transducer. Atrial heart rate (beats per minute, bpm) were recorded on a Beckman RM dyanograph recorder with Model 481B preamplifiers and Model 482M8 amplifiers.

Cumulative dose-response curves for the agonist, 4-methylhistamine, induced atrial rates before (curve I) and in the presence of (curve II) test compounds or cimetidine were generated as described below. After three washes of buffer 15 min apart, a control fast record (25 mm/s) was obtained to determine the atrial resting rate, followed by administration of the agonist. Resting rates varied from 180 to 200 bpm. After each agonist response peak, another fast record was obtained before the next dose of agonist. Maximum increases in heart rate were 150–180 bpm.

The agonist was given in cumulative doses of 10^{-7}, 3×10^{-7}, 10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5}, and 10^{-4} M final bath concentrations. The rate of response of 4-methylhistamine peaked within 3 min and remained stable for a number of minutes thereafter. All fast records were taken within 4 min after administration of each dose of agonist.

Upon completion of the cumulative agonist responses, the tissue was washed repeatedly with changes of buffer 10 to 15 min apart until the atrial rate returned to control levels ± 15 bpm. Fifteen minutes after control atrial rates were reached, the test compound (3×10^{-5} M) was added and the process repeated.

A nonlinear fit with a common maximum and slope to quantitative data was performed using program EDXXPH[5,6] (delta response). This analyzes the two curves simultaneously, estimates the potency ratio of the EC_{50} max value with SE, and calculates the parallelism variance ratio. The potency ratio has a 95% confidence region [±SE (t)].

The potency ratio was derived by dividing the agonist EC_{50} max of curve II by the agonist EC_{50} max of curve I. The potency ratio reports how much more agonist was needed in the presence of the test compound to obtain the same heart rate response as with agonist alone.

Modified Ringer–Locke solution was prepared by dissolving 9.0 g of NaCl, 0.42 g of KCl, 1.0 g of $NaHCO_3$, 0.317 g of $CaCl_2 \cdot 2H_2O$, 0.005 g of $MgCl_2 \cdot 6H_2O$, 0.5 g of dextrose, and 0.3 mg of atropine sulfate in 1 L of triple distilled water. The pH was maintained at 7.4 by bubbling 95% O_2/5% CO_2 (Matheson) constantly through the solution and adding acid or base as needed. The finished solution was placed in a reservoir which maintains a constant temperature of 37 °C. The buffer was made fresh each day.

Acknowledgment. We are greatful to S. England, E. Schoeb, R. B. Scott, C. Spurlock, and F. A. MacKellar for spectral data, C. E. Childs and his staff for the microanalyses, and K. Webster for biological assay.

Antiinflammatory 5,6-Dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acids[1]

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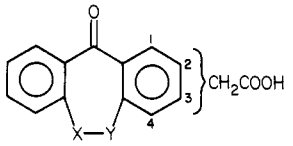
A number of 5,6-dihydro-11-oxodibenz[*b,e*]azepine-3-acetic acids were synthesized. The compounds were up to ~30 times more potent than phenylbutazone as antiinflammatory agents. However, unlike some closely related compounds, for example, the isomeric 2-acetic acids, the compounds were almost devoid of activity in the mouse writhing analgesic assay.

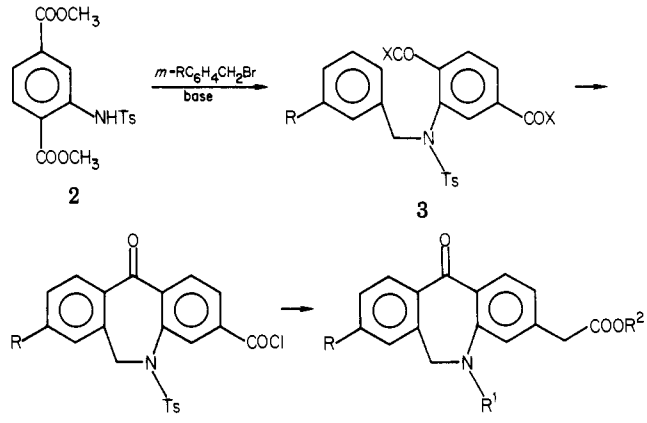
In recent years, substantial antiinflammatory and analgesic activities have been reported for arylacetic and arylpropionic acids, in which the aryl group consisted of a tricyclic moiety with a seven-membered central ring. Thus, the 3-substituted dibenzotropones **1a**,[2] the 2- and



1a, X-Y = CH=CH
b, X-Y = CH_2O
c, X-Y = CH_2S
d, X-Y = CH_2N

3-substituted dibenzoxepins **1b**,[3,4] and the 3-substituted dibenzothiepins **1c**[5] have been subjected to advanced study as potential antiarthritic agents. The syntheses and biological activities of a number of acetic and propionic acids attached to the 2 position of 5,6-dihydro-11-oxodibenz[*b,e*]azepine (**1d**) have also been described.[6] We report here the preparation and bioassays of the isomeric 3-acetic and 3-propionic acids.

Scheme I[a]



[a] Ts = p-$CH_3C_6H_4SO_2$.

Chemistry. The compounds were synthesized as shown in Scheme I. Base-catalyzed alkylation of dimethyl 2-(*p*-toluenesulfonamido)terephthalate (**2**) with benzyl bromide or 3-methoxybenzyl bromide gave the products **3** (X = OCH_3), which were converted to the acids by base hydrolysis. Attempted cyclization to the tricycle **4** using polyphosphoric acid was unsuccessful, but the derived acid chlorides (**3**, X = Cl) could be cyclized in the presence of

(1) Contribution No. 565 from the Syntex Institute of Organic Chemistry.
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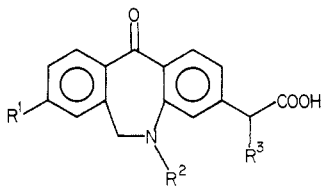
Table I. Antiinflammatory and Analgesic Activities of 11-Oxodibenz[b,e]azepine-3-acetic Acids



no.	R^1	R^2	R^3	rat paw assay (phenylbutazone = 1)	mouse writhing assay (aspirin = 1)
6	H	H	H	29 (14-66)[a]	<0.7 (8)[b]
7	H	CH_3	H	7 (4-11)[a]	<0.2 (32)[b]
8[c]	H	CH_3	CH_3	11 (3-36)[a]	1 (24)[b]
9	H	C_2H_5	H	2.3 (1.1-4.6)[a]	<0.2 (16)[b]
10	H	$COCH_3$	H	<0.3 (12)[b,a]	<0.2 (8)[b]
11	CH_3O	H	H	<0.1 (12)[b]	<0.2 (8)[b]
12	CH_3O	CH_3	H	6.7 (4.0-11.3)[a]	<0.5 (16)[b]

[a] 95% confidence limits. [b] Number of animals. [c] Tested as the dicyclohexylamine salt. [d] A greater than sign indicates that the agent was inactive at the highest dose tested. If it were active at higher doses, the relative potency would not be greater than the value shown.

aluminum chloride or stannic chloride. The products **4** were homologated using the Arndt–Eistert reaction, and the *p*-toluenesulfonyl group was then removed by refluxing hydrochloric acid/acetic acid. Difficulty was experienced in attempted N-methylation of the products **5** (R^1 = H; R^2 = C_2H_5) using either methyl iodide and base or formic acid/formaldehyde. However, treatment of the NH compounds with alcoholic methyl or ethyl iodide at 100 °C in a bomb afforded good yields of the respective N-alkylated compounds.

Biological Activity. The compounds were examined in the rat carrageenan paw edema antiinflammatory assay and in the mouse phenylquinone writhing analgesic assay (see Experimental Section). The results are shown in Table I. Most of the compounds showed moderate to high antiinflammatory activity. The most active compound (**6**) was of comparable activity to both the dibenzothiepin and dibenzoxepin analogues, for which activities of 40[5] and 30[4b] times phenylbutazone have been reported. N-Alkylation caused a progressive decrease in activity (cf. **6**, **7**, and **9**), and N-acetylation abolished antiinflammatory activity. Unexpectedly, there was an almost complete lack of analgesic activity in these compounds. There is thus an interesting variation in activity among the six series of compounds **1b–d** (dibenzoxepins, dibenzothiepins, and dibenzazepines, 2- or 3-acetic acids). Both dibenzoxepin isomers are active in both antiinflammatory and analgesic assays;[3,4] in the dibenzothiepin series, the 3-acetic acid is 10 to 100 times more potent than the 2-isomer.[5] In the dibenzazepine compounds, both the 2- and 3-acetic acids have significant antiinflammatory activity, but only in the 2-series is significant analgesic activity present.[6,8] It is thus apparent that both the nature of the heteroatom in the central ring and the location of the acetic acid moiety profoundly affect the biological activity. In addition, the present series provides a unique instance within the six series of compounds of a pronounced split between antiinflammatory and analgesic activities, presumably due to a subtle difference in the structural requirements for the two effects. As was noted for the dibenzothiepinacetic acids,[5] the chemical shifts of the 1- and 10-hydrogens of the dibenzazepine nucleus are markedly different (see Experimental Section), indicating that the benzophenone substructure is considerably distorted from planarity. There is, however, no apparent correlation between the degree of distortion, as indicated by the chemical-shift difference, and biological activity. Since 8-substituents have been found to lead to increased activity in the dibenzothiepin-3-acetic acid series,[7] the two methoxy compounds **11** and **12** were prepared. As can be seen from Table I, however, no enhancement was obtained.

Experimental Section

Melting points are uncorrected. The NMR spectra were measured on a Varian A-60 or HA-100 spectrometer in $CDCl_3$. The chemical shifts are expressed in parts per million (ppm) on the δ scale from internal Me_4Si; d = doublet; dd = double doublet. The spectroscopic data of all new compounds were consistent with the assigned structure. Microanalytical data were within ±0.4% of theory unless otherwise stated.

Dimethyl 2-(*p*-Toluenesulfonamido)terephthalate (2). *p*-Toluenesulfonyl chloride (2.73 g, 0.014 mol) was added over 4 h to a solution of dimethyl 2-aminoterephthalate (3.0 g, 0.014 mol) in pyridine (50 mL) at 0 °C. After 24 h at room temperature, the solution was poured into water and the product was isolated by EtOAc extraction: yield 3.1 g (60%); mp 168–170 °C (EtOAc). Anal. ($C_{17}H_{17}NO_6S$) C, H, N.

Dimethyl 2-(*N*-Benzyl-*N*-*p*-toluenesulfonamido)terephthalate (3, X = OCH_3; R = H). Sodium hydride (280 mg, 0.006 mol of a 50% oil dispersion) was added to a solution of **2** (2.0 g, 0.0057 mol) in DMF (20 mL); when H_2 evolution had stopped, benzyl bromide (1.2 g, 0.007 mol) was added. The mixture was left for 16 h and then poured into water. The product was extracted with EtOAc and recrystallized from EtOAc/hexane: yield 2.5 g (96%); mp 110–113 °C. Anal. ($C_{24}H_{23}NO_6S$) C, H, N.

***N*-(*p*-Toluenesulfonyl)-5,6-dihydro-11-oxodibenz[*b*,*e*]azepine-3-carbonyl Chloride (4, R = H).** The ester **3** (X = OCH_3; R = H) was hydrolyzed in 90% yield to the acid **3** (X = OH; R = H), mp 212–213 °C (EtOAc), by heating at reflux for 3 h in aqueous methanolic sodium hydroxide. The diacid was converted to the acid chloride by heating at reflux in thionyl chloride until a clear solution was obtained. The diacid chloride (**3**, X = Cl; R = H) (5.2 g, 0.011 mol) was dissolved in CH_2Cl_2 (100 mL) at 0 °C, and aluminum chloride (5.6 g, 0.042 mol) was added. After 30 min at 0 °C, the mixture was added to 100 mL of 3 N hydrochloric acid. The organic solution was dried and evaporated, and the residue was triturated with Et_2O to yield 3.2 g (68%) of **4** (R = H), mp 115–122 °C.

Ethyl *N*-(*p*-Toluenesulfonyl)-5,6-dihydro-11-oxodibenz[*b*,*e*]azepine-3-acetate (5, R^1 = *p*-Toluenesulfonyl; R^2 = C_2H_5). The acid chloride **4** (R = H) (9.0 g, 0.0196 mol) was dissolved in CH_2Cl_2 (100 mL) at 0 °C, and an excess of ethereal diazomethane was added. After 30 min, excess diazomethane was removed in an N_2 stream, and the volume was reduced to ~50 mL. The diazo ketone was filtered off and dried under vacuum: yield 8.2 g (90%). This compound (8.0 g, 0.019 mol) was dissolved in refluxing EtOH (240 mL), and silver benzoate (1.5 g, 0.0065 mol) was added. The solution was heated at reflux for 5 min, cooled, filtered, and evaporated. The residue was chromatographed on silica gel (750 g) (2:1 hexane/EtOAc) to afford **5** (R^1 = *p*-toluenesulfonyl; R^2 = C_2H_5): mp 118–121 °C (acetone–

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(7) Unpublished results from these laboratories.

(8) For example, the dibenzazepine-2-acetic acid isomeric to **6** has an ED_{50} of 5.1 mg/kg in the mouse writhing assay, compared to a value of 130 mg/kg for phenylbutazone (data from ref 6).

hexane); yield 6.2 g (80%). Anal. ($C_{25}H_{23}NO_5S$) C, H, N.

5,6-Dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acid (6). The ester 5 (R^1 = *p*-toluenesulfonyl; $R^2 = C_2H_5$) (7.5 g, 0.018 mol) was heated at reflux for 4 h in HOAc (60 mL) and concentrated hydrochloric acid (120 mL). The solution was cooled and poured into water, and the crude product was extracted with EtOAc. This material was chromatographed on silica gel (500 g) (EtOAc/hexane/HOAc, 40:60:2) to produce 6: yield 3.2 g (71%); mp 224 °C dec; partial NMR δ 8.11 (d, *J* = 9 Hz, 1-H), 7.75 (dd, *J* = 8 and 1 Hz, 10-H). Anal. ($C_{16}H_{13}NO_3$) C, H, N.

***N*-Alkyl-5,6-dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acids (7 and 9) and Methyl Ester (5).** The acid 6 (600 mg, 0.00225 mol) was heated to 100 °C for 12 h in a steel bomb with MeOH (5 mL) and MeI (4 mL). The cooled mixture was poured into water and extracted with Et_2O. The extract was washed with aqueous $NaHCO_3$, dried, and evaporated. Recrystallization from Et_2O–hexane then gave 5 ($R^1 = R^2 = CH_3$): yield 481 mg (73%); mp 88–90 °C. Anal. ($C_{18}H_{17}NO_3$) C, H, N. Base hydrolysis of the ester using 1 equiv of $LiOH·H_2O$ in 3:2 aqueous MeOH at room temperature for 12 h then afforded the acid 7 in 81% yield: mp 155–158 °C (acetone–hexane) (lit.[6] mp 161–162.5 °C); partial NMR δ 8.25 (d, *J* = 8 Hz, 1-H), 7.73 (dd, *J* = 8 and 1 Hz, 10-H). Anal. ($C_{17}H_{15}NO_3$) C, H, N. Use of EtI instead of MeI gave, after chromatography on silica gel (7:3 hexane/EtOAc), a 51% yield of the *N*-ethyl ester 5 ($R^1 = R^2 = C_2H_5$) as an oil. Base hydrolysis then produced the acid 9 in 71% yield: mp 139–141 °C (acetone–hexane); partial NMR δ 8.24 (d, *J* = 8 Hz, 1-H), 7.71 (dd, *J* = 8 and 1 Hz, 10-H). Anal. ($C_{18}H_{17}NO_3$) C, H, N.

***dl*-2-(*N*-Methyl-5,6-dihydro-11-oxodibenz[*b,e*]azepin-3-yl)propionic Acid (8).** A 1.6 M solution of *n*-BuLi in hexane (1.01 mL, 0.001616 mol) was added to isopropylcyclohexylamine (0.228 g, 0.0016 mol) in THF (10 mL) at 0 °C. After 30 min, the solution was cooled to −78 °C and 5 ($R^1 = R^2 = CH_3$) (481 mg, 0.0016 mol) was added. After 40 min, MeI (430 mg, 0.0032 mol) was added, and the reaction was warmed to room temperature. The solution was poured into water and extracted with Et_2O. The crude product was chromatographed on silica gel (50 g) (7:3 EtOAc/hexane) to afford 429 mg (85%) of the methyl ester of 8, which was hydrolyzed as described above to produce a 91% yield of 8, characterized as the dicyclohexylamine salt: mp 157–159 °C (C_6H_6–hexane); partial NMR (Me_2SO-d_6) δ 7.97 (d, *J* = 8 Hz, 1-H); 10-H resonance was not resolved from the aromatic multiplet. Anal. ($C_{30}H_{40}N_2O_3$) H, N; C: calcd, 75.5; found, 75.15.

***N*-Acetyl-5,6-dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acid (10).** The acid 6 (600 mg, 0.00225 mol) was stirred for 48 h in HOAc (12 mL) and acetic anhydride (6 mL). The mixture was poured into water and extracted with EtOAc. The extract was dried and evaporated, and the residue was chromatographed on silica gel (50 g) (EtOAc/hexane/HOAc, 60:40:2) to give 10: yield 540 mg (78%); mp 175–178 °C (acetone–hexane); partial NMR δ 8.25 (dd, *J* = 8 and 1 Hz, 10-H), 8.15 (d, *J* = 9 Hz, 1-H). Anal. ($C_{18}H_{15}NO_4$) C, H, N.

8-Methoxy-5,6-dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acid (11) and 8-Methoxy-*N*-methyl-5,6-dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acid (12). Condensation between 3-methoxybenzyl bromide and 2, as described above, followed by base hydrolysis and treatment with thionyl chloride, gave a 45% overall yield of the diacid chloride 3 (R = OCH_3, X = Cl). This compound (10.0 g, 0.02 mol) was dissolved in C_6H_6 (200 mL), and $SnCl_4$ (15.7 g, 0.061 mol) was added. After 18 h, the mixture was poured into dilute hydrochloric acid, and the product was extracted with EtOAc. The solution was dried and evaporated, and the residue was triturated with CH_2Cl_2 to afford a 60% yield of a mixture of 4 (R = OCH_3) and the corresponding carboxylic acid. Treatment of this mixture with thionyl chloride as described above yielded pure 4 (R = OCH_3), which was subjected to the Arndt–Eistert reaction to produce 5 (R = OCH_3; R^1 = *p*-toluenesulfonyl; $R^2 = C_2H_5$), mp 119–124 °C (acetone–hexane), which upon acid hydrolysis gave 11 (61% overall): mp 170–173 °C (acetone–hexane); partial NMR δ 8.17 (d, *J* = 8 Hz, 1-H), 7.75 (dd, *J* = 8 and 1 Hz, 10-H). Anal. ($C_{17}H_{15}NO_4$) C, H, N. This compound was converted in 56% yield, as described above, to the *N*-methyl acid 12: mp 167–168 °C (acetone–hexane); partial NMR δ 8.15 (d, *J* = 8 Hz, 1-H), 7.63 (dd, *J* = 8 and 1 Hz, 10-H). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

Inhibition of Carrageenan-Induced Edema. This assay was carried out essentially as described in a recent publication[9] from these laboratories (see also ref 10). Thus, 80–90 g female rats were given the test agent orally 1 h prior to the injection of carrageenan into one of the hind paws. The test agents were given in a vehicle containing 0.9% sodium chloride, 0.5% sodium carboxymethylcellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol, and 97.3% distilled water. The rats were sacrificed 4 h after drug administration, and both hind paws were excised and weighed. The potencies relative to phenylbutazone were determined by dose–response plots of the percent increase in weight of the treated over the nontreated paw. Six rats were used for each dose group. Relative potencies were calculated according to standard statistical procedures employing an analysis of variance.[11] The dose–response curves for the test materials and reference standard were linear and parallel. At least four dose levels were used to obtain the dose–responses on which the relative potencies are based.

Inhibition of Phenylquinone-Induced Writhing. The assay was performed as described in ref 12, modified as described in ref 9. Thus, 18–20 g male mice were given the test agent orally in the aqueous vehicle noted above, 20 min prior to an intraperitoneal injection of phenylquinone. The mice were observed for the next 10 min, and the potencies, relative to aspirin, were determined as described above. Eight mice were used for each dose group.

Acknowledgment. We thank W. H. Rooks II and A. Tomolonis for providing the bioassay data.

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