The Et_2O extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in $CH_3C{\equiv}N$ and washed with *n*-pentane to remove mineral oil. The crude olefins were purified by chromatography on alumina (Woelm neutral, Grade I) and eluted with 3:1 Et_2O–Skellysolve B to give **7a** and **7b** in yields averaging 75–80%.

A stirred solution of 0.035 mol of **7a** or **7b** in 120 ml of 48% HBr was heated at 120 °C for 20 h. Concentration of the reaction mixture gave the crystalline HBr salt. Recrystallization from the appropriate solvent gave analytically pure **8a·HBr** and **8b·HBr**.

Method B: N–H (9a,b). A mixture of 3.8 mmol of **8a** or **8b**, 1 g of NaOAc, and 15 ml of Ac_2O was heated on a steam bath for 3 h. Ac_2O was removed at reduced pressure. The residue was treated with dilute Na_2CO_3 and extracted with $CHCl_3$ to give the phenol acetate in quantitative yield (GC 100%). A refluxing solution of this acetate in 30 ml of benzene was treated with 11.0 mmol of ethyl chloroformate. Heating was continued for 6 h. The reaction mixture was washed with dilute HOAc and dilute $NaHCO_3$, and concentrated to give the carbamate ester (GC 100%). Treatment of this material with 15 ml of 48% HBr, 15 ml of H_2O, and 30 ml of HOAc and 40 h of heating on a steam bath gave after concentration the crystalline HBr salt. Purification was achieved by recrystallization.

Method C: *N*-Cyclopropylmethyl, *N*-Cyclobutylmethyl, *N*-Cyclopropylethyl (10a–f). A stirred solution of 3.0 mmol of **9a** or **9b** in a mixture of CH_2Cl_2 and TEA was treated with 9.0 mmol of acyl chloride. Stirring was continued for 20 h. The reaction mixture was washed with dilute HOAc and dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the amido ester. This was reduced with an excess of $LiAlH_4$ in THF by refluxing for 20 h. After careful treatment with saturated Na_2SO_4 solution, a saturated ammonium tartrate solution was added and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude product. Purification was achieved by salt formation and recrystallization.

Method D: *N*-Allyl (10g). A mixture of 3.0 mmol of **9b**, 3.3 mmol of allyl bromide, and 1.7 g of K_2CO_3 in 20 ml of absolute EtOH was heated at reflux for 20 h. The reaction mixture was filtered and concentrated to dryness. The residue was treated with H_2O and extracted with EtOAc. Evaporation of the solvent gave an oil which was purified by recrystallization of its HBr salt.

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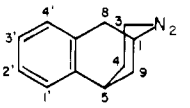
References and Notes

(1) Compounds of this general ring system are also commonly known as 6,7-benzomorphans. For clarity the numbering of the benzomorphan (I), 2,6-methano-3-benzazocine (II), and 1,4:2,6-dimethano-3-benzazocine (III) ring systems is given.



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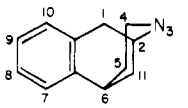

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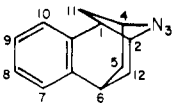

III

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Dibenz[*b,e*]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 2. Dihydro-10-oxofuro- and -thieno[3,2-*c*][1]benzoxepin-8-acetic Acids

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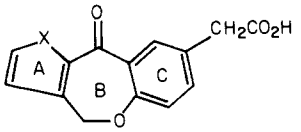
4,10-Dihydro-10-oxofuro[3,2-*c*][1]benzoxepin-8-acetic acid and 4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid were evaluated in the carrageenan paw edema assay with the thieno analogue being ten times more active than the furano compound and 1.3 times more active than indomethacin. The therapeutic ratio (antiinflammatory activity/gastric irritation liability) of the thieno analogue was 25 times that of indomethacin.

We have recently reported the synthesis of 6,11-dihydrodibenz[*b,e*]oxepinacetic acids,[1] many of which exhibited good antiinflammatory activity. One of these, 6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-acetic acid (**10**),

Table I. 4,10-Dihydro-10-oxohetero[3,2-c][1]benzoxepin-8-acetic Acids



No.	X	Mp, °C[a]	% yield[b]	Empirical formula	Analyses	CPE ED_{50},[c] mg/kg po	Gi ID_{50},[d] mg/kg po	Therapeutic ratio, ID_{50}/ED_{50}
1	O	177-178	42	$C_{14}H_{10}O_5$	C, H	33.26 (24.31-52.04)	–[e]	–
2	S	162-164	40	$C_{14}H_{10}O_4S$	C, H, S	3.37 (3.20-3.54)	33.72 (28.04-40.96)	10
10	CH=CH					6.36 (5.19-8.26)	82.47 (72.97-94.58)	13
Indomethacin						4.35 (3.72-5.26)	1.8 (1.1-2.9)	0.4

[a] Recrystallization solvents: compound 1, MeCN; compound 2, Et_2O. [b] Yields of analytically pure material; no efforts were made to optimize yields. [c] CPE = carrageenan paw edema in rats; values in parentheses are 95% confidence limits. [d] ID_{50} is defined as the dose required to produce gastric irritation in 50% of the rats tested. [e] A dash (–) means not tested.

was found to possess potent antiinflammatory activity coupled with an impressive therapeutic ratio. We now wish to report on the synthesis and pharmacological activity of two heterobenzoxepin analogues of this compound.

The synthetic sequence utilized in the preparation of the hetero analogues is illustrated in Scheme I. Condensation of ethyl 4-hydroxyphenylacetate (**5**) with methyl 3-bromomethyl-2-furoate (**6**) in butanone followed by alkaline hydrolysis afforded the diacid **3**. A modification of a method used by Bisagni et al.[2] was used to effect the cyclization. The diacid **3** was converted to the diacid chloride with phosphorus pentachloride and this product was then cyclized with stannic chloride to provide the oxofurano analogue **1**.

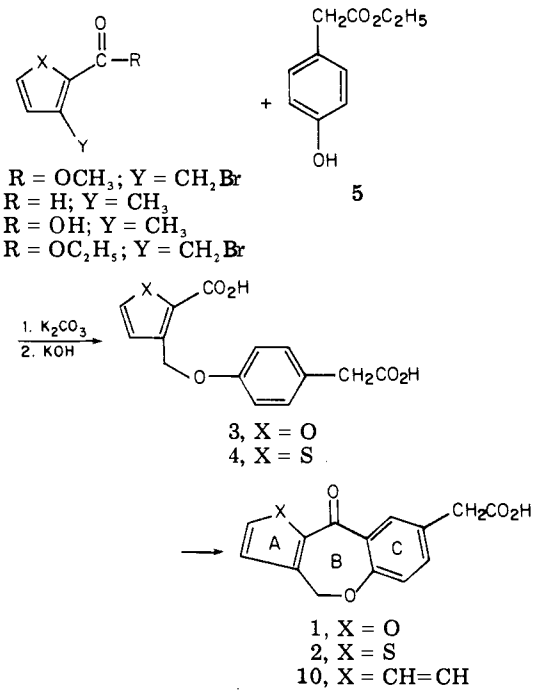
Initially, the 3-methyl-2-thiophenecarboxylic acid (**8**) required for the synthesis of **2** was prepared by a multistep sequence[3] from 3-methylthiophene in which the overall yield was only 45%. Application of a general method used by Campaigne et al.[4] which relied upon a silver oxide oxidation provided the desired acid **8** in 86% yield from 3-methyl-2-thiophenecarboxaldehyde (**7**). Esterification followed by bromination with *N*-bromosuccinimide afforded the ethyl 3-bromomethyl-2-thiophenecarboxylate (**9**) which was condensed with **5** to provide the diacid **4**. Modification of a phosphorus pentoxide–ethanol cyclization approach used by Stach and Spingler[5] gave the oxothieno compound **2**.

Compounds **1** and **2** were evaluated for antiinflammatory activity in the carrageenan paw edema test in rats.[1] A minimum of three different doses was administered orally to groups of ten rats at each dose level. The ED_{50} values were determined according to the method of Litchfield and Wilcoxon.[6] Activity data for these compounds as well as for **10**, and indomethacin by way of comparison, are presented in Table I.

As can be seen from these results, replacement of an ethylene group in the "A" ring of **10** by an oxygen (**1**) results in a fivefold decrease in potency while a similar replacement with sulfur (**2**) caused a twofold increase in potency. This is in general accord with the reported[7] bioisosteric nature of –CH=CH– and –S– and their nonequivalence to –O–. The validity of such bioisosteric relationships in this case is, however, somewhat surprising in view of previous results found with the dibenz[*b*,*e*]-oxepin series wherein the reported[7] bioisosteric equivalency of divalent oxygen and sulfur did not hold.[1]

Since **2** appeared to offer potency advantages over the carbocyclic analogue **10**, its gastric irritation[1] liability in rats was determined for comparison. As shown in Table I, compound **2** is approximately 2.5 times more irritating than **10**. Thus, compound **10** has a therapeutic ratio 1.3 times that of **2**; both compounds appear to represent significant advances over indomethacin, having therapeutic ratios 25–30 times greater.

Scheme I



6, X = O; R = OCH_3; Y = CH_2Br
7, X = S; R = H; Y = CH_3
8, X = S; R = OH; Y = CH_3
9, X = S; R = OC_2H_5; Y = CH_2Br

5

3, X = O
4, X = S

1, X = O
2, X = S
10, X = CH=CH

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Labs., Skokie, Ill. The structures of all compounds are supported by their IR (Perkin-Elmer 457) and NMR (Jeolco $C_{60}HL$) spectra.

The following known intermediates were prepared according to the cited literature references: 2-acetyl-3-methylthiophene,[3] 3-methyl-2-thiophenecarboxylic acid,[3] ethyl 3-methyl-2-thiophenecarboxylate,[8] ethyl 3-bromomethyl-2-thiophenecarboxylate,[8] ethyl 4-hydroxyphenylacetate,[9] methyl 3-methyl-2-furoate,[10] methyl 3-bromomethyl-2-furoate.[11]

4,10-Dihydro-10-oxofuro[3,2-c][1]benzoxepin-8-acetic Acid (**1**). This compound was synthesized by a modification of a method devised by Bisagni et al.[2] To a mixture of 9.62 g (0.034 mol) of 4-(2-carboxy-3-furylmethoxy)phenylacetic acid in 140 ml

of anhydrous benzene was added 14.43 g (0.069 mol) of phosphorus pentachloride and the suspension stirred at ambient temperature for 4 h. The clear solution was concentrated in vacuo to provide the diacid chloride as a light tan solid which was dissolved in 140 ml of anhydrous methylene chloride; 17.9 g (0.068 mol) of stannic chloride in 20 ml of methylene chloride was slowly added and the solution was stirred at ambient temperature for an additional 24 h. The reaction was made basic and filtered; the organic layer was separated and after extraction with ether the aqueous phase was acidified with concentrated hydrochloric acid to provide a brown solid which was washed with water and dried. Recrystallization from acetonitrile provided 3.71 g of a light brown solid, mp 177–178 °C.

4,10-Dihydro-10-oxothieno[3,2-c][1]benzoxepin-8-acetic Acid (2). This compound was prepared by modification of a method used by Stach and Spingler.[5] To 3.5 ml of absolute ethanol was slowly added 5.80 g (0.04 mol) of phosphorus pentoxide, the temperature being kept below 80 °C; the white viscous mixture was then heated at 110 °C for 1 h. After adding 25 ml of sulfolane, the reaction temperature was adjusted to 81–83 °C and 2.70 g (0.01 mol) of 4-(2-carboxy-3-thienylmethoxy)-phenylacetic acid was added. After 3 h, the mixture was decanted into water, made basic, and extracted with toluene. Acidification of the ice-cooled aqueous phase with concentrated hydrochloric acid provided a brown solid which was extracted with chloroform, dried (Na_2SO_4), filtered, and concentrated in vacuo to a yellow solid. Trituration with ether provided 1.0 g of light yellow crystals, mp 162–164 °C.

4-(2-Carboxy-3-furylmethoxy)phenylacetic Acid (3). A mixture of 20.0 g (0.09 mol) of methyl 3-bromomethyl-2-furoate, 15.12 g (0.09 mol) of methyl 3-(4-hydroxyphenyl)acetate, 52.0 g (0.4 mol) of potassium carbonate, 360 ml of 2-butanone, and 1.0 g of sodium iodide was refluxed for 17 h. The reaction was cooled and filtered, and the filtrate was concentrated in vacuo to a dark brown oil. The oil was dissolved in ether, washed with water, 5% sodium hydroxide, and water, and dried (Na_2SO_4). Filtration and concentration in vacuo gave an oil which was refluxed with 51.0 g (0.91 mol) of potassium hydroxide in 255 ml of ethanol and 26 ml of water for 17 h. The reaction was concentrated in vacuo to a brown solid which was dissolved in water and extracted with ether; the aqueous phase was acidified with concentrated hydrochloric acid and the resulting brown precipitate was filtered and dried. Recrystallization from acetonitrile afforded 3.78 g (33%) of off-white crystals, mp 204–205 °C. Anal. ($C_{14}H_{12}O_6$) C, H.

4-(2-Carboxy-3-thienylmethoxy)phenylacetic Acid (4). This compound was prepared according to the method used for compound **3**. Recrystallization from 2-propanol followed by washing with ether provided 16.5 g (62%) of beige crystals, mp 222 °C. Anal. ($C_{14}H_{12}O_5S$) C, H, S.

3-Methyl-2-thiophenecarboxylic Acid (8). This compound was prepared by a procedure developed by Campaigne et al.[4] To 8.40 g (0.21 mol) of sodium hydroxide in 72 ml of water was added 18.0 g (0.11 mol) of silver nitrate and the suspension cooled to 5 °C; 6.30 g (0.05 mol) of 3-methylthiophene-2-carboxaldehyde was then added portionwise. The mixture was stirred at ambient temperature for 1.5 h and filtered, and the precipitate was washed with 70 ml of water. Acidification of the ice-cooled filtrate provided a solid which was collected and dried to yield 6.10 g (86%) of colorless crystals, mp 141–143 °C (lit.[3] 147–148 °C, H_2O) (IR, NMR).

Acknowledgment. The authors wish to express their gratitude to Mr. Marc N. Agnew for determination of NMR spectra and Mrs. Charlsa Kochesky for expert technical assistance in the pharmacological testing.

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Synthesis and Antitumor Activity of 1,2-Dihydro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-oxo-5-methylpyrazine 4-Oxide, a Structural Analogue of Thymidine

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1,2-Dihydro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-oxo-5-methylpyrazine 4-oxide was synthesized by condensation of the silylated pyrazine base with the blocked chloro sugar, followed by removal of the protecting groups. The compound inhibited the growth of leukemia L1210 cells in vitro by 50% at 9×10^{-7} M. At 400 mg/kg/day × 6 it increased the life-span of leukemia L1210 bearing mice by approximately 55%, without apparent toxicity to the host.

We have previously reported on the synthesis and biological activity of pyrazine analogues of various natural pyrimidine and purine nucleosides[1-3] and showed that some of these compounds have pronounced antibacterial activity, while being essentially inactive against leukemia L1210 cells. We have now prepared the pyrazine analogue