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Dibenz[*b*,*e*]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 3. ω-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)alkanoic Acids

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ω-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)butyric, -hexanoic, and -octanoic acids were evaluated in the carrageenan paw edema assay. The most active compound, the butyric acid analogue, was 1.80 times more potent than the hexanoic compound, 1.15 times more potent than the octanoic analogue, and 0.43 times as potent as indomethacin.

In earlier papers we reported on the synthesis of 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetic acid[1] (**7**) and 4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid[2] which were found to possess potent antiinflammatory activity. We now wish to report on the synthesis and pharmacological activity of a series of related dibenz[*b*,*e*]oxepinalkanoic acids.

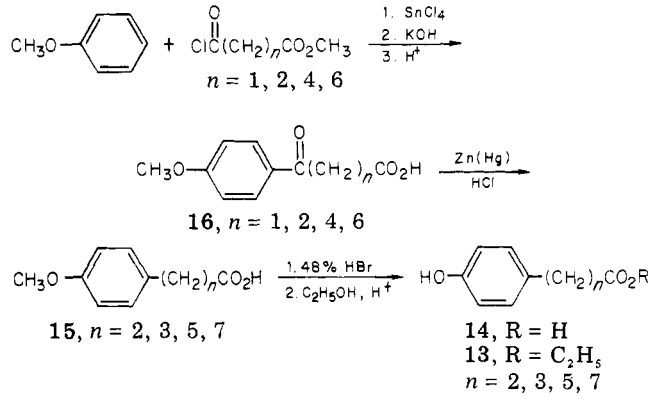
The synthetic approach used in the preparation of the required precursor alkyl ω-(4-hydroxyphenyl)alkanoates is depicted in Scheme I. Anisole was allowed to react with the acid chlorides of monomethyl esters of alkanedioic acids in the presence of stannic chloride to provide the ω-(4-methoxybenzoyl)alkanoic acids (**16**). Application of the Martin[3] modification of the Clemmensen reduction gave the ω-(4-methoxyphenyl)alkanoic acids (**15**). Demethylation of these intermediates with 48% hydrobromic acid according to the method of Fieser et al.[4] afforded the desired ω-(4-hydroxyphenyl)alkanoic acids (**14**) which were then esterified under Fischer–Speier[5] conditions to yield the esters **13**.

As shown in Scheme II, the ethyl ω-(4-hydroxyphenyl)alkanoates were then condensed with ethyl α-bromo-*o*-toluate in the presence of potassium carbonate to provide the diesters which were hydrolyzed with potassium hydroxide to yield the diacids **8**–**11**. Cyclization of the intermediates **9**–**11** was effected by using the polyphosphoric–acetic acid mixture, while the diacid **8** was cyclized using a phosphorus pentoxide–ethanol reagent in sulfolane.

Compounds **1**–**10** were evaluated for antiinflammatory activity in the carrageenan paw edema test in rats.[1] A minimum of three different doses was administered orally using 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 indomethacin are presented in Tables I and II.

As shown in Table I, increasing the chain length of the acid from two carbons (**7**) to three carbons (**1**) somewhat

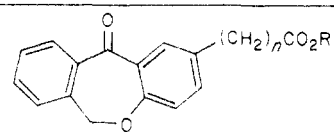
Scheme I



surprisingly[7] results in a complete loss of antiinflammatory activity. However, an increase in chain length from two carbons (**7**) to four (**2**), six (**3**), or eight (**4**) carbons still provides analogues with good antiinflammatory effects. The butyric acid analogue **2** is the most potent of the group **2**–**4**, being 0.63 times as potent as **7** and 0.43 times as potent as indomethacin. The possibility exists that an in vivo β-oxidation[8] to the acetic acid compound **7** is occurring which would be blocked in the case of the propionic acid derivative **1**. This explanation may, however, be somewhat of an oversimplification for while minor differences do exist, the potencies of **2**–**4** are rather similar. If β-oxidation to **7** were the chief operant mechanism, one might expect larger potency differences between **2** and **4** given the limited test period for such metabolism to occur. An alternative explanation could involve the ability of the antiinflammatory receptor(s) for steric reasons to accommodate only dibenzoxepins bearing alkanoic acid chains shorter or longer than three carbons. Further work is necessary to clarify these results.

Both the methyl (**5**) and the isopropyl (**6**) esters were less potent than the parent compound **2**. The diacid precursors were inactive in the carrageenan assay.

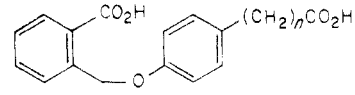
Table I. ω-(6,11-Dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)alkanoic Acids and Esters



No.	*n*	R	Mp, °C[a]	% yield[b]	Method[c]	Recrystn solvent[d]	Emp formula	Analyses[e]	ED_{50}, mg/kg po, CPE[f,g]
1	2	H	128-130	68	*c*	I	$C_{17}H_{14}O_4$	C, H	11%↑ at 50[h]
2	3	H	116-118	53	A	B	$C_{18}H_{16}O_4$	C, H	10.1 (9.1-11.1)
3	5	H	98-100	38	A	AN	$C_{20}H_{20}O_4$	C, H	18.2 (16.3-20.4)
4	7	H	66-68	46	A	AN	$C_{22}H_{24}O_4$	C, H	11.7 (11.3-12.0)
5	3	CH_3	83-85	50	B	M	$C_{19}H_{18}O_4$	C, H	31.7%↓ at 25[h]
6	3	$CH(CH_3)_2$	47-49	43	B	H	$C_{21}H_{22}O_4$	C, H	43.7%↓ at 25[h]
7	1	H							6.4 (5.2-8.3)[i]
Indomethacin									4.4 (3.7-5.3)[i]

[a] Uncorrected. [b] Yields of analytically pure material; no efforts were made to optimize yields. [c] Refer to the Experimental Section. [d] AN = MeCN; B = benzene; H = hexane; I = 2-propanol; M = MeOH. [e] Elements shown analyzed correctly to ±0.4% of calculated values. [f] CPE = carrageenan paw edema; values in parentheses are 95% confidence limits. [g] ↑ is percent stimulation; ↓ is percent inhibition. [h] The data reported for these compounds were obtained at the highest dose tested. [i] See ref 1.

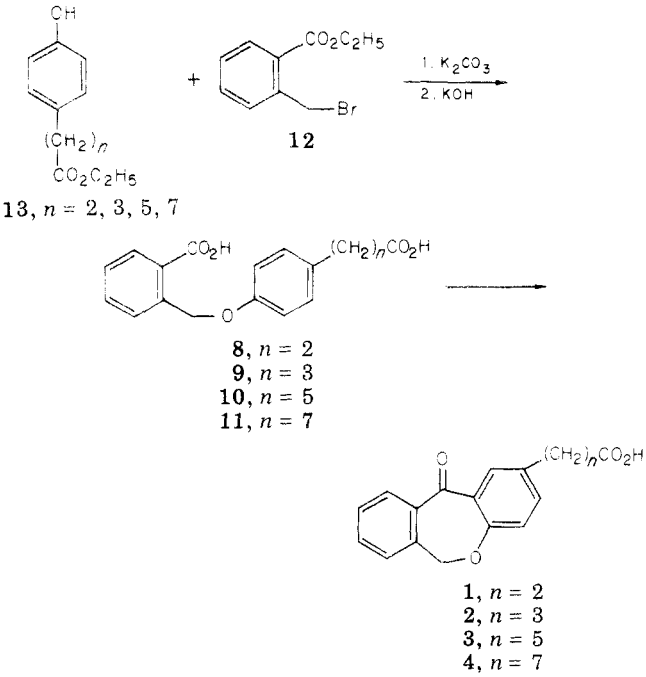
Table II. ω-[4-(2-Carboxybenzyloxy)phenyl]alkanoic Acids



No.	*n*	Mp, °C[a]	% yield[b,c]	Recrystn solvent[d]	Emp formula	Analyses[e]
8	2	176-178	42	E-W	$C_{17}H_{16}O_5$	C, H
9	3	149-150	41	AN	$C_{18}H_{18}O_5$	C, H
10	5	138-140	56	AN	$C_{20}H_{22}O_5$	C, H
11	7	116-118	28	AN	$C_{22}H_{26}O_5$	C, H

[a] Uncorrected. [b] Yields of analytically pure material; no efforts were made to optimize yields. [c] Refer to the Experimental Section. [d] AN = Me_3CN; E = EtOH; W = H_2O. [e] Elements shown analyzed correctly to ±0.4% of calculated values.

Scheme II



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 (Jeol $C_{60}HL$) spectra.

The following known intermediates were prepared according to the cited literature references: ethyl α-bromo-*o*-toluate,[9] monomethyladipoyl chloride,[10] monomethyl suberate,[10] monomethylsuberoyl chloride,[10] 4-hydroxyphenylbutyric acid.[11]

ω-[4-(2-Carboxybenzyloxy)phenyl]alkanoic Acids 8-11. A mixture of 0.113 mol of an ω-(4-hydroxyphenyl)alkanoate, 0.112 mol of ethyl α-bromo-*o*-toluate, 0.451 mol of potassium carbonate, 450 mL of 2-butanone, and 2.0 g of sodium iodide was refluxed for 17 h. The reaction was cooled, the salts were filtered and washed with ether, and the solvent was removed in vacuo to provide a dark yellow oil. The crude product was dissolved in ether, washed with water and 5% sodium hydroxide, dried (Na_2SO_4), filtered, and concentrated in vacuo to yield a yellow oil. This crude product was then refluxed with 1.28 mol of potassium hydroxide in 358 mL of 95% ethanol and 36 mL of water for 17 h. The solution was concentrated in vacuo and the semisolid was dissolved in water and extracted with ether. Acidification with concentrated hydrochloric acid provided the product which was then crystallized from the appropriate solvent listed in Table II.

Method A.[1] A mixture of 0.035 mol of an ω-[4-(2-carboxybenzyloxy)phenyl]alkanoic acid, 54.0 g of polyphosphoric acid, and 42 mL of glacial acetic acid was heated at 90–95 °C for 5 h and then hydrolyzed with 300 mL of water. The suspension was cooled with stirring and the resulting precipitate collected by filtration and dissolved in ether or chloroform. Drying (Na_2SO_4), filtration, and concentration in vacuo provided an ω-(6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)alkanoic acid which was then crystallized from the appropriate solvent shown in Table I.

Method B.[1] To 0.8 g of Amberlite IR-120 HC.P. in 25 mL of the required anhydrous alcohol was added 0.009 mol of the ω-(6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)alkanoic acid. The mixture was refluxed for 16 h, cooled, diluted with ether, and filtered to remove the residue. The filtrate was washed with 5% sodium hydroxide and water, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the ester which was then crystallized from the appropriate solvent indicated in Table I.

3-(6,11-Dihydro-11-oxodibenz[*b,e*]oxepin-2-yl)propionic Acid (1). To 7.4 mL of absolute ethanol under a nitrogen atmosphere was slowly added portionwise 10.4 g (0.73 mol) of

phosphorus pentoxide at such a rate that the temperature remained below 80 °C. The mixture was then stirred at 110 °C for 1 h and then 53.1 mL of sulfolane was added and the temperature adjusted to 85 °C. After adding 5.0 g (0.017 mol) of 3-[4-(2-carboxybenzyloxy)phenyl]propionic acid, the reaction was stirred for 3.5 h, decanted into ice water, and basified with sodium hydroxide. The aqueous phase was extracted with toluene and then cooled and acidified with concentrated hydrochloric acid to provide a precipitate which was collected by filtration, triturated with 2-propanol, and dried to yield 3.22 g (68%) of beige crystals, mp 128–130 °C.

ω-(4-Methoxybenzoyl)alkanoic Acids 16. To 0.625 mol of a monomethyl diacid in 610 mL of dry benzene was added with ice cooling 131.5 g (0.625 mol) of phosphorus pentachloride. Upon dissolution of the phosphorus pentachloride, the ice bath was removed and the solution stirred at ambient temperature for 3 h and then concentrated in vacuo at 80 °C to an oil. To 138.6 g (1.30 mol) of anisole in 1450 mL of dry ethylene chloride was added dropwise, at 5–10 °C, 162.5 g (0.625 mol) of stannic chloride. The acid chloride was dissolved in 150 mL of dry ethylene chloride and added dropwise at 5–10 °C. After the addition, the solution was stirred at ambient temperature for 60 h, refluxed for 1 h, and then hydrolyzed with 1600 mL of 1 N hydrochloric acid for 48 h. The mixture was extracted with ether, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide a methyl ω-(4-methoxybenzoyl)alkanoate which was dissolved in 300 mL of ethanol and 73 mL of water containing 25.0 g (0.45 mol) of potassium hydroxide. After refluxing for 4 h, the mixture was concentrated in vacuo and diluted with water. The solution was extracted with ether and the aqueous phase acidified with concentrated hydrochloric acid to provide the product which was vacuum oven dried and used crude. The compounds prepared by this method were the 5-(4-methoxybenzoyl)valeric acid, mp 123–125 °C, and the 7-(4-methoxybenzoyl)heptanoic acid, mp 103–105 °C (lit.[12] mp 83–86 °C).

ω-(4-Methoxyphenyl)alkanoic Acids 15. These compounds were prepared by applying the Martin[3] modification of the Clemmensen reduction. To 87.0 g (1.33 mol) of mossy zinc and 8.70 g (0.031 mol) of mercuric chloride in a 1-L Erlenmeyer flask were added 131 mL of water and 3.0 mL of concentrated hydrochloric acid. After shaking for 5 min, the aqueous layer was decanted and the activated zinc mixed with 72.0 mL of water, 154.0 mL of concentrated hydrochloric acid, 87.0 mL of toluene, 0.18 mol of an ω-(4-methoxybenzoyl)alkanoic acid, and 3.5 mL of glacial acetic acid. The mixture was refluxed for 48 h; after the first 16 h, 29 mL of concentrated hydrochloric acid was added every 8 h. The reaction was then cooled and filtered, and the toluene separated; the aqueous layer was then extracted with ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the product.

Thusly prepared were 6-(4-methoxyphenyl)hexanoic acid, mp 45–47 °C (lit.[12] mp 47 °C), and 8-(4-methoxyphenyl)octanoic acid, mp 46–47 °C (lit.[12] mp 50–52 °C).

ω-(4-Hydroxyphenyl)alkanoic Acids 14. These compounds were synthesized by applying the procedure of Fieser et al.[4] To 157 mL of glacial acetic acid was added 0.31 mol of an ω-(4-methoxyphenyl)alkanoic acid and 69.5 mL of 48% hydrobromic acid. The solution was refluxed for 6 h, cooled, decanted into 300 mL of ice water, and set overnight at ambient temperature. The reaction mixture was extracted with ether, dried (Na_2SO_4), filtered, and concentrated in vacuo to a solid which was washed with water and vacuum dried. Thusly prepared were 6-(4-hydroxyphenyl)hexanoic acid, mp 99–102 °C (lit.[13] mp 110 °C), and 8-(4-hydroxyphenyl)octanoic acid, mp 87–89 °C (lit.[12] mp 98–103 °C).

Ethyl ω-(4-Hydroxyphenyl)alkanoates 13. The method of Fischer and Speier[5] was used for the preparation of these compounds. A solution of 0.13 mol of an ω-(4-hydroxyphenyl)alkanoic acid, 15 mL of concentrated sulfuric acid, and 400 mL of absolute ethanol was refluxed for 16 h and then concentrated in vacuo to an oil. Water was added and the product extracted with ether; the combined ether extracts were washed with 5% sodium hydroxide and water, dried (Na_2SO_4), filtered, and concentrated in vacuo to an oil which was then distilled. The following esters were prepared by this method: ethyl 4-(4-hydroxyphenyl)butyrate, bp 150–155 °C (0.30 Torr); ethyl 6-(4-hydroxyphenyl)hexanoate, bp 148–150 °C (0.15 Torr); and ethyl 8-(4-hydroxyphenyl)octanoate as an undistilled oil.

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