Nonsteroidal Antiinflammatory Agents. 1. 10,11-Dihydro-11-oxodibenz[*b*,*f*]oxepinacetic Acids and Related Compounds[1]

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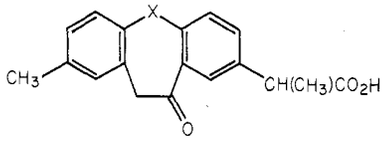
10,11-Dihydro-11-oxodibenz[*b*,*f*]oxepinacetic acids and related compounds were synthesized as potential antiinflammatory agents. Among them, 2-(8-methyl-10,11-dihydro-11-oxodibenz[*b*,*f*]oxepin-2-yl)propionic acid (**16b**) and its thiepin analogue (**16c**) showed excellent antipyretic activity together with potent antiinflammatory and analgesic properties in biological tests. Structure–activity relationships are discussed.

In recent years a number of arylacetic acid derivatives have been reported to possess potent antiinflammatory activity in animal tests,[2] and several of them have been clinically used.[3] Shen[4] has proposed a hypothetical antiinflammatory receptor site for indomethacin-type nonsteroidal agents, and for optimal receptor interaction, the two aromatic rings in a molecule should be out of plane. We, therefore, carried out the synthesis of the arylacetic acid derivatives containing tricyclic systems, such as dibenz[*b*,*f*]oxepin and dibenzo[*b*,*f*]thiepin, their 10,11-dihydro-11-oxo and 10,11-dihydro-11-hydroxy analogues, and 10,11-dihydro-11-oxodibenz[*b*,*f*][1,4]oxazepin, in which the two benzene rings are held in a noncoplanar orientation by the two-atom bridge, and subjected them to biological tests. Consequently, it was found that 2-(8-methyl-10,11-dihydro-11-oxodibenz[*b*,*f*]oxepin-2-yl)propionic acid (**16b**) and its thiepin analogue (**16c**) were highly active as



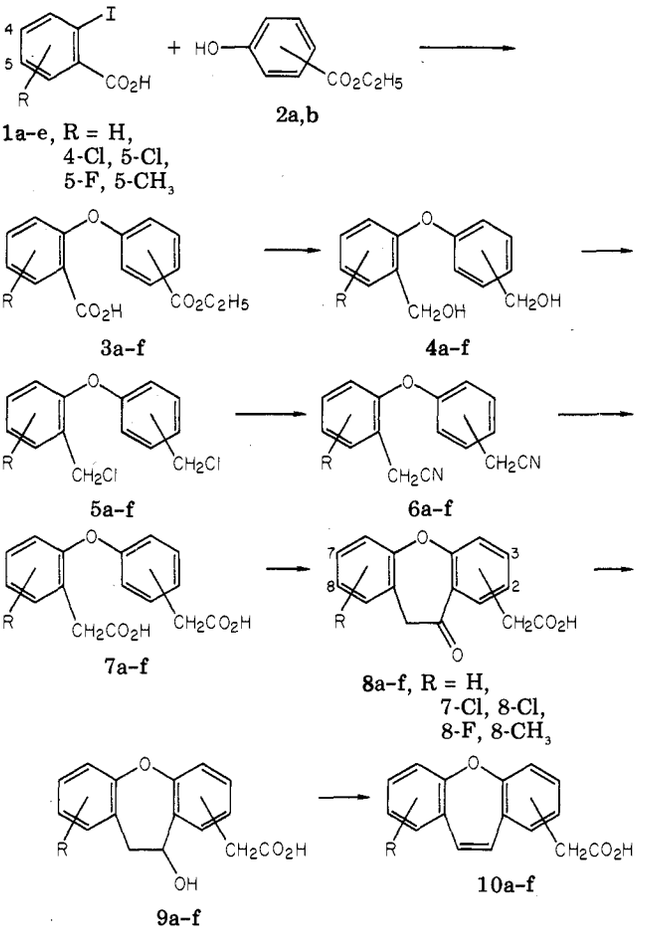
16b, X = O
c, X = S

antiinflammatory, analgesic, and antipyretic agents. Based on these data, they have been selected for further study.

Recently, the Nippon Chemiphar group has reported an analogous study in a patent[5] independently of our work.[6]

Chemistry. Dibenz[*b*,*f*]oxepinacetic acid derivatives (**8–10**) have been synthesized by the route shown in Scheme I. Ullmann reaction between 2-iodobenzoic acids **1** and ethyl hydroxybenzoates **2** gave the diphenyl ethers **3**, which were reduced with lithium aluminum hydride to afford the diols **4**. On chlorination, followed by reaction with sodium cyanide, **4** gave the bis(cyanomethyl) derivatives **6**. Hydrolysis of **6** and subsequent cyclization with

Scheme I



polyphosphoric acid (PPA) gave 10,11-dihydro-11-oxodibenz[*b*,*f*]oxepinacetic acids **8**. Reduction of **8** with sodium borohydride gave the 11-ol derivatives **9**, which were dehydrated with PPA to afford dibenz[*b*,*f*]oxepinacetic acids **10**.

Dibenz[*b*,*f*]oxepin- and dibenzo[*b*,*f*]thiepinpropionic acid derivatives (**16–18**) have been synthesized by the general route shown in Scheme II. Ullmann reaction between 2-iodoacetophenones **11** and 4-substituted phenylpropionates **12** gave the diphenyl ethers and thioether **13**, which were subjected to Willgerodt reaction, followed by acid hydrolysis, to afford the dicarboxylic acids **15**. Cyclization of **15** gave the propionic acids **16**, which were converted into the 11-ols **17** and their dehydrated products **18** in the similar procedure mentioned above.

Dibenz[*b*,*f*][1,4]oxazepin derivatives **25** were prepared from *o*-bromonitrobenzene **19** and hydroxyphenylpropionates **20**, which were subjected to Ullmann reaction and then hydrogenation to afford the diphenyl ethers **22** (Scheme III). Treatment of **22** with phosgene, followed by cyclization with aluminum trichloride ($AlCl_3$), afforded

(1) Yasutaka Nagai, Akira Irie, Hideo Nakamura, Katsuhiko Hino, Hitoshi Uno, and Haruki Nishimura, Abstracts, 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, Apr, 1981, p 351.
(2) (a) R. A. Scherrer and M. W. Whitehouse, Eds., "Antiinflammatory Agents. Chemistry and Pharmacology", Academic Press, New York, 1974. (b) S. Wong, *Annu. Rep. Med. Chem.*, **10**, 172–181 (1975), and previous papers in this series.
(3) (a) S. S. Adams, K. F. McCullough, and J. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, **178**, 115 (1969). (b) L. Julou and J. C. Guyonnet, *J. Pharmacol.*, **2**, 259 (1971). (c) A. Roszkowski, W. H. Rooks, A. J. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, **179**, 114 (1971). (d) S. Wong, J. F. Gardocki, and T. P. Pruss, *ibid.*, **185**, 127 (1973).
(4) T. Y. Shen, "Non-steroidal Anti-inflammatory Drugs", Excerpta Medica, Amsterdam, 1965, p 13.
(5) Nippon Chemiphar Co., German Offen. 2754561 (1979); *Chem. Abstr.*, **91**, 39448*f* (1979).
(6) Dainippon Pharmaceutical Co., Japan Kokai 122284 (1979).

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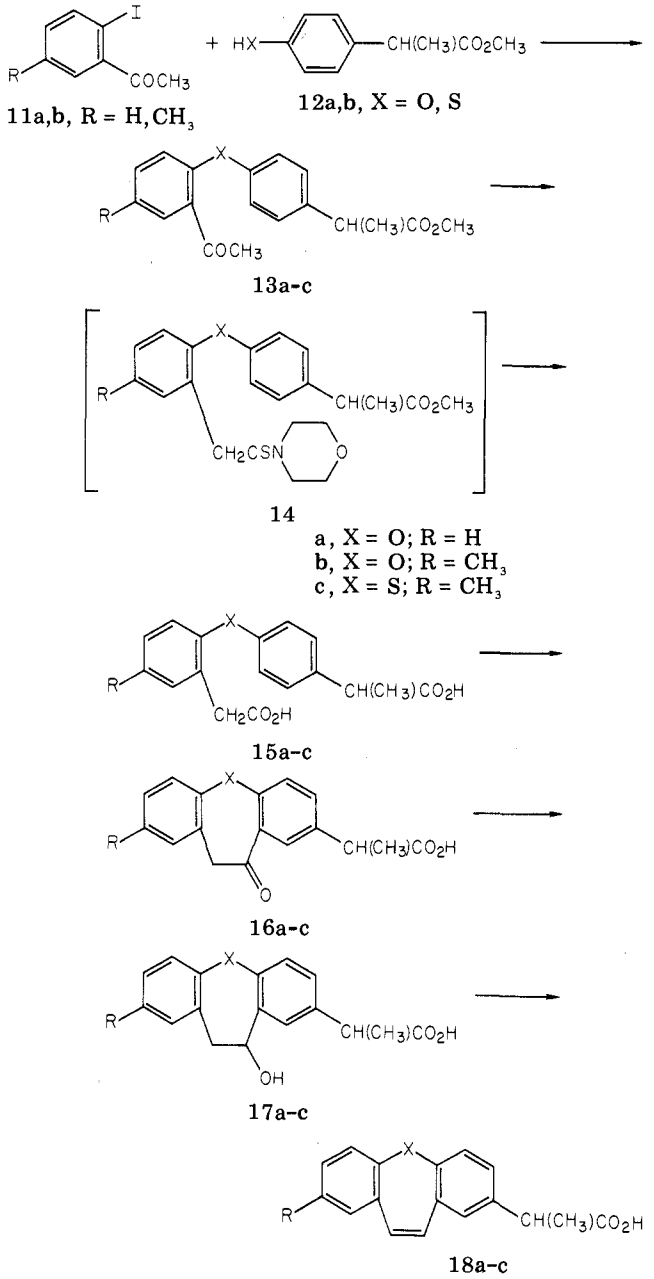
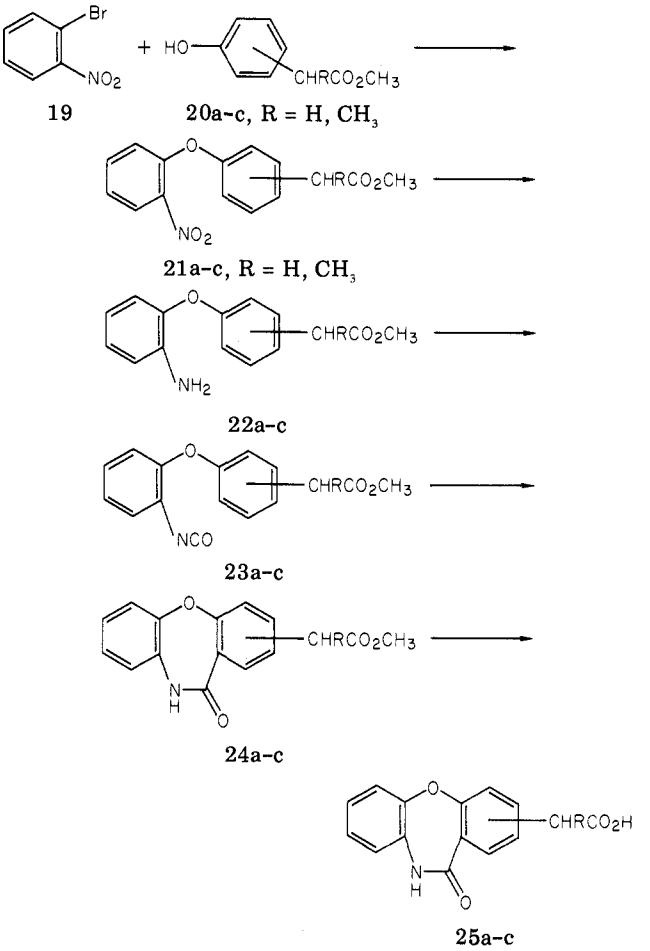
Scheme II



Scheme III



the oxazepinpropionates **24**, which were converted to the acids **25** by hydrolysis.

Pharmacological Results and Discussion

The antiinflammatory and analgesic activities of the compounds obtained in this study were initially measured using the carrageenan paw edema and the phenylquinone writhing assays, respectively (see the Experimental Section). Median effective doses (ED_{50}) were determined for the compounds that showed activity at 80 mg/kg for the former and at 100 mg/kg for the latter.

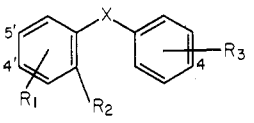
As to the antiinflammatory activity, 10,11-dihydro-11-oxodibenz[*b,f*]oxepin-2-acetic acid (**8a**) was far more potent than the 3-acetic acid **8f**. The introduction of a halogen atom on the benzene ring of **8a** caused a decrease of the activity (e.g., **8b–d**). However, the introduction of a methyl group at the 8-position of **8a** increased the potency significantly (e.g., **8e**). When a methyl group was introduced to the α-position of the acetic acid moiety of **8a**, the potency increased markedly (e.g., **16a**), but in the case of the 8-methyl analogue **8e**, which had potent activity, such introduction did not produce a marked change in potency (e.g., **16b**). Replacement of the oxygen atom in the 5-position of **16b** by the often bioisosteric sulfur atom led, as expected, to a similar order of potency as the parent (e.g., **16c**).

Variation in the center ring of the 10,11-dihydro-11-oxodibenz[*b,f*]oxepin and -dibenzo[*b,f*]thiepin nuclei tended to reduce the antiinflammatory activity. Reduction of the oxo group in the 11-position to an hydroxy group (e.g., **9** and **17**) and the introduction of a double bond between the 10- and 11-position (e.g., **10** and **18**) dramatically caused a decrease or elimination of the activity. The dibenz[*b,f*][1,4]oxazepinacetic acid derivatives **25**, in which the methylene group at the 10-position of the 10,11-dihydro-11-oxodibenz[*b,f*]oxepin nucleus is replaced by an amino group, also did not retain any potency. These facts suggest that although the conformational structure to satisfy the requirements of Shen's receptor model may be very important in determining the activity at the site of action, the overall in vivo activity is also affected by pharmacodynamics and other factors.

As to the analgesic activity, **8a**, **8e**, **10b**, and **16a–c** showed potent activity. Therefore, it is suggested that the structural requirements for this activity in general seem to be parallel to those for the antiinflammatory activity. There was, however, one case (e.g., **10b**) for which the analgesic potency would not have been correctly predicted on the basis of this parallelism.

In consideration of the efficacy of the compounds in both assays, **16b** and **16c** were selected for further pharmacological tests. The results obtained are shown in Table III. Measurement was made of the effect on the ultraviolet-induced erythema in guinea pigs for antiinflammatory activity. Both compounds were considerably more potent

Table I. Chemical Data on Various Intermediates



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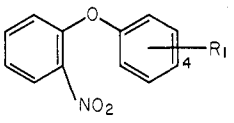

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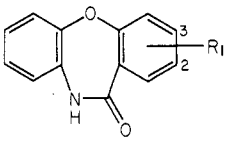

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no.	X	R_1	R_2	R_3	yield, %	mp, °C	recrystn solvent	formula[a]
3a	O	H	CO_2H	4-$CO_2C_2H_5$	72	152-153	dil EtOH	$C_{16}H_{14}O_5$
3b	O	5'-Cl	CO_2H	4-$CO_2C_2H_5$	45	152-154	dil EtOH	$C_{16}H_{13}ClO_5$
3c	O	4'-Cl	CO_2H	4-$CO_2C_2H_5$	41	oil		$C_{16}H_{13}ClO_5$
3d	O	4'-F	CO_2H	4-$CO_2C_2H_5$	49	135-140	toluene	$C_{16}H_{13}FO_5$
3e	O	4'-CH_3	CO_2H	4-$CO_2C_2H_5$	50	80-90	toluene	$C_{17}H_{16}O_5$
3f	O	H	CO_2H	3-$CO_2C_2H_5$	52	136-138	dil EtOH	$C_{16}H_{14}O_5$
6a	O	H	CH_2CN	4-CH_2CN	73	oil		$C_{16}H_{12}N_2O$
6b	O	5'-Cl	CH_2CN	4-CH_2CN	66	121-123	ether	$C_{16}H_{11}ClN_2O$
6c	O	4'-Cl	CH_2CN	4-CH_2CN	60	oil		$C_{16}H_{11}ClN_2O$
6d	O	4'-F	CH_2CN	4-CH_2CN	69	oil		$C_{16}H_{11}FN_2O$
6e	O	4'-CH_3	CH_2CN	4-CH_2CN	49	oil		$C_{17}H_{14}N_2O$
6f	O	H	CH_2CN	3-CH_2CN	53	oil		$C_{16}H_{12}N_2O$
7a	O	H	CH_2CO_2H	4-CH_2CO_2H	57	150-152	EtOH-toluene	$C_{16}H_{14}O_5$
7b	O	5'-Cl	CH_2CO_2H	4-CH_2CO_2H	69	183-184	EtOH-toluene	$C_{16}H_{13}ClO_5$
7c	O	4'-Cl	CH_2CO_2H	4-CH_2CO_2H	69	164-165	EtOH-toluene	$C_{16}H_{13}ClO_5$
7d	O	4'-F	CH_2CO_2H	4-CH_2CO_2H	74	154-155	EtOH-toluene	$C_{16}H_{13}FO_5$
7e	O	4'-CH_3	CH_2CO_2H	4-CH_2CO_2H	73	159-160	EtOH-toluene	$C_{17}H_{16}O_5$
7f	O	H	CH_2CO_2H	3-CH_2CO_2H	66	133-134	EtOH-toluene	$C_{16}H_{14}O_5$
15a	O	H	CH_2CO_2H	4-$CH(CH_3)CO_2H$	45	170-172	EtOH-toluene	$C_{17}H_{16}O_5$
15b	O	4'-CH_3	CH_2CO_2H	4-$CH(CH_3)CO_2H$	43	129-132	EtOH-toluene	$C_{18}H_{18}O_5$
15c	S	4'-CH_3	CH_2CO_2H	4-$CH(CH_3)CO_2H$	32	145-146	toluene	$C_{18}H_{18}O_4S$
21a		4-$CH_2CO_2CH_3$			46	oil		$C_{15}H_{13}NO_5$
21b		4-$CH(CH_3)CO_2CH_3$			44	oil		$C_{16}H_{15}NO_5$
21c		3-$CH_2CO_2CH_3$			49	oil		$C_{15}H_{13}NO_5$
24a		2-$CH_2CO_2CH_3$			42	112	ether	$C_{16}H_{13}NO_4$
24b		2-$CH(CH_3)CO_2CH_3$			43	147-148	ether	$C_{17}H_{15}NO_4$
24c		3-$CH_2CO_2CH_3$			26	174-175	ether	$C_{16}H_{13}NO_4$

[a] All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values.

than indomethacin. As for the analgesic activity measured according to the acetic acid induced writhing and silver nitrate induced arthritic pain method, they were comparable or more active than indomethacin. The antipyretic activity was also examined in yeast-induced fever assay. They were at least ten times as potent as indomethacin. In addition, the induction of gastric ulcers was tested, and they tended to be less potent than indomethacin. They had far lower acute toxicity as compared with indomethacin.

From the pharmacological and toxicological points of view, **16b** and **16c** showed good potential as antiinflammatory, analgesic, and antipyretic agents. In particular, their antipyretic activities would be the strongest among the existing drugs. Further studies are in progress and will be published elsewhere.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on a Hitachi EPI-S2 spectrometer. Organic extracts were dried over $MgSO_4$.

Ethyl (2'-Carboxyphenoxy)benzoates (3). A mixture of **1** (0.04 mol), **2** (0.04 mol), K_2CO_3 (8.3 g, 0.06 mol), and Cu (0.2 g) in nitrobenzene (13 mL) was heated at 140–150 °C with stirring for 30 min. After the addition of H_2O, the mixture was made acidic with dilute HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with aqueous $NaHCO_3$ and then the extract was made acidic with dilute HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and concentrated. The crude product, if solid, was recrystallized; if an oil, it was purified by chromatography on silica gel with $CHCl_3$–MeOH (10:1).

[2'-(Cyanomethyl)phenoxy]benzylnitriles (6). A solution of **3** (0.1 mol) in dry tetrahydrofuran (THF; 100 mL) was added to a stirred suspension of lithium aluminum hydride (7.6 g, 0.2 mol) in dry THF (250 mL) at room temperature. The mixture was heated under reflux with stirring for 4 h and then cooled and treated with H_2O. The resulting mixture was concentrated, and to the residue was added dilute HCl. The solution was extracted with $CHCl_3$, and the extract was dried and concentrated. The oily residue (**4**) was used for the next step without further purification.

To a solution of crude **4** in $CHCl_3$ (150 mL) was added thionyl chloride (36 g, 0.3 mol) dropwise at room temperature, and the mixture was heated under reflux for 1 h and concentrated. To the residue was added dilute NH_4OH, and the mixture was extracted with toluene. The extract was dried and concentrated to give crude **5** as an oily product, which was used for the next step.

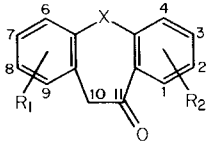
A solution of crude **5** and sodium cyanide (12 g, 0.2 mol) in a mixture of dioxane (90 mL), EtOH (90 mL), and H_2O (45 mL) was heated under reflux for 6 h and concentrated. To the residue was added toluene, and the solution was dried and concentrated. The crude product, if solid, was recrystallized from ether; if an oil, it was purified by chromatography on silica gel with $CHCl_3$–hexane (1:2): IR (film) ν 2250 (C≡N) cm^{-1}.

[2'-(Carboxymethyl)phenoxy]phenylacetic Acids (7). A solution of **6** (0.1 mol) and KOH (40 g, 0.71 mol) in a mixture of EtOH (300 mL) and H_2O (75 mL) was heated under reflux with stirring for 16 h, and EtOH was removed in vacuo. The residue was acidified with HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated. The residue was recrystallized from EtOH and toluene to give **7**.

2-[4-[2'-(Carboxymethyl)phenoxy(or phenylthio)]-phenyl]propionic Acids (15). A mixture of **11** (0.05 mol), **12** (0.05 mol), K_2CO_3 (6.8 g, 0.05 mol), and Cu (1.0 g) in pyridine (15 mL) was heated at 140–150 °C with stirring for 3 h. After the mixture was cooled, $CHCl_3$ was added. The resulting solution was washed with dilute HCl and H_2O, dried, and concentrated to give crude **13** as an oily product.

To crude **13** were added sulfur (2.2 g, 0.069 mol) and morpholine (8.5 g, 0.1 mol), and the resulting mixture was heated at 140–150

Table II. Chemical and Pharmacological Data on Tricyclic Acetic Acids



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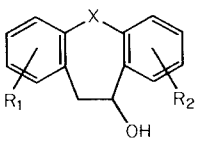

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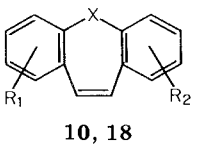

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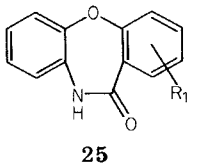

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no.	X	R_1	R_2	yield, %	mp, °C	recrystn solvent	formula[a]	ED_{50}, mg/kg po CPE[b]	ED_{50}, mg/kg po PQW[c]
8a	O	H	2-CH_2CO_2H	68	158-160	toluene-EtOH	$C_{16}H_{12}O_4$	10.8 (3.44-34.0)[d]	34.4 (15.9-74.4)
8b	O	7-Cl	2-CH_2CO_2H	65	183-185	EtOH	$C_{16}H_{11}ClO_4$	⩾80	>100
8c	O	8-Cl	2-CH_2CO_2H	85	191-193	EtOH	$C_{16}H_{11}ClO_4$	⩾80	⩾100
8d	O	8-F	2-CH_2CO_2H	80	177-179	dil EtOH	$C_{16}H_{11}FO_4$	⩾80	>100
8e	O	8-CH_3	2-CH_2CO_2H	84	154-155	toluene-EtOH	$C_{17}H_{14}O_4$	2.20 (1.00-4.82)	13.8 (5.73-74.4)
8f	O	H	3-CH_2CO_2H	56	143-145	toluene	$C_{16}H_{12}O_4$	56.9 (14.0-231)	⩾100
16a[e]	O	H	2-$CH(CH_3)CO_2H$	70	152-154	toluene	$C_{17}H_{14}O_4$	3.65 (1.65-8.08)	17.8 (4.19-75.2)
16b	O	8-CH_3	2-$CH(CH_3)CO_2H$	64	128-129	toluene	$C_{18}H_{16}O_4$	3.38 (2.17-5.27)	6.51 (2.44-17.4)
16c	S	8-CH_3	2-$CH(CH_3)CO_2H$	63	157-159	toluene	$C_{18}H_{16}O_3S$	2.08 (1.29-3.36)	3.10 (1.42-6.76)
9a	O	H	2-CH_2CO_2H	72	172-174	toluene-EtOH	$C_{16}H_{14}O_4$	24.3 (8.73-67.6)	44.6 (13.7-146)
9b	O	7-Cl	2-CH_2CO_2H	79	130-132	toluene-MeOH	$C_{16}H_{13}ClO_4$	>80	>100
9c	O	8-Cl	2-CH_2CO_2H	86	184-185	dil EtOH	$C_{16}H_{13}ClO_4$	>80	>100
9d	O	8-F	2-CH_2CO_2H	80	161-162	dil EtOH	$C_{16}H_{13}FO_4$	>80	>100
9e	O	8-CH_3	2-CH_2CO_2H	75	165-167	ether	$C_{17}H_{16}O_4$	>80	>100
9f	O	H	3-CH_2CO_2H	62	125-130	toluene-EtOH	$C_{16}H_{14}O_4$	>80	>100
17a	O	H	2-$CH(CH_3)CO_2H$	51	144-147	toluene-EtOH	$C_{17}H_{16}O_4$	>80	>100
17b	O	8-CH_3	2-$CH(CH_3)CO_2H$	92	oil		$C_{18}H_{18}O_4$	>80	>100
17c	S	8-CH_3	2-$CH(CH_3)CO_2H$	87	180-182	ether-PE[f]	$C_{18}H_{18}O_3S$	>80	>100
10a[g]	O	H	2-CH_2CO_2H	56	193-195	toluene-EtOH	$C_{16}H_{12}O_3$	28.3 (20.2-39.6)	>100
10b	O	7-Cl	2-CH_2CO_2H	89	210-213	THF-ether	$C_{16}H_{11}ClO_3$	61.4 (15.8-239)	9.53 (5.34-17.0)
10c	O	8-Cl	2-CH_2CO_2H	83	195-197	dil EtOH	$C_{16}H_{11}ClO_3$	>80	>100
10d	O	8-F	2-CH_2CO_2H	68	212-214	EtOH	$C_{16}H_{11}FO_3$	>80	>100
10e	O	8-CH_3	2-CH_2CO_2H	15	175-179	acetone	$C_{17}H_{14}O_3$	>80	
10f	O	H	3-CH_2CO_2H	44	169-171	toluene	$C_{16}H_{12}O_3$	>80	>100
18a	O	H	2-$CH(CH_3)CO_2H$	16	162-164	toluene	$C_{17}H_{14}O_3$	⩾80	>100
18b	O	8-CH_3	2-$CH(CH_3)CO_2H$	15	158-160	toluene	$C_{18}H_{16}O_3$	>80	>100
18c	S	8-CH_3	2-$CH(CH_3)CO_2H$	25	120-123	ether-PE	$C_{18}H_{16}SO_2$	>80	>100
25a		2-CH_2CO_2H		89	241-242	dil MeOH	$C_{15}H_{11}NO_4$	>80	>100
25b		2-$CH(CH_3)CO_2H$		96	205-206	dil MeOH	$C_{16}H_{13}NO_4$	>80	>100
25c		3-CH_2CO_2H		87	223-224	dil MeOH	$C_{15}H_{11}NO_4$	>80	>100
indomethacin								3.30 (2.10-7.30)	0.62 (0.61-0.63)

[a] All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values. [b] CPE = carrageenan paw edema. [c] PQW = phenylquinone writhing. [d] 95% confidence limits. [e] See ref 5. [f] PE = petroleum ether. [g] See ref 15.

Table III. Pharmacological Data on Tricyclic 11-Oxo Propionic Acids

no.	X	ED$_{50}$, mg/kg po					gastric ulcer UD$_{50}$, mg/kg (rats), po	LD$_{50}$, mg/kg (rats), po
		CPE[a] (rats)	UV erythema (guinea pigs)	PQW[b] (mice)	acetic acid writhing (rats)	$AgNO_3$ pain (rats)	yeast fever (rats)		
16b	O	3.38	0.30	6.51	0.28	2.60	0.021	13.8	147
		(2.17–5.27)[c]	(0.079–1.10)	(2.44–17.4)	(0.128–0.591)	(1.25–6.86)	(0.012–0.036)	(8.96–21.3)	(99.0–217)
16c	S	2.08	0.85	3.10	0.84	1.41	0.015	11.3	⩾100
		(1.29–3.36)	(0.35–3.55)	(1.42–6.76)	(0.54–1.30)	(0.62–3.20)	(0.007–0.029)		
indomethacin		3.30	9.12	0.62	0.44	4.30	0.22	8.0	18.5
		(2.10–7.30)	(5.73–14.5)	(0.61–0.63)	(0.224–0.870)	(2.00–8.10)	(0.104–0.480)		(13.0–23.7)

[a] CPE = carrageenan paw edema. [b] PQW = phenylquinone writhing. [c] 95% confidence limits.

°C with stirring for 5 h. After the mixture was cooled, $CHCl_3$ was added to the reaction mixture. The solution was washed with dilute HCl and H_2O and concentrated to give crude **14**.

The crude thiomorpholide **14** was dissolved in a mixture of acetic acid (90 mL), concentrated H_2SO_4 (16 mL), and H_2O (30 mL), and the solution was heated under reflux for 6 h. The reaction mixture was poured into H_2O, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and then extracted with aqueous $NaHCO_3$. The extract was made acidic with dilute HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and concentrated. The residual solid was recrystallized from a suitable solvent to give **15**.

Tricyclic 11-Oxo Acetic Acids (8 and 16). A mixture of **7** (or **15**) (0.02 mol) and PPA (50 g) was heated at 130 °C with stirring for 30 min. The solution was poured into ice–H_2O, and the resulting mixture was extracted with ethyl acetate. The extract was washed with H_2O, dried, and concentrated. The residue was recrystallized from a suitable solvent to give **8** (or **16**).

Tricyclic 11-Hydroxy Acetic Acids (9 and 17). To a solution of **8** (or **16**) (0.01 mol) in EtOH (30 mL) was added sodium borohydride (0.013 mol) with ice cooling, and the resultant solution was heated under reflux for 1 h. The solution was concentrated, and to the residue was added dilute HCl. The mixture was extracted with $CHCl_3$, and the extract was dried and concentrated. The crude product, if solid, was recrystallized from a suitable solvent; if an oil, it was purified by chromatography on silica gel with $CHCl_3$–MeOH (5:1).

Tricyclic Unsaturated Acetic Acids (10 and 18). A mixture of **9** (or **17**) (0.01 mol) and PPA (30 mL) was heated at 110 °C with stirring for 1.5 h. The mixture was poured into ice–H_2O, and the resulting mixture was extracted with $CHCl_3$. The extract was dried and concentrated. The residue was recrystallized from a suitable solvent to give **10** (or **18**).

Methyl (2′-Nitrophenoxy)phenylacetates (21). Compound **19** (6.8 g, 0.034 mol) was added slowly to a mixture of **20** (0.034 mol) and KOH (1.89 g, 0.034 mol) at 150 °C with stirring, and the mixture was stirred at the same temperature for 30 min. After the addition of H_2O, the mixture was made acidic with dilute HCl and extracted with ether. The extract was washed with H_2O, dried, and concentrated. To the residue were added MeOH (100 mL) and concentrated H_2SO_4 (0.2 mL), and the resulting solution was heated under reflux for 30 min. The solution was poured into ice–H_2O, and the mixture was extracted with ether. The extract was dried and concentrated. The residue was chromatographed on silica gel (50 g), and the fraction eluted with toluene gave **21** as an oily product.

Methyl 10,11-Dihydro-11-oxodibenz[*b*,*f*][1,4]oxazepin-2-acetates (24). To a solution of **21** (0.03 mol) in MeOH (50 mL) was added PtO_2 (70 mg), and the mixture was submitted to catalytic hydrogenation under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst was removed by filtration. The filtrate was concentrated to give crude **22** as an oily product in quantitative yield.

Into a solution of crude **22** in toluene (60 mL) was passed $COCl_2$ under ice cooling for 30 min and then on the water bath for 30 min, and the resulting solution was concentrated. The oily residue (**23**) was used for the next step: IR (film) ν 2230 (NCO) cm^{-1}.

A solution of crude **23** in *o*-dichlorobenzene (35 mL) was added to a suspension of pulverized $AlCl_3$ (4 g, 0.03 mol) in *o*-dichlorobenzene (35 mL) at 100 °C with stirring during 15 min, and the mixture was heated at 150 °C with stirring for 1 h. The resulting mixture was poured into ice–H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated. The residue was chromatographed on silica gel (100 g) and eluted with $CHCl_3$. The crude product was recrystallized from ether to give **24**.

10,11-Dihydro-11-oxodibenz[*b*,*f*][1,4]oxazepin-2-acetic Acids (25). To a solution of **24** (0.01 mol) in a mixture of MeOH (25 mL) and dioxane (20 mL) was added 10% NaOH (20 mL), and the solution was stirred at room temperature for 30 min. The resulting solution was made acidic with dilute HCl under ice cooling. The precipitate was collected and recrystallized from dilute MeOH to give **25**.

Pharmacology Methods. Materials. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and administered.

Statistics. ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[7]

Carrageenan-Induced Paw Edema (CPE).[8] Five to ten male rats of the Wistar strain, weighing 120–150 g, were used per dose. Hind paw edema was induced by a subcutaneous injection of a 1% carrageenan aqueous solution into the left hind paw. ED_{50} was determined 3 h after carrageenan injection.

Phenylquinone-Induced Writhing (PQW).[9] Five to fifteen female mice of the ddN strain, weighing 18–22 g, were used per dose. The writhing was induced by an intraperitoneal injection of phenylquinone (0.03%), and the number of writhes was calculated for 15 min.

Ultraviolet-Induced Erythema.[10] Erythema was induced on the depilated skin of the dorsal trunk of female guinea pigs of the Hartlet strain (350–450 g). ED_{50} was determined 3 h after irradiation of ultraviolet light.

Acetic Acid Induced Writhing.[11] The writhing was induced by an intraperitoneal injection of a 1% acetic acid aqueous solution in male Wistar rats (90–120 g).

Silver Nitrate Induced Arthritic Pain.[12] Arthritis was induced by an injection of a 1% silver nitrate aqueous solution into the ankle joint of right hind leg of male Wistar rats (130–180 g).

Antipyretic Assay.[13] Hyperthermia was induced by a subcutaneous injection of a 15% yeast suspension in male Wistar rats (350–500 g).

Gastric Ulcer Assay.[14] Male Wistar rats were used. The rats, fasted for 24 h, were sacrificed 6 h after a single oral administration of test compounds, and the stomach was removed and macroscopically observed. The dose (UD_{50}) producing ulcers in 50% of the rats was calculated according to the regression line of each compound.

Acute Lethal Toxicity. LD_{50} was determined from the 7-day mortality in male Wistar rats (150–230 g).

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1,1,2-Triphenylbut-1-enes: Relationship between Structure, Estradiol Receptor Affinity, and Mammary Tumor Inhibiting Properties

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1,1,2-Triphenylbut-1-enes, which are substituted with acetoxy groups on one, two, or three aromatic rings in the para and/or meta positions, were synthesized. The identity of the occurring *E* and *Z* isomers were established by ^1H NMR spectroscopy. A study on structure–activity relationships was carried out with regard to estradiol receptor affinity and to inhibiting effects on the growth of a postmenopausal human mammary carcinoma implanted in nude mice. The para-substituted compounds generally exhibited a higher receptor affinity and a better antitumor activity than the corresponding meta-substituted ones. The *E* isomers were superior to the respective *Z* isomers in those two properties. The tumor-inhibiting effect of the mono- and disubstituted compounds was better than that of the trisubstituted ones. Except for the trisubstituted compounds, they all showed a good correlation between estradiol receptor affinity and antitumor activity. One of the compounds was also tested on the 9,10-dimethylbenz[*a*]-anthracene-induced, hormone-dependent mammary carcinoma of the Spraque–Dawley rat, and the results corresponded to those obtained in the xenograft tumor.

Many compounds of the triarylethylene type have been tested with regard to their mammary tumor inhibiting properties.[1] One of these compounds, tamoxifen, is now widely used for the treatment of advanced breast cancer.[1] It is of great interest that the *E* isomer of tamoxifen[2] and the metabolite hydroxytamoxifen[2] show contrasting biological properties concerning estradiol receptor affinity, uterotrophic and antiuterotrophic activity, and mammary tumor inhibiting effects. For example, the estradiol receptor affinity of tamoxifen (*Z* configuration) is higher than that of its *E* isomer.[3] Furthermore, compared with ta-

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