p-$(EtO)_2P(O)CH_2C_6H_4CN$, 1552-41-6; o-$H_2NC_6H_4NH_2$, 95-54-5; cyclohexanone, 108-94-1; 3,5-dichloro-4-hydroxypyridine, 17228-71-6; 4-piperidone hydrochloride, 41979-39-9; 1-hydroxyisoquinoline, 491-30-5; 1,2,3,4-tetrahydro-2,4-dioxopyrimidine, 66-22-8; 4-hydroxypyridine, 626-64-2; 3-hydroxypyridazine, 504-30-3; 1,4,5,6-tetrahydropyridazin-6-one, 61468-81-3; pyrimidin-4-ol, 4562-27-0; 6-hydroxy-3-pyridazinecarboxylic acid ethyl ester, 63001-31-0; 1,1-dioxo-3,4,5,6-tetrahydro-1,2-thiazine, 37441-50-2; 2-hydroxypyrazine, 6270-63-9; pyrimidin-2-ol hydrochloride, 38353-09-2; 1-hydroxy-2,3-benzodiazine, 119-39-1; 3-hydroxypyridine, 109-00-2; 4-pyridinecarbonyl chloride, 14254-57-0; chloroacetone, 78-95-5; 2,4-dichlorobenzaldehyde, 874-42-0; ethylenediamine, 107-15-3; 3,4-diaminopyridine, 54-96-6; 2,3-diaminopyridine, 452-58-4; 2-pyrrolidinone, 616-45-5.

Synthesis and Antiinflammatory Activity of *cis*- and *trans*-6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic and -oxepinacetic Acids

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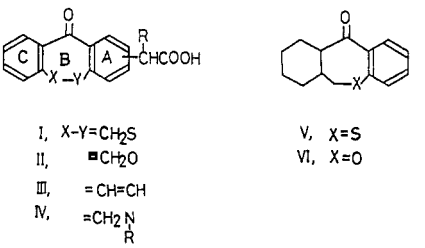
A series of *cis*- and *trans*-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids (**6–9**) and -oxepinacetic acids (**10–13**) were prepared and their antiinflammatory activity was examined in the rat carrageenan hind paw edema test. The antiinflammatory activity of these compounds depended on their stereochemical feature (C6a, C10a, and C2′). The 6a,10a-trans compounds exhibited considerable antiinflammatory activity, whereas the 6a,10a-cis compounds were inactive. Among the trans compounds, 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-propionic acid (**9a**) and its oxepin analogue (**13a**) showed an antiinflammatory activity superior to that of indomethacin. The phenethyl ester (**25**) of **9a** showed potent antiinflammatory activity, and its safety index (UD_{50}/ED_{50}) was over 14 times higher than that of indomethacin. The phenethyl ester (**25**) is the most favorable compound with high antiinflammatory activity and little ulcerogenicity.

Vane et al.[1] found that nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin and indomethacin had an inhibitory activity on prostaglandin biosynthesis and this activity was correlative with their antiinflammatory activity. Shen[2] has proposed an interesting hypothesis concerning the receptor-site model for NSAIDs.

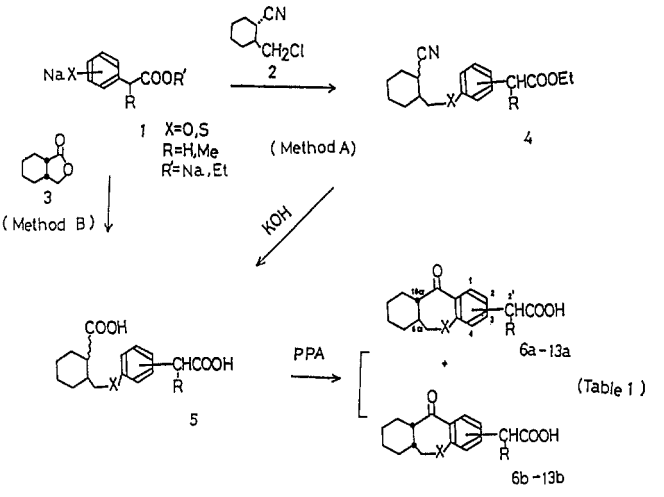
Many tricyclic arylacetic acids having a 6–7–6-membered ring have recently been reported as potent antiinflammatory agents, for example, dibenzothiepin- (I),[3] dibenzoxepin- (II),[4] dibenzotroponone- (III),[5] and dibenzazepinacetic acids (IV).[6] In each of these, two six-membered rings consist of benzene rings.

Since it is of interest for us to examine the effect of partial saturation of the 6–7–6-ring system on the antiinflammatory properties of this class of NSAIDs, we had studied 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin (V) and -oxepin (VI) derivatives[7] (Chart I). As an extension of these works, we now wish to report the synthesis and preliminary pharmacological evaluation of a number of octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids (**6–9**) and their oxepin analogues (**10–13**). Some of them were highly active in animal models as NSAIDs. On the basis of these data, compound **9a** appears to offer several advantages over indomethacin.

Chart I



Scheme I



In the clinical use of NSAIDs, gastrointestinal lesions have been the most troublesome problem. In order to lessen this side effect, **9a** was led to its esters and amides. Among the synthesized compounds, the phenethyl ester (**25**) of **9a** showed a potent antiinflammatory activity and weak irritative effect on gastric mucosa, and hence was selected for further investigation.

Chemistry. The *cis*- and *trans*-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids (**6–9**) and -oxepinacetic acids (**10–13**) were synthesized by the two

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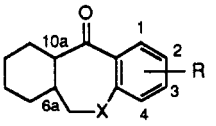
(6) Dunn, J. P.; Muchowski, J. M.; Nelson, P. H. *J. Med. Chem.* **1981**, *24*, 1097.
(7) Kurokawa, M.; Yoshida, K.; Nagai, Y.; Uno, H. *Chem. Pharm. Bull.* **1983**, *31*, 4312.

0022-2623/90/1833-0504$02.50/0

Table I. Chemical and Pharmacological Data for Octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic Acids and -oxepinacetic Acids



compd	R	X	cis or trans[a]	ratio of isomer[b] A/B	chemical shift, δ, and multiplicity for CH_3[i] isomer A	isomer B	method[c]	% yield[d]	mp,[e] °C	recrystn solvent	formula[f]	antiinflam act. CPE:[g] ED_{50} mg/kg po, rats
6a	2-CH_2COOH	S	trans				B	48	155	ether	$C_{16}H_{18}O_3S$	>40
6b	2-CH_2COOH	S	cis				B	3	oil		$C_{16}H_{18}O_3S$	>40
7a	2-$CH(CH_3)COOH$	S	trans	50/50	1.498 d	1.508 d	B	54	oil		$C_{17}H_{20}O_3S$	ca. 40
7b	2-$CH(CH_3)COOH$	S	cis	50/50	1.501 d	1.511 d	B	3	oil		$C_{17}H_{20}O_3S$	>40
8a	3-CH_2COOH	S	trans				A	56	152	AcOEt	$C_{16}H_{18}O_3S$	3.24 (2.27–4.63)[h]
8b	3-CH_2COOH	S	cis				A	3	130	ether	$C_{16}H_{18}O_3S$	>40
9a	3-$CH(CH_3)COOH$	S	trans	50/50	1.510 d	1.517 d	B	70	134	H_2O	$C_{17}H_{20}O_3S$	1.53 (1.07–2.19)
9b	3-$CH(CH_3)COOH$	S	cis	50/50	1.506 d	1.510 d	B	4	145	H_2O	$C_{17}H_{20}O_3S$	>40
10a	2-CH_2COOH	O	trans				A	9	115	toluene	$C_{16}H_{18}O_4$	>40
10b	2-CH_2COOH	O	cis				A	1	138	toluene	$C_{16}H_{18}O_4$	>40
11a	2-$CH(CH_3)COOH$	O	trans	50/50	1.496 d	1.504 d	A	12	oil		$C_{17}H_{20}O_4$	>40
11b	2-$CH(CH_3)COOH$	O	cis	50/50	1.495 d	1.503 d	A	1	oil		$C_{17}H_{20}O_4$	>40
12a	3-CH_2COOH	O	trans				B	17	117	toluene	$C_{16}H_{18}O_4$	22.1 (13.6–35.9)
12b	3-CH_2COOH	O	cis				B	2	144	toluene	$C_{16}H_{18}O_4$	>40
13a	3-$CH(CH_3)COOH$	O	trans	50/50	1.501 d	1.505 d	A	11	oil		$C_{17}H_{20}O_4$	1.52 (0.61–3.71)
13b	3-$CH(CH_3)COOH$	O	cis	50/50	1.501 d	1.506 d	A	1	oil		$C_{17}H_{20}O_4$	>40
9aA	3-$CH(CH_3)COOH$	S	trans	100/0	1.508 d		C	23	181	AcOEt	$C_{17}H_{20}O_3S$	37.1 (25.4–54.3)
9aB	3-$CH(CH_3)COOH$	S	trans	0/100		1.518 d	C	14	162	AcOEt	$C_{17}H_{20}O_3S$	1.89 (1.24–2.88)
9bA	3-$CH(CH_3)COOH$	S	cis	100/0	1.504 d		D	13	191	AcOEt	$C_{17}H_{20}O_3S$	>40
9bB	3-$CH(CH_3)COOH$	S	cis	25/75	1.509 d	1.515 d	D	8	147	AcOEt	$C_{17}H_{20}O_3S$	>40
indomethacin												3.3 (2.1–7.3)

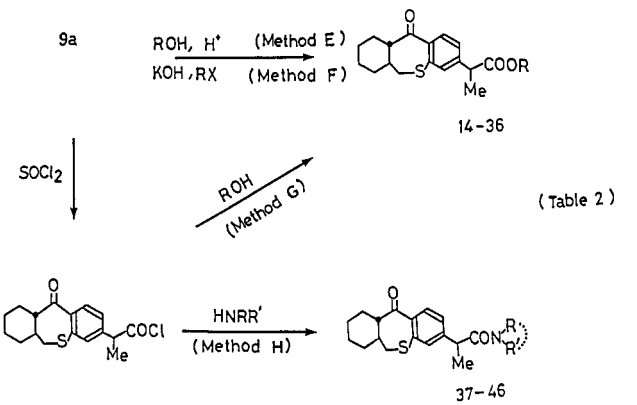
[a] Relative stereochemistry between H6a and H10a. [b] Diastereoisomer A and B. [c] Synthetic methods are described in the Experimental Section. [d] The yield of products (6–13) based on the phenylacetic acids (1). [e] Purities of oily compounds were checked by HPLC and ^1H NMR spectra. [f] All compounds were analyzed for C, H, S; analytical results were within ±0.4% of the theoretical values. [g] Carrageenan hind paw edema. [h] 95% confidence limits. [i] In $CDCl_3$; d = doublet.

routes shown in Scheme I. Reaction of *trans*-2-(chloromethyl)cyclohexanecarbonitrile (**2**)[8] with ethyl 3-mercapto-, 3-hydroxy-, and 4-hydroxyphenylacetates (**1**, as the sodium salts) gave the corresponding cyano esters (**4**), which were then hydrolyzed under alkaline conditions to the diacids (**5**). Cyclization of **5** with polyphosphoric acid (PPA) gave **8**, **10**, **11**, and **13** (method A). On the other hand, *cis*-hexahydrophthalide (**3**)[9] was treated with the disodium salts (**1**) of 3-hydroxyphenylacetic acid, and 3- and 4-mercaptophenylacetic acids to give the diacids (**5**), which were cyclized with PPA to afford **6**, **7**, **9**, and **12** (method B).

The acetic acid derivatives (**6**, **8**, **10**, and **12**) having two asymmetric carbons (C6a and C10a) were obtained as a mixture of two diastereoisomers (cis and trans compounds). On the other hand, the propionic acid derivatives (**7**, **9**, **11**, and **13**) have another asymmetric carbon (C2′), and accordingly, four diastereoisomers could exist. Analyses by HPLC showed that the thiepin analogues (**6–9**) were composed of 95% of the trans compound and 5% of the cis compound, and the oxepin analogues (**10–13**) contained about 12% of the cis compound. The trans (**6a–13a**) and cis compounds (**6b–13b**) were isolated by preparative HPLC. Furthermore, the *trans*-propionic acid (**9a**) was separated by fractional crystallization to give the diastereoisomers A (**9aA**) and B (**9aB**) (method C). Similarly, two cis diastereoisomers A and B (**9bA** and **9bB**) were obtained from the cis compound (**9b**) (method D). Purity and a ratio of the two stereoisomers (A/B) were determined by ^1H NMR spectra.

The cis and trans configurations of the compounds (**6–13**) were assigned on the basis of ^1H NMR analysis, particularly coupling constants.[10] Thus the J_{6a-10a} values

Scheme II



of the compounds (**6a–13a**) were 11.4–11.7 Hz; therefore, **6a–13a** were assignable as trans compounds. On the other hand, the two protons H6a and H10a of **6b–13b** were assigned to be cis, owing to their smaller coupling constants (J = 5.4–7.2 Hz). The relative composition ratio of the diastereoisomers A and B in each compound (**7a**, **7b**, **9a**, **9b**, **11a**, **11b**, **13a**, and **13b**) was determined by chemical shift of the C2′-methyl protons as shown in Table I. For convenience, one isomer of each pair was identified as diastereoisomer A on the basis of an upfield shift of the C2′-methyl signal by 1.5–3.0 Hz/300 MHz compared with that of other isomer (B).

The esters and amides of **9a** were synthesized as shown in Scheme II. Treatment of **9a** with an appropriate alcohol in the presence of a catalytic amount of Lewis acid (method E) afforded the corresponding esters (**14–18**, **22**,

(8) Christol, H.; Donche, A.; Plenat, F. *Bull. Soc. Chim., Fr.* **1966**, 1315.
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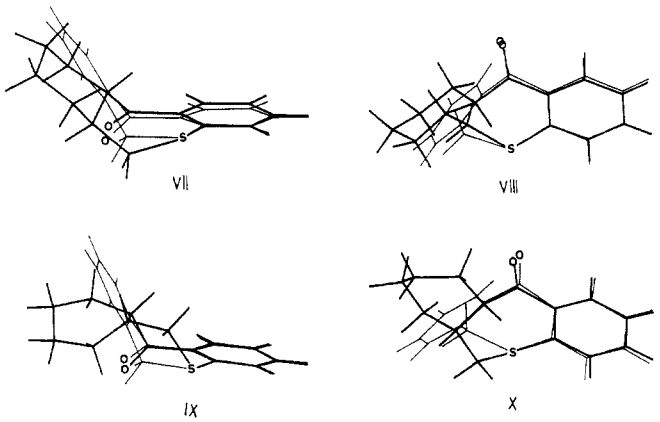

Figure 1. Superimposition of 6,11-dihydro-11-oxodibenzo[*b*,*e*]thiepin (I, light lines) and *trans*-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin (VII and VIII, heavy lines, upper) and *cis*-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin nuclei (IX and X, heavy lines, lower) by the program COMPAR.[12] The benzene ring (A ring), carbonyl carbon, and sulfur atom were subjected to a least-squares fit.

27, 31, and 32). The potassium salt of **9a** was treated with halides in toluene to give the esters (**24**, **25**, **29**, and **30**) (method F). Reaction of **9a** with thionyl chloride ($SOCl_2$), followed by treatment with alcohols (method G), gave the esters (**19–21**, **23**, **26**, **28**, and **33–36**). The amides (**37–46**) were prepared by the reaction of the acid chloride of **9a** with amines (method H).

Pharmacological Results and Discussion. Pharmacological methods are described in the Experimental Section. The antiinflammatory activities of the compounds (**6–13**) were examined by using the carrageenan hind paw edema assay in rats. The compounds were administered orally at a dose of 40 mg/kg. Median effective dose (ED_{50}) for the compounds showing the activity at a dose of 40 mg/kg was determined (Table I).

The antiinflammatory activity of these compounds depended on their stereochemical feature (C6a, C10a, and C2′). All the cis compounds (**6b–13b**) were almost inactive, whereas the trans compounds (**7a**, **8a**, **9a**, **12a** and **13a**) possessed considerable activity. Among the *trans*-thiepin derivatives, the activity of **8a** (ED_{50} = 3.2 mg/kg), having the acetic acid group at C3, was almost equal to that of indomethacin (3.3 mg/kg). Introduction of a methyl group to C2′ of **8a** (giving **9a**) caused an enhancement in activity (1.5 mg/kg). Comparison between the two diastereoisomers (**9aA** and **9aB**) showed that **9aB** was 20 times as potent as **9aA**; this result was in accordance with the fact that one stereoisomer of aryl-α-methylacetic acid type NSAIDs with *S* configuration at the carbon bearing a α-methyl group is more active than another isomer.[11] However, the absolute configuration at C2′ of **9aB** remains to be determined. On the other hand, the activity of **6a** and **7a**, having an acidic group at C2, was lower or nonexistent. Replacement of sulfur atom at position 5 of **9a** with its bioisostere oxygen atom maintained the activity (**13a**, 1.5 mg/kg), whereas this the same conversion for **8a** resulted in a considerable decrease in activity (**12a**, 22 mg/kg).

On the basis of the above results and computer-generated graphics, the conformations of the nuclei of *trans*-**9a**, *cis*-**9b** and dibenzothiepin (I) were determined, and they are depicted in Figure 1. Each of the nuclei of **9a** and **9b** provide two configurational isomers (VII and VIII, and IX and X), and the cyclohexyl rings of the trans (VII and VIII) and cis compounds (IX and X) have chair and boat conformations, respectively. When the molecular models for VII and VIII are compared with that for I, the cyclohexyl rings of VII and VIII practically overlap with the phenyl ring (C ring) of I, whereas IX and X do not. That is, the trans (B/C ring) partial saturation of the dibenzothiepin substantially retains the low-energy conformation of the parent nucleus, whereas the cis partial saturation does not. These findings suggest that the conformations of these tricyclic rings are important to exhibit the antiinflammatory activity.

It was expected that the esterification or amidation of **9a** might give compounds whose ulcerogenicity became lower than that of the parent acid (**9a**) in a sense of reducing their acidity but with retention of the antiinflammatory activity. The esters and amides (**14–46**) were evaluated for the inhibitory activity of carrageenan hind paw edema (Table II) by oral administration to rats at a dose of 5 mg/kg. All the esters (**14–36**) of **9a** possessed a considerable activity; the ethyl (**15**) and phenethyl esters (**25**) showed the highest activity. On the other hand, the activity of the amide derivatives was depended on the substituent of the amide nitrogen. Unsubstituted amide **37**, hydroxamic acid **38**, and amides substituted with hydroxyethyl and carboxymethyl groups (**42** and **43**) were less potent than **15** and **25**.

On the basis of the above results, compounds **9a**, **15**, and **25**, having the high activity in the carrageenan hind paw edema test, were selected for the evaluation of their analgesic activity by the acetic acid writhing assay in rats. Their ulcerogenicity on the stomach was also examined in rats (Table III). Analgesic potency of the ethyl ester (**15**) was better than that of the phenethyl ester (**25**). Compound **25** did not show significant ulcerogenicity at a dose of 124 mg/kg po. The LD_{50} value of **25** in mice was 644 mg/kg po. In comparison with indomethacin, the safety index (UD_{50}/ED_{50}) of **25** was over 14 times higher than that of indomethacin. Compound **25** therefore was suggested to be promising as an antiinflammatory agent with low gastric irritability and low acute toxicity.

Experimental Section

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian XL-300 spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. Infrared (IR) spectra were recorded on a Hitachi 260-10 grating infrared spectrophotometer and mass (EIMS) spectra were done on a JEOL D-300 mass spectrometer. High-performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-4A system. Elemental analyses are given only by symbols of the elements, and analytical results were within ±0.4% of the theoretical values. Organic extracts were dried over Na_2SO_4 and the solvent was removed with a rotatory evaporator under reduced pressure. Purities of oily compounds were checked by HPLC.

The following known compounds were prepared according to the cited literature; 2-(3-hydroxyphenyl)- and 2-(4-hydroxyphenyl)propionic acids,[13] 3-mercaptophenyl-[14] and 4-mercaptophenylacetic acids,[15] and 2-(3-mercaptophenyl)-[16] and 2-(4-mercaptophenyl)propionic acids.[17]

***trans*- and *cis*-2-(6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenz[*b*,*e*]oxepin-3-yl)propionic Acid (13a and 13b). (Method A).** To a stirred solution of ethyl 2-(3-hydroxy-

(11) Juby, P. F.; Goodwin, W. R.; Hudyma, T. W.; Partyka, R. A. *J. Med. Chem.* **1972**, *15*, 1297.
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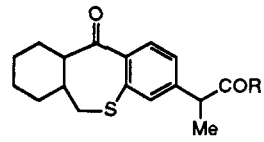
Table II. Chemical and Pharmacological Data for the Ester and Amide Derivatives of *trans*-Octahydro-11-oxodibenzo[*b*,*e*]thiepinpropionic Acid (**9a**)



compd	R	method	% yield	k'[a]	formula[b]	% inhibn CPE[c] 5 mg/kg po, rats
14	OCH_3	E	83	3.01	$C_{18}H_{22}O_3S$	21.6[d]
15	OCH_2H_5	E	80	3.49	$C_{19}H_{24}O_3S$	38.3[e]
16	O-nC_3H_7	E	70	3.93	$C_{20}H_{26}O_3S$	25.4[e]
17	O-iC_3H_7	E	75	3.77	$C_{20}H_{26}O_3S$	25.6[e]
18	O-nC_4H_9	E	84	4.49	$C_{21}H_{28}O_3S$	26.0[e]
19	O-iC_4H_9	G	64	4.39	$C_{21}H_{28}O_3S$	29.3[e]
20	O-nC_5H_{11}	G	65	5.16	$C_{22}H_{30}O_3S$	22.1[d]
21	O-nC_6H_{13}	G	82	6.37	$C_{23}H_{32}O_3S$	28.3[e]
22	—O-⬡	E	8	5.69	$C_{23}H_{30}O_3S$	15.6[e]
23	O-Ph	G	52	3.72	$C_{23}H_{24}O_3S$	22.0[e]
24	OCH_2Ph	F	58	3.85	$C_{24}H_{26}O_3S$	25.6[e]
25	$O(CH_2)_2Ph$	F	74	4.28	$C_{25}H_{28}O_3S$	39.1[e]
26	$O(CH_2)_3Ph$	G	76	4.65	$C_{26}H_{30}O_3S$	26.0[e]
27	$OCH_2CH{=}CH_2$	E	53	3.49	$C_{20}H_{24}O_3S$	33.5[e]
28	$OCH_2CH{=}CHPh$	G	51	4.26	$C_{26}H_{28}O_3S$	20.3[e]
29	OCH_2COPh	F	65	3.12	$C_{25}H_{26}O_4S$	26.6[e]
30	$OCH_2COOC_2H_5$	F	55	3.05	$C_{21}H_{26}O_5S$	20.2[e]
31	$O(CH_2)_2OC_2H_5$	E	53	3.21	$C_{21}H_{28}O_4S$	34.6[e]
32	$O(CH_2)_2O(CH_2)_2OH$	E	39	2.39	$C_{21}H_{28}O_5S$	28.1[e]
33	$O(CH_2)_2$—N⬡O	G	55	2.85	$C_{23}H_{31}NO_4S$	22.2[d]
34	OCH_2-2-Py	G	85	2.81	$C_{23}H_{25}NO_3S$	30.6[e]
35	OCH_2-3-Py	G	58	2.87	$C_{23}H_{25}NO_3S$	29.9[e]
36	$O(CH_2)_2$-2-Py	G	59	3.01	$C_{24}H_{27}NO_3S$	25.5[e]
37	NH_2	H	86	2.07	$C_{17}H_{21}NO_2S$	30.5[e]
38	NHOH	H	79	1.02	$C_{17}H_{21}NO_3S$	29.9[e]
39	$NHCH_3$	H	69	2.22	$C_{18}H_{23}NO_2S$	14.6[d]
40	$N(CH_3)_2$	H	83	2.54	$C_{19}H_{25}NO_2S$	2.7
41	$NHCH_2Ph$	H	62	2.83	$C_{24}H_{27}NO_2S$	−5.5
42	$NH(CH_2)_2OH$	H	83	2.15	$C_{19}H_{25}NO_3S$	22.3[e]
43	$NHCH_2COOH$	H	40	0.97	$C_{19}H_{23}NO_4S$	29.7[e]
44	—N⬡	H	62	3.03	$C_{22}H_{29}NO_2S$	5.3
45	—N⬡O	H	14	2.55	$C_{21}H_{27}NO_3S$	7.1
46	—N⬡NCH_3	H	63	3.01	$C_{22}H_{30}N_2O_2S$	5.3
indomethacin						36.3[e]

[a] Column Develosil $5C_8$, 250 × 4.6 mm i.d.; mobil phase 85% acetonitrile; flow rate 1 mL/min; detection 254 nm. [b] All compounds were analyzed for C, H, N, S; analytical results were within ±0.4% of the theoretical values. [c] Carrageenan hind paw edema: the swelling rate and SE of the vehicle control were 67.1 ± 1.0% (n = 104) at 3 H after carrageenan injection. [d] $0.01 < P < 0.05$. [e] $P < 0.01$, significantly different from the matched vehicle control (n = 8).

Table III. Pharmacological Data for *trans*-Octahydro-11-oxodibenzo[*b*,*e*]thiepinpropionic Acid (**9a**) and Its Ester Derivatives (**15** and **25**)

compd	antiinflam act., CPE:[a] ED_{50}[b]	analgesic act, AcOH writhing: ED_{50}[b]	ulcerogenicity: UD_{50}[b]	acute toxicity: LD_{50}[c]	safety index: UD_{50}/ED_{50} CPE
9a	1.53 (1.07–2.19)[d]	0.39 (0.19–0.83)	ca. 30	ca. 200	ca. 20
15	2.24 (1.52–3.31)	0.31 (0.14–0.66)	ca. 57	NT[e]	ca. 25
25	3.53 (2.33–4.83)	1.50 (0.56–4.23)	>124	644 (490–846)	>35
indo[f]	3.3 (2.1–7.3)	0.44 (0.22–0.87)	ca. 8	23 (18.7–27.5)	ca. 2.4

[a] Carrageenan hind paw edema. [b] Rats, mg/kg po. [c] Mice, mg/kg po. [d] 95% confidence limits. [e] Not tested. [f] Indomethacin.

phenyl)propionate (**1**, 1.94 g, 0.010 mol) and Na (0.23 g, 0.010 g-atom) in ethanol (EtOH, 10 mL) was added a solution of *trans*-2-(chloromethyl)cyclohexanecarbonitrile (**2**, 1.52 g, 0.010 mol) in EtOH (10 mL) and the mixture was refluxed for 48 h. The reaction mixture was concentrated to leave **4** as an oil (1.9 g, 60%): IR (film) 2220, 1720 cm^{-1}; EIMS m/z 315 (M^+).

The compound **4** (1.9 g) was dissolved in 60% diethylene glycol (13 mL) and KOH (2.8 g, 0.050 mol) was added. The mixture was heated at 250 °C with stirring for 5 h and then poured into water. The solution was acidified with 2 N hydrochloric acid (HCl) and extracted with ethyl acetate (AcOEt). The extract was washed with water, dried, and concentrated to give crude **5** as an oil (1.5 g, 81%): IR (film) 1700 cm^{-1}; EIMS m/z 306 (M^+).

A mixture of the crude **5** (1.5 g) and PPA (20 g) was stirred for 1 h at 95 °C. The reaction mixture was poured into cold water and extracted with toluene. The extract was washed with water

and dried and the solvent was removed to give a mixture of **13a** and **13b**. Analysis of the mixture by HPLC, using a Shimadzu ODS-H column and a mobile phase consisting of a 1/1 mixture of 1% acetic acid (AcOH) and acetonitrile (CH_3CN), showed that the mixture consisted of 88% **13a** (t_R 4.9 min) and 12% **13b** (t_R 5.6 min). The separation of **13a** and **13b** was achieved by preparative HPLC. The first fraction gave **13a** as an oil (0.32 g, 22%) and the second fraction gave **13b** as an oil (0.03 g, 2%).

***trans*- and *cis*-2-(6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionic Acid (9a and 9b). (Method B).** A stirred mixture of *cis*-hexahydrophthalide (**3**, 1.40 g, 0.010 mol) and disodium 2-(3-mercaptophenyl)propionate (2.26 g, 0.010 mol) was heated at 220 °C for 0.5 h. The reaction mixture was dissolved in water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water and dried and the solvent was removed to give crude **5** as an oil (2.7 g, 83%): IR (film) 1700 cm^{-1}; EIMS m/z (322 (M^+).

A mixture of crude **5** (2.7 g) and PPA (20 g) was stirred for 1 h at 95 °C. The reaction mixture was poured into cold water and extracted with toluene. The extract was washed with water and dried and the solvent was removed to give a mixture of **9a** and **9b**. Analysis of the mixture by HPLC, using a Shimadzu ODS-H column and a mobile phase consisting of a 1/1 mixture of 1% AcOH and CH_3CN, showed that the mixture consisted of 95% **9a** (t_R 7.2 min) and 12% **9b** (t_R 8.9 min). Separation of **9a** and **9b** was achieved by preparative HPLC. The first fraction gave **9a** (2.1 g, 82%) and the second fraction gave **9b** (0.12 g, 5%).

Separation of Two Trans Diastereoisomers (9aA and 9aB). (Method C). To **9a** (39 g) was added AcOEt (25 mL) for crystallization. The crystalline precipitate was collected by filtration and recrystallized repeatedly from AcOEt to give **9aA** (diastereoisomer A) (9 g, 23%): IR (KBr) 1705, 1680 cm^{-1}; EIMS m/z 304 (M^+).

The mother liquor was evaporated and the residue was crystallized from an appropriate amount of AcOEt. The crystalline precipitate was collected and recrystallized repeatedly from AcOEt to give **9aB** (diastereoisomer B) (5.5 g, 14%): IR (KBr) 1690, 1665 cm^{-1}; EIMS m/z 304 (M^+).

Separation of Two Cis Diastereoisomers (9bA and 9bB). (Method D). Compound **9b** (4 g) was treated in the same manner as described for the separation of **9aA** and **9aB**. The diastereoisomer A was separated first. It was recrystallized repeatedly from AcOEt to give **9bA** (0.5 g, 13%): IR (KBr) 1690, 1660 cm^{-1}; EIMS m/z 304 (M^+).

From the mother liquor, the diastereoisomer B was obtained. It was recrystallized repeatedly from AcOEt to give **9bB** (0.3 g, 8%): IR (KBr) 1690, 1685 cm^{-1}; EIMS m/z 304 (M^+).

Ethyl *trans*-2-(6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionate (15). (Method E). A solution of **9a** (3.04 g, 0.010 mol) in EtOH (60 mL) and 35% HCl–EtOH (4 mL) was refluxed for 8 h. The reaction mixture was poured into water and extracted with toluene. The extract was washed with water and dried and the solvent was removed. The residue was chromatographed on a silica gel column, using toluene as an eluent, to give pure **15** as an oil (2.67 g, 80%).

Phenethyl *trans*-2-(6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionate (25). (Method F). To a solution of **9a** (3.04 g, 0.010 mol) in methanol (MeOH, 20 mL) was added a solution of KOH (0.56 g, 0.010 mol) in MeOH (30 mL). After the solution was concentrated to dryness, to the residual potassium salt was added a solution of phenethyl bromide (1.85 g, 0.010 mol) in toluene (70 mL) and the mixture was refluxed for 16 h. The reaction mixture was poured into water. The toluene layer was separated, washed with water, and dried and the solvent was removed. The residue was chromatographed on a silica gel column, using toluene as an eluent, to give pure **25** as an oil (3.02 g, 74%).

2-Pyridylmethyl *trans*-2-(6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionate (34). (Method G). A mixture of **9a** (3.04 g, 0.010 mol) and $SOCl_2$ (20 mL) was heated under reflux for 2 h and concentrated. The oily residue was dissolved in toluene and the solution was added at room temperature to a stirred solution of 2-(hydroxymethyl)pyridine (2.18 g, 0.020 mol) in toluene (40 mL). The mixture was heated at 100 °C for 1 h and poured into water. The toluene layer was separated, washed with water, and dried and the solvent was removed. The residue was chromatographed on a silica gel column, using chloroform ($CHCl_3$) as an eluent, to give pure **34** as an oil (3.36 g, 85%).

***trans*-2-(6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-yl)propionamide (37). (Method H).** A mixture of **9a** (3.04 g, 0.010 mol) and $SOCl_2$ (20 mL) was heated under refluxed for 2 h and concentrated. The oily residue was dissolved in AcOEt (50 mL). The solution was saturated with NH_3 under ice cooling and then allowed to stand at room temperature for 2 h and evaporated. The residue was chromatographed on a silica gel column, using $CHCl_3$ as an eluent, to give pure **37** as an oil (2.6 g, 86%).

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

Statistics. ED_{50}, UD_{50}, and LD_{50} values were calculated according to the method of Litchfield and Wilcoxon.[18]

Carrageenan Hind Paw Edema (CPE).[19] Five to ten male Wistar rats, weighing 120–150 g, were used. Hind paw edema was induced by a subcutaneous injection of a 1% carrageenan aqueous solution into the left hind paw. ED_{50} values were determined 3 h after carrageenan injection.

Acetic Acid Induced Writhing.[20] The writhing was induced by an intraperitoneal injection of a 1% acetic acid aqueous solution in male Wistar rats (90–120 g).

Gastric Ulcerogenicity Assay.[21] Male Wistar rats, weighing 130–180 g, were used. The rats, fasted for 24 h, were sacrificed 6 h after a single oral administration of test compounds, and their stomachs were removed and macroscopically observed.

Acute Lethal Toxicity. LD_{50} values were determined from the 7-day mortality in mice.

Conformational Analysis Method. NMDO[22] calculations with geometry optimization in MOPAC[23] were carried out on the nuclei of **9a**,**b** and dibenzothiepin (I).

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Registry No. 1 (X = S, R = H, R′ = Et), 123964-00-1; 1 (X = O, R = H, R′ = Et), 17138-28-2; 1 (X = O, R = H)·2Na, 123964-01-2; 1 (X = S, R = H)·2Na, 123964-02-3; 1 (X = S, R = Me)·2Na, 123964-03-4; 1 (X = O, R = Me, R′ = Et), 15399-05-0; 1 (X = O, R = Me, R′ = Et), 56355-15-8; 1 (X = S, R = Me)·2Na, 123964-05-9; **2**, 10479-49-9; **4** (X = O, R = Me), 123964-04-5; **5** (X = O, R = Me), 80772-64-1; **5** (X = S, R = Me), 80772-62-9; **6a**, 123963-92-8; **6b**, 123963-93-9; **7aA**, 124093-93-2; **7aB**, 124094-02-6; **7bA**, 124093-94-3; **7bB**, 124095-63-2; **8a**, 123963-94-0; **8b**, 123963-95-1; **9a**, 80772-14-1; **9aA**, 124093-95-4; **9aB**, 124093-96-5; **9bA**, 124094-00-4; **9bB**, 124094-01-5; **10a**, 123963-96-2; **10b**, 123963-97-3; **11aA**, 124093-97-6; **11aB**, 124094-03-7; **11bA**, 124093-98-7; **11bB**, 124094-04-8; **12a**, 116628-01-4; **12b**, 116628-11-6; **13aA**, 124093-99-8; **13aB**, 124094-05-9; **13bA**, 124094-07-1; **13bB**, 124094-06-0; **14**, 123963-98-4; **15**, 80772-21-0; **16**, 80772-26-5; **17**, 80772-27-6; **18**, 80772-28-7; **19**, 80772-29-8; **20**,

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80772-30-1; **21**, 80772-32-3; **22**, 80772-46-9; **23**, 80772-34-5; **24**, 80772-35-6; **25**, 80772-71-0; **26**, 80772-36-7; **27**, 80772-22-1; **28**, 80772-37-8; **29**, 80772-38-9; **30**, 80772-39-0; **31**, 80772-40-3; **32**, 80772-41-4; **33**, 80772-25-4; **34**, 80772-44-7; **35**, 80772-45-8; **36**, 80772-24-3; **37**, 80772-61-8; **38**, 80772-52-7; **39**, 123963-99-5; **40**, 80772-54-9; **41**, 80772-55-0; **42**, 80772-59-4; **43**, 80772-51-6; **44**, 80772-56-1; **45**, 80772-57-2; **46**, 80772-58-3; *cis*-hexahydrophthalide, 6939-71-5; 2-(hydroxymethyl)pyridine, 586-98-1; *N*-(2-hydroxyethyl)morpholine, 622-40-2; 3-(hydroxymethyl)pyridine, 100-55-0; 2-(2-hydroxyethyl)pyridine, 103-74-2.

Supplementary Material Available: A table listing ^{1}H NMR data for H6a and H10a of **6a,b–13a,b** (1 page). Ordering information is given on any current masthead page.

Aldosterone Antagonists. 3. Synthesis and Activities of Steroidal 7α-(Alkoxycarbonyl)-15,16-methylene Spirolactones

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Several A- and D-ring substituted steroidal 7α-alkoxycarbonyl spirolactones were synthesized with the purpose of increasing the aldosterone antagonistic potency and reducing the endocrinological side effects relative to the standard drug spironolactone. It was found that the 15β,16β-methylene derivative **17** exhibited a 2-fold higher aldosterone antagonistic activity compared to either spironolactone or the 15,16-unsubstituted derivative **29** while showing remarkably reduced antiandrogenicity.

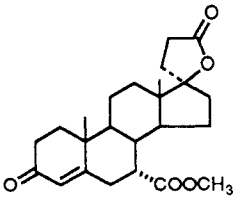
In a previous paper of this series,[1] we described the synthesis and pharmacological activity of some spironolactone derivatives. We have shown that introduction of a 15β,16β-cyclopropane ring in the spironolactone molecule enhances the aldosterone antagonistic activity. The endocrinological side effects are reduced by the introduction of a 1,2-double bond. It was known that the replacement of the 7α-acetylthio moiety by the 7α-alkoxycarbonyl function leads also to potent aldosterone antagonists.[2] In this paper we report our results with A- and D-ring substituted 7α-alkoxycarbonyl spirolactones in regard to their aldosterone antagonistic and endocrinological activity.

Chemistry

Although 7α-alkoxycarbonyl steroids have been prepared previously,[2-4] the reported methods result in only low yields under drastic conditions. We therefore sought a mild and efficient synthesis of these compounds. As starting material for our efforts we chose the known double unsaturated ketones **1–4**.[1] By reacting these ketones with diethylaluminum cyanide[5] in tetrahydrofuran (THF), a cyano group could be introduced stereoselectively at the 7α-position of the steroid framework in high yields (Scheme I, Table I). In case of the 1α,2α:15β,16β-dimethylene derivative **2** the introduction of a 7α-cyano group accessed in higher yields by using potassium cyanide in dimethylformamide. The reduction of the cyano ketones **5–8** with diethylaluminum hydride in THF or dichloromethane led directly to the aldehydes **9–12**. These compounds were obtained as mixtures of diastereomeric alcohols at the 3- and 5′-positions and were further transformed without purification. Jones oxidation of aldehydes **9–12** gave the carboxylic acid derivatives **13–16**. For the subsequent esterification, three different methods were employed. The methyl esters were prepared by reaction of the carboxylic acids with diazomethane. The higher esters were obtained either by preparing the mixed anhydride with butyl chloroformate followed by reaction with the appropriate alcohol[2] or directly by reaction of the carboxylic acids with an alkyl halide and silver oxide catalysis. The introduction of the 1,2-double bond was achieved by treatment of the α,β-unsaturated ketones **17–19** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford **26–28** (Table II).

Biological Results and Discussion

In the 15β,16β-methylene series (**17–19**), the methyl ester **17** showed clearly the highest aldosterone antagonistic activity exhibiting a 2-fold higher potency than spironolactone (Table III). On the basis of in vitro experiments, **17–19** have similar affinities for the androgen and progesterone receptors. As it was found in other series,[1,6] the introduction of a 15β,16β-methylene moiety led to a remarkable enhancement of the aldosterone antagonistic potency (**17** compared to **29**). The affinity for the androgen receptor was practically the same, whereas the affinity for the progesterone receptor was increased.



29 (SC 25152)

By introduction of a 1,2-double bond (compounds **26–28**) the affinities for the androgen and progesterone receptors were significantly decreased; however, the aldosterone

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