from which ester analogues **8b,c** were prepared. The oxazoline **11** was prepared from the acid chloride **9** and 2-amino-2-methyl-1-propanol to give amido alcohol **10**, which was cyclized with thionyl chloride.

Results and Discussion

The compounds included in Table I, with exception of the acid chloride **9**, were evaluated for potential analgesic (phenylquinone-induced writhing, PQW) and antiinflammatory (carrageenan-induced paw edema, CPE) activities. With respect to PQW, only compound **7** displayed significantly enhanced activity in comparison with the lead compound **6**. In CPE, none of the compounds was significantly more active than **6** or indomethacin. Compounds for which an ED_{50} in CPE was determined were additionally evaluated in the gastric irritation (GI) assay for potential side-effect liability, and a therapeutic ratio (GI ED_{50}/CPE ED_{50}) may be calculated from these data. Of the compounds investigated, derivatives **4a**, **4b**, and **8b** exhibited significantly less GI than **6**. Compound **4b** is most notable, since this butanol derivative displays moderate analgesic-like activity in PQW, is approximately half as potent as indomethacin or **6** as an antiinflammatory agent in CPE, and is characterized by an extremely low propensity for GI liability. This combination of properties results in an apparently quite favorable therapeutic ratio for **4b** (>46) in comparison to **6** (9.9) or indomethacin (0.4). The biotransformation of **4b** to **5a** and then to **6** has been demonstrated.[8] Whether or not **6** is the only biologically

Scheme II[a]



[a] A = K_2CO_3/$BrCH_2CO_2CH_3$/$(CH_3)_2NC(=O)H$; B = $BH_3 \cdot (CH_3)_2S$/c-$(CH_2)_4O$ and then $(RCO)_2O$/pyridine. C = excess $SOCl_2/CH_2Cl_2$; D = $H_2NC(CH_3)_2CH_2OH/CH_2Cl_2$; E = $SOCl_2/CH_2Cl_2$.

active species present remains to be discerned from further investigation of **4b** and its metabolites. Compound **4b** was subsequently selected for clinical evaluation.

Experimental Section

The structures of all compounds are supported by their IR (Pye Unicam SP3-200), ^1H NMR (JEOL C60HL; tetramethylsilane), and MS (Finnigan 4023) spectra. Melting points were taken on a Thomas-Hoover capillary melting point apparatus. All melting and boiling points are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL. Results are within ±0.4% of theoretical values unless otherwise noted. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents. Reactions requiring an inert atmosphere were conducted under a dry nitrogen atmosphere. The following starting materials were prepared according to the cited literature procedures with minor modifications as indicated: methyl 3-(bromomethyl)-2-thiophenecarboxylate [**1**; bp 103 °C (0.04 torr); ethyl ester originally reported[9]]; 4-(4-hydroxyphenyl)butyric acid and ethyl 4-(4-hydroxyphenyl)butyrate (**2b**), prepared from 4-(4-methoxyphenyl)butyric acid (Aldrich Chemical Co.) as described by Aultz et al.;[3] 4-(4-hydroxyphenyl)butanol [**2a**; bp 148–150 °C (0.28 torr)], prepared by borane reduction of 4-(4-hydroxyphenyl)butyric acid under conditions reported by Yoon et al.[10] for the synthesis of 2-hydroxybenzyl alcohol from salicyclic acid; 4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid (**6**), prepared as described by Aultz et al.[2]

3-[[4-(4-Hydroxybutyl)phenoxy]methyl]-2-thiophenecarboxylic acid (3a; method A) was prepared by refluxing a

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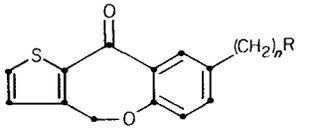
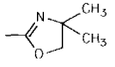
(9) Gogte, V. N.; Tilak, B. D.; Gadekar, K. N.; Sahasrabudhe, M. B. *Tetrahedron* **1967**, *23*, 2443.
(10) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* 1973, *38*, 2768.

Table I. 4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepine Derivatives[a]



compd	*n*	R	starting material	method	yield,[b] %	mp,[c] °C	recrystn solvent[d]	formula	anal.[e]	PQW,[f] ED_{50} or % inhibn at 25 mg/kg po	CPE,[f] ED_{50} or % inhibn at 20 mg/kg po	GI,[f] ED_{50} or % inhibn at dose, mg/kg po
4a	4	$OC(=O)CF_3$	**3a**	A, B	84	65.5-67	I	$C_{18}H_{15}F_3O_4S$	C, H	9.1 (8.4-10.0)	16.5 (14.9-18.4)	50% at 300
4b	4	OH	**4a**	C	90	52-54	T-Cy	$C_{16}H_{16}O_3S$	C, H	7.4 (6.8-8.1)	8.6 (8.4-8.8)	40% at 400
4c	4	$OC(=O)CH_3$	**4b**	D	87	53.5-55	H[g]	$C_{18}H_{18}O_4S$	C, H	5.8 (5.0-6.6)	38%	
5a	3	CO_2H	**3b**	A, B	73	107-109.5	T	$C_{16}H_{14}O_4S$	C, H	94%	38%[h]	
5b	3	CO_2CH_3	**5a**	E	96	40-42	H[g]	$C_{17}H_{16}O_4S$	C, H	10.8 (9.4-12.3)	10.3 (8.4-12.2)	60% at 100
5c	3	$CO_2C_2H_5$	**5a**	E	81	oil		$C_{18}H_{18}O_4S$	C, H	8.2 (7.4-9.0)	40%	
5d	3	$CO_2CH(CH_3)_2$	**5a**	E	71	oil		$C_{19}H_{20}O_4S$	C, H	8.5 (7.7-9.5)	44%	
5e	3	$CO_2C(CH_3)_3$	**5a**	F	34	oil		$C_{20}H_{22}O_4S$	C, H	93%	49%	
6[i]	1	CO_2H				162-164	E[g]	$C_{14}H_{10}O_4S$		3.1 (3.0-3.3)	3.4 (3.2-3.5)	33.7 (28.0-41.0)
7	1	$CO_2CH_2CO_2CH_3$	**6**	G	78	78-80	H[g]	$C_{17}H_{14}O_6S$	C, H	1.5 (1.2-1.8)	43%	
8a	2	OH	**6**	H	66	oil		$C_{14}H_{12}O_3S$	C, H	19.7 (16.6-23.3)	62%	
8b	2	$OC(=O)CH_3$	**8a**	D	86	40-42	H[g]	$C_{16}H_{14}O_4S$	C, H	52%	11.4 (10.9-11.9)	175 (117-261)
8c	2	$OC(=O)C_2H_5$	**8a**	D	79	oil		$C_{17}H_{16}O_4S$	C, H	22%	35%	
9	1	$C(=O)Cl$	**6**	I	84	89-93	C	$C_{14}H_{19}ClO_3S$		NT	NT	
10	1	$C(=O)NHC(CH_3)_2CH_2OH$	**9**	J	87	162-163	A	$C_{18}H_{19}NO_4S$	C, H, N	19%	21%	
11	1		**10**	K	52	85-87	D[g]	$C_{18}H_{17}NO_3S$	C, H, N	7.2 (6.7-7.8)	49%	
indomethacin										0.7 (0.4-1.4)	4.4 (3.7-5.3)	1.8 (1.1-2.9)

[a] All compounds exhibited IR, ^1H NMR, and MS spectra consistent with the assigned structures. [b] Yield of analytically pure material; yields were not optimized. [c] Melting points are uncorrected. [d] A = acetonitrile; C = carbon tetrachloride, Cy = cyclohexane; D = diisopropyl ether; E = ether; H = hexane; I = 2-propanol; T = toluene. [e] Analytical results within ±0.4% of the theoretical values unless otherwise noted. Compound 9 was not analyzed. [f] PQW = phenylquinone-induced writhing; CPE = carrageenan-induced paw edema; GI = gastric irritation; po = per os. The numbers in parentheses are 95% confidence intervals. GI ED_{50} is defined as the dose required to cause irritation in 50% of the test animals. NT = not tested. [g] The compound was triturated with the indicated solvent. [h] Percent inhibition at 50 mg/kg po. [i] Synthesis previously reported by Aultz et al.[2]

stirred mixture of **2a** (40 g, 0.24 mol), anhydrous potassium carbonate (97.86 g, 0.71 mol), powdered potassium iodide (2 g), 2-butanone (400 mL), and 1 (56.43 g, 0.24 mol) for 24 h with exclusion of moisture. The hot mixture was filtered, and the filtrate was concentrated to afford an oil. A dichloromethane solution of the oil was washed with 10% sodium hydroxide solution, and the dried (Na_2SO_4) organic phase was concentrated to give the methyl ester of **3a** as a solid: yield 82.3 g. A sample was recrystallized from cyclohexane to provide analytically pure material, mp 67–68.5 °C. Anal. ($C_{17}H_{20}O_4S$) C, H. A stirred solution of the methyl ester, potassium hydroxide (144.2 g, 2.57 mol), water (150 mL), and 95% ethanol (900 mL) was refluxed for 3 h. The solution was concentrated, the residual syrup was diluted with water (1 L) and ice (1 L), and the mixture was acidifed with concentrated hydrochloric acid. The precipitate was collected, washed with water, dried, and recrystallized from 95% ethanol to afford **3a** (58 g, 79% from **2a**) as beige crystals, mp 144.5–146 °C. Anal. ($C_{16}H_{18}O_4S$) C, H. Similar condensation of 1 and **2b** and alkaline hydrolysis gave **3b**, mp 147–151 °C (2-propanol). Anal. ($C_{16}H_{16}O_5S$) C, H.

4-(4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)-butyl trifluoroacetate (4a; method B) was prepared by treating a stirred solution of **3a** (14.3 g, 0.047 mol) and dichloromethane (150 mL) over a few seconds with trifluoroacetic anhydride (22.6 g, 0.11 mol). After refluxing for 4 h, the cooled solution was treated with water (100 mL). The organic phase was washed with 5% sodium bicarbonate solution, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to an oil, which was dissolved in 2-propanol (15 mL). After standing overnight, the crystalline precipitate was collected, washed with 2-propanol, and dried to afford **4a** (15 g, 84%) as colorless crystals. Properties of **4a**, and of **5a** prepared in a similar manner from **3b**, are included in Table I.

4-(4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)-butanol (4b; method C) was prepared by refluxing a stirred solution of **4a** (11.42 g, 0.03 mol), acetone (480 mL), and 0.7 M hydrochloric acid (250 mL) for 20 h. The cooled solution was concentrated, and the residual material was extracted with ether. The dried (Na_2SO_4) organic phase was concentrated to an oil, which was dissolved in toluene and diluted to the cloud point with cyclohexane to afford **4b** (7.73 g, 90%) as a colorless solid. Properties of **4b** are included in Table I.

4-(4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)-butyl acetate (4c; method D) was prepared by treating a stirred solution of **4b** (8.07 g, 0.028 mol) and pyridine (25 mL) over 0.5 min with acetic anhydride (8.58 g, 0.084 mol). After stirring for 3 h at ambient temperature, the solution was warmed (steam bath) for 15 min and decanted into water. The mixture was extracted with dichloromethane (70 mL), and the organic phase was washed sequentially with 5% hydrochloric acid and sodium bicarbonate solutions. The dried (Na_2SO_4) organic phase was filtered and concentrated to an oil, which crystallized on trituration with hexane to give **4c** (8.1 g, 87%). Properties of **4c**, and of **8b** and **8c** prepared in similar manner from acetic and propionic anhydrides, are included in Table I.

Methyl 4-(4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)butyrate (5b; method E) was prepared by refluxing a stirred solution of **5a** (7.0 g, 0.023 mol), methanol (5 mL), and concentrated sulfuric acid (0.2 mL) for 4 h. The cooled solution was diluted with water and extracted with ether. After washing with 5% sodium bicarbonate solution, the dried (Na_2SO_4) organic phase was concentrated to give an oil, which crystallized on standing. Trituration with hexane afforded **5b** (7.0 g, 96%) as a colorless solid. Properties of **5b**, and of **5c,d** prepared in similar manner, are included in Table I.

***tert*-Butyl 4-(4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)butyrate (5e; method F)** was synthesized by dropwise treatment at ambient temperature of a stirred solution of lithium *tert*-butoxide (prepared from 37 mL of *tert*-butyl alcohol and 5.7 mL of 2.2 M *n*-butyllithium in hexane) with an ethereal solution of the acid chloride of **5a** (prepared from 3.0 g of **5a** by method I) under nitrogen. After stirring overnight, the suspension was diluted with water and extracted with ethyl acetate and ether. The combined dried (Na_2SO_4) organic phase was concentrated to give **5e** (1.2 g, 34%) as an oil. Properties of **5e** are included in Table I.

Methyl [(4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)acetoxy]acetate (7; method G) was prepared by dropwise treatment of a warm (60 °C), stirred mixture of **6** (12.54 g, 0.046 mol), anhydrous potassium carbonate (3.18 g, 0.033 mol), and dimethylformamide (100 mL) with methyl bromoacetate (7.7 g, 0.05 mol). After stirring overnight at 60 °C, the mixture was decanted into water and extracted with ether. The organic phase was washed with 5% sodium bicarbonate solution and water, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to afford an oil, which was triturated with hexane to give **7** (12.5 g, 78%) as a colorless solid. Properties of **7** are included in Table I.

2-(4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)-ethanol (8a; method H) was prepared by dropwise treatment at 25 °C of a stirred solution of **6** (10 g, 0.036 mol) and tetrahydrofuran (50 mL) with a 1 M solution of borane–methyl sulfide complex in dichloromethane (72 mL) under nitrogen. After stirring overnight at ambient temperature, the ice–water cooled mixture was treated dropwise with methanol to decompose excess borane. The mixture was concentrated, and the residue was partitioned between dichloromethane and water. The organic phase was washed with 5% sodium bicarbonate solution, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to afford the crude material. Trituration with boiling hexane and drying provided **8a** (6.2 g, 66%) as an oil. Properties of **8a** are included in Table I.

4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetyl chloride (9; method I) was prepared by dropwise treatment of a warm, stirred solution of **6** (20 g, 0.073 mol), dichloromethane (400 mL), and dimethylformamide (3 drops) with thionyl chloride (9.5 g, 0.08 mol). The solution was refluxed for 1 h, treated with additional thionyl chloride (9.5 g), and refluxed for another hour. The cooled solution was concentrated, and the residue was triturated with hexane to give **9** (18 g, 84%) as a colorless solid. A sample was recrystallized from carbon tetrachloride, and the properties of **9** are included in Table I.

***N*-(1-Hydroxy-2-methyl-2-propyl)-2-(4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)acetamide (10; method J)** was prepared by dropwise treatment of a stirred solution of 2-amino-2-methyl-1-propanol (13.35 g, 0.15 mol, Eastman) and dichloromethane (50 mL) with a solution of **9** (15 g, 0.051 mol) and dichloromethane (200 mL). After the mixture was stirred overnight, the precipitated material was collected and triturated with water to give 11 g of a water-insoluble solid. The organic filtrate was washed with 5% hydrochloric acid and 10% sodium hydroxide solutions, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to give 4.4 g of solid (combined yield of **10**: 15.4 g, 87%). A sample was recrystallized from acetonitrile to give analytically pure material. Properties of **10** are included in Table I.

2-[(4,10-Dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-yl)-methyl]-4,4-dimethyloxazoline (11; method K) was prepared by dropwise treatment of a cold (5 °C), stirred suspension of **10** (8.3 g, 0.024 mol) and dichloromethane (200 mL) with thionyl chloride (3.09 g, 0.026 mol). After stirring overnight at ambient temperature, the solution was washed with 10% sodium hydroxide solution, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to give an oil, which was triturated with diisopropyl ether to provide **11** (4.1 g, 52%) as an almost colorless solid. Properties of **11** are included in Table I.

Pharmacological Methods. ED_{50} values were determined by linear regression analysis. Compounds were prepared as aqueous suspensions with 1 drop of "Tween 80"/10 mL or solubilized in an emulphor/alcohol/distilled water (1:1:8) mixture when the material was an oil. The dosage was administered orally in a volume of 10 mL/kg of body weight. Control animals received vehicle (10 mL/kg).

Carrageenan-Induced Rat Paw Edema (CPE). Male Wistar rats (Charles River) weighing between 130 and 200 g were arranged in groups of 7–10. The rats were fasted overnight (water ad libitum). A modification of the carrageenan-induced rat paw edema method described by Winter et al.[11] was used. Compounds were administered orally at 1, 2, and/or 4 h prior to the subplantar

(11) Winter, C. A.; Risley, E. A.; Nuss, G. V. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.

injection of 0.1 mL of a 1% aqueous suspension of carrageenan into the left hind paw. Paw volume measurements were taken immediately after and 3 h after the carrageenan injection by means of mercury displacement. Drug activity was expressed as the percent difference between the test and control groups edema. Dose ranges included at least three doses of the drug.

Phenylquinone-Induced Writhing (PQW). The procedure employed was a modification of the method of Siegmund et al.[12] A 0.125% concentration of phenylquinone (phenyl-*p*-benzoquinone, Eastman) in a 5% aqueous ethanol solution was injected into male CD-1 Charles River mice, weighing 18–24 g, at 10 mL/kg ip. Animals were fasted overnight (water ad libitum). Groups of five mice were treated with test drug orally at various time intervals prior to phenylquinone injection. Control mice were treated with an equal volume of vehicle. After phenylquinone injection, the mice were placed individually in 1000-mL beakers, and 5 min later, the number of writhes was recorded for a 10-min period. The peak time of test drug activity was thereby determined. A dose–response study was performed in a similar manner, except that 8 to 10 animals per group were used at the peak time of activity. Animals were dosed and tested in a randomized manner using four drug doses and one control group. Drug activity is expressed as the percent inhibition of the control group per number of writhes.

Gastric Irritation (GI). Groups of 10 male Wistar rats weighing 150–175 g were fasted 48 h (water ad libitum) prior to administration of the test drug orally (10 mL/kg). Control rats received vehicle only (10 mL/kg). For a time response, animals were treated with a highly active antiinflammatory dose of the test drug and then sacrificed at 3, 5, and 7 h after drug administration. Stomachs and intestines were removed and examined for the presence of lesions. The presence of single or multiple lesions (erosion, ulcer, or perforation) was considered an ulcerogenic effect. A dose–response was performed at the peak time using four doses of the test drug.

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Synthesis and Antifolate Properties of 10-Alkyl-8,10-dideazaminopterins

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The synthesis of 10-alkyl analogues of the potent antitumor agent 8,10-dideazaminopterin is described. Alkylation of appropriate α-alkyl homoterephthalate esters with 2,4-diamino-6-(bromomethyl)-8-deazapteridine afforded 10-alkyl-10-carboxy-4-amino-4-deoxy-8,10-dideazapteroic acid diesters. Ester cleavage and decarboxylation at C-10 were accomplished by heating with sodium cyanide in Me_2SO at 170–180 °C to afford the 2,4-diamino-10-alkyl-8,10-dideazapteroic acids. The acids were coupled with diethyl glutamate, followed by saponification, to give the 10-alkyl-8,10-dideazaminopterins. The compounds were potent inhibitors of growth in folate-dependent bacteria, *Streptococcus faecium* and *Lactobacillus casei*. The 10-methyl and 10-ethyl analogues gave the highest percent increases in life span for mice infected with L1210 leukemia with ILS values of +203 and +235%, respectively.

In previous papers we have reported the synthesis and antifolate activities of 10-deazaminopterin[1,2] and its 10-alkyl analogues.[3] These compounds were found to be powerful antifolates with transport and pharmacokinetic properties that made them prime candidates as antitumor agents for human use.[4-6] As an extension of this research program, we have also investigated the synthesis of ring deazapteridines. In a recent paper we described the synthesis and biological activity of 8,10-dideazaminopterin (**6a**).[7] This compound was found to be a very potent inhibitor of dihydrofolate reductase and encouraged us to investigate the 10-alkyl analogues **6b–d**. We report the synthesis and properties of these analogues in this article.

Chemistry. We have previously reported[7,8] two independent syntheses of **6a** that proceeded through 9,10-didehydrofolate intermediates. However, neither of these routes was considered to be convenient for the synthesis of the 10-alkyl analogues **6b–d**.

Dimethyl homoterephthalate (**2a**) was converted (Scheme I) to its anion by treatment with potassium hydride in dimethylformamide. The ester anion was alkylated with 2,4-diamino-6-(bromomethyl)-8-deazapteridine

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