cooled in liquid nitrogen. Control atria, without any drug added, were frozen under the same experimental conditions. The atria thus obtained were stored at –80 °C until analyzed for cyclic AMP. Cyclic AMP was measured by radioimmuno assay by using a cyclic AMP kit obtained from Becton Dickinson.

Experimental Design of Cardiac Studies. Cumulative dose–response (CDR) curves were performed in order to measure the effects of compound **14** on force and rate.

Propranolol (10^{-7} M) was first injected and gave no significant alteration of basal tensions (mean of the differences between tension values before and after propranolol = -0.06 ± 0.03; six experiments, $p > 0.05$). The same dose of propranolol had previously blocked the inotropic effect of histamine (10^{-2} M) on the same experimental model.[17] The effect of histamine under these circumstances was entirely due to the release of norepinephrine. Compound **14** (3×10^{-3} M) was injected after propranolol; tension and cyclic AMP were measured 1.5 min after the administration of compound **14**.

For the determination of isoprenaline potentiation by **14**, the following procedure was undertaken in order to correct the shift to the right of isoprenaline CDR curves, commonly observed when CDR curves were successively obtained for each atrium, and the first one was discarded. The second was used as a control for the isoprenaline ED_{50} in the absence of **14**. The third one was performed in the presence of **14**. For each set of six experiments, the same series of three CDR curves was done on one atrium without **14**, which allowed for the calculation, for each dose of isoprenaline, of the percentage of decrease of the effect between the second and the third CDR. These percentages were used to correct the effect of each dose of the second isoprenaline CDR curve for the remaining five atria. The corrected curves were used to calculate the control ED_{50}'s of each CDR curve in the presence of **14**.

Calculation of Results and Statistics. All ED_{50}'s have been calculated by interpolation of dose-response curves. Numbers are given as the mean plus or minus the standard error of the mean (SEM). Comparisons were done using the Student's t test for unpaired or paired data; $p \leq 0.05$ was considered significant.

Synthesis and Antiinflammatory Activity of [(Cycloalkylmethyl)phenyl]acetic Acids and Related Compounds

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[(Cycloalkylmethyl)phenyl]acetic acid derivatives and related compounds were synthesized to test their antiinflammatory and analgesic activities. Some of the compounds in this series were found to have good activity in the carrageenan edema test. Among them, sodium 2-[4-[(2-oxocyclopentyl)methyl]phenyl]propionate dihydrate (**15**) and 2-[4-[(2-oxocyclohexylidene)methyl]phenyl]propionic acid (**13b**) showed potent analgesic and antiadjuvant arthritis activities with excellent antipyretic properties.

In recent years, numerous arylacetic and propionic acid derivatives have been synthesized in the search for nonsteroidal antiinflammatory agents.[1]

In a previous paper,[2] we reported the synthesis and antiinflammatory activity of indanylacetic acid derivatives **1**, among which 2-(2-isopropyl-5-indanyl)propionic acid [R = CH(CH₃)₂] exhibited particularly potent antiinflammatory activity. The indanylacetic acid derivatives **1** can be related to the structure of ibuprofen (**2**, R = CH₃) by drawing a dotted line between the isobutyl group and the benzene ring (Chart I). In the continuation and extension of our synthetic studies of nonsteroidal antiinflammatory agents, we have synthesized the spiro indanylacetic acid derivatives **3**.[3] These compounds **3**,[3] however, showed only weak antiinflammatory activity. We, therefore, carried out the synthesis of a number of phenylacetic and propionic acid derivatives **4** having the cycloalkylmethyl group at the paraposition of phenylacetic acid.

Chemistry. [(Cycloalkylmethyl)phenyl]acetic and propionic acid derivatives **8** were synthesized by the two basic routes shown in Scheme I. In the first procedure [A], the compounds were prepared as follows: Treatment of ethyl [p-(chloromethyl)phenyl]acetate (**5**)[4] with ethyl 2-oxocycloalkanecarboxylate **6** gave the condensed products **7**. Hydrolysis of **7**, followed by decarboxylation, afforded the [4-[(2-oxocycloalkyl)methyl]phenyl]acetic acid derivatives **8**. The other synthetic method [B] utilized the morpholino enamine of cycloalkanone as starting material.

Chart I
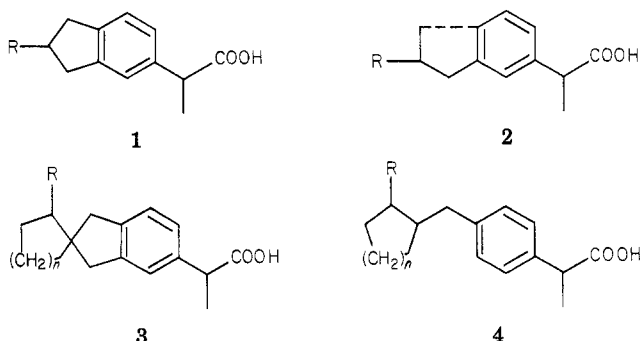
Reaction of **5** with enamine **9**, followed by hydrolysis with HCl, gave **8**. The methylene compound **10** was obtained by Clemmensen reduction of **8b**. The 2-oxo derivatives **8** were converted to the oximes **11** by reaction with hydroxylamine.

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(1) (a) R. A. Scherrer and M. W. Whitehouse, Ed. "Antiinflammatory Agents. Chemistry and Pharmacology", Vol I, Academic Press, New York, 1974. (b) *Annu. Rep. Med. Chem.*, 16, 189 (1981), and previous papers in this series.
(2) N. Yoshida, A. Terada, K. Tomita, K. Wachi, S. Naruto, S. Tanaka, H. Miyazawa, K. Tanaka, E. Misaka, Y. Iizuka, Y. Umemuro, T. Kojima, and R. Tachikawa, *Annu. Rep. Sankyo Res. Lab.*, 32, 65 (1980).
(3) Unpublished data from our laboratories. For example, the ID₅₀ value for 2-[spiro(cyclopentane-1,2'-indan)-5'-yl]propionic acid was 85 mg/kg in the carrageenan edema test.
(4) J. W. Baker and J. A. L. Brieux, *J. Chem. Soc.*, 404 (1956).

Table I. Chemical and Pharmacological Data
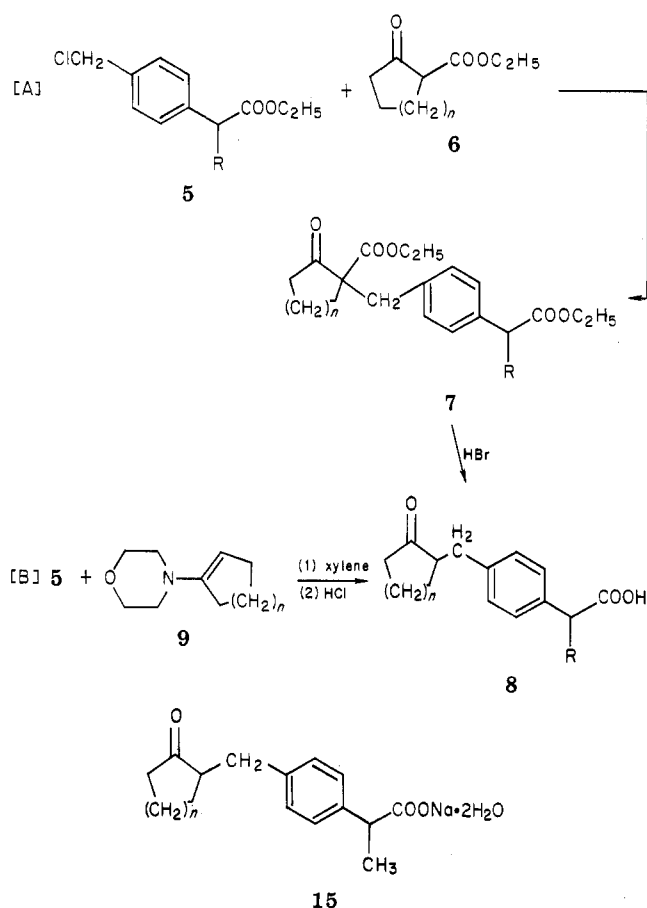

8a-e, 10, 11a-e   13a-c

compd	X	n	R	method	mp or bp (mmHg), °C	yield, %	formula[a]	ID$_{50}$, mg/kg po CPE[b]	SP[c]
8a	O	1	H	A	185–190 (0.7)	33	$C_{14}H_{16}O_3$	9.1	23
8b	O	1	CH$_3$	A	200–202 (0.7)	54	$C_{15}H_{18}O_3$	1.7	0.8
8c	O	2	H	B	190–195 (0.3)	60	$C_{15}H_{18}O_3$	45.7	53.8
8d	O	2	CH$_3$	B	87.5–90	68	$C_{16}H_{20}O_3$	1.2	9.1
8e	O	3	CH$_3$	B	200–205 (0.3)	31	$C_{17}H_{22}O_3$	>100	>100
10	H$_2$	1	CH$_3$		160–163 (0.3)	58	$C_{15}H_{22}O_2$	>100	5.1
11a	NOH	1	H		136–139	90	$C_{14}H_{17}NO_3$	24.8	15.0
11b	NOH	1	CH$_3$		147–148	93	$C_{15}H_{19}NO_3$	1.3	4.9
11c	NOH	2	H		177–178	89	$C_{15}H_{19}NO_3$	23.5	31.1
11d	NOH	2	CH$_3$		143–150	86	$C_{16}H_{21}NO_3$	1.4	3.6
11e	NOH	3	CH$_3$		149–151	82	$C_{17}H_{23}NO_3$	>100	>100
13a	O	1	CH$_3$	C	106–107	27	$C_{15}H_{16}O_3$	1.5	1.3
13b	O	2	CH$_3$	C	108–110	45	$C_{16}H_{18}O_3$	0.9	1.8
13c	O	3	CH$_3$	D	210–215 (0.3)	45	$C_{17}H_{20}O_3$	>100	>100
ibuprofen								10.8	15.9

[a] All compounds were analyzed for C, H, and N.   [b] CPE = carrageenan paw edema.   [c] SP = scald-induced pain.

Scheme I

Scheme II

amine 9, followed by hydrolysis, gave the 2-[4-[(2-oxo-cycloalkylidene)methyl]phenyl]propionic acid derivatives 13 (Method C). In the other procedure [D], 13 was prepared by the reaction of 12 with cycloalkanone 14 in the presence of base.

Pharmacological Results and Discussion

The antiinflammatory and analgesic activities of the compounds obtained in this study were measured by the carrageenan paw edema and the scald pain test, respectively (see Experimental Section), and their results are listed in Table I.

[(Cycloalkylidenemethyl)phenyl]propionic acid derivatives 13 were synthesized as shown in Scheme III. Reaction of ethyl (p-formylphenyl)propionate 12[5] with en-

(5) J. Maillard, M. Langlois, P. Delaunay, V. V. Tri, R. Mrin, M.-J. Lefebvre, C. Manuel, and A.-M. Verro, *Chim. Ther.*, 487 (1973).

Table II. Pharmacological Data for Sodium 2-[4-[(2-Oxocyclopentyl)methyl]phenyl]propionate Dihydrate (15) and 2-[4-[(2-Oxocyclohexylidene)methyl]phenyl]propionic Acid (13b)

15

13b

| compd | ID$_{50}$, mg/kg po | | | ED$_{50}$, mg/kg po | | ID$_{50}$, mg/kg po | UD$_{50}$, mg/kg po |
	CPE^a	adjuvant arthritis	SP^b	R–S^c	BP^d	LBS fever	gastric lesion
15	1.2	0.59	0.76	0.13	0.4	0.76	16.1
	(0.93–1.50)^e	(0.37–0.94)	(0.54–1.2)	(0.05–0.33)	(0.21–0.78)	(0.44–1.3)	(11.1–33.7)
13b	1.2	0.06	1.7	0.94	4.5	1.5	14.3
	(0.95–1.6)	(0.03–0.1)	(1.3–2.3)	(0.43–2.1)	(1.9–11.0)	(1.0–2.2)	(9.7–18.5)
IDM^f	2.2	0.13	3.5	2.8	8.3	9.5	6.4
	(1.7–2.8)	(0.1–0.17)	(2.3–5.4)	(0.9–8.0)	(4.7–14.5)	(6.7–14.5)	(4.5–9.2)

^{a} CPE = carrageenan paw edema. ^{b} R–S = Randall–Selitto. ^{c} SP = scald-induced pain. ^{d} BP = Bradykinin pain. ^{e} 95% confidence limits. ^{f} IDM = indomethacin.

Scheme III
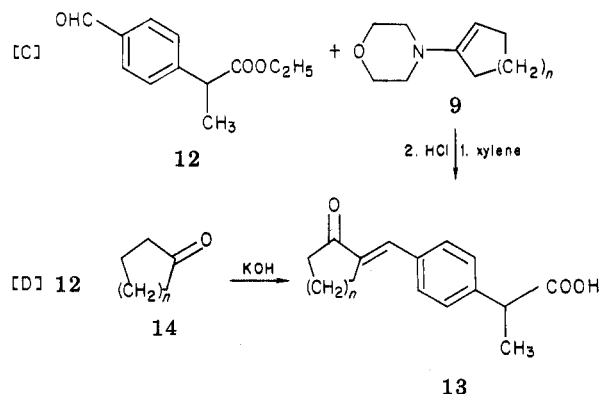
Some of the compounds (e.g., **8b,d**, **11b,d**, and **13a,b**) in this series were far more active than ibuprofen in both procedures. Reduction of the oxo group (**8b**) to the methylene group (**10**) caused a dramatic decrease in activity, while introduction of a methyl group at the α-position of the acetic acid moiety markedly increased it (**8b,d**). The compounds having five- and six-membered rings (**8b,d** and **13a,b**) showed similar activity, but an increase in size to seven-membered ring compounds (**8e** and **13c**) dramatically decreased the activity. The oxime compounds (**11a,b**) exhibited almost the same activity as the parent oxo compounds (**8b,d**).

Since **8b** has two asymmetric carbon atoms, it is a mixture of diastereoisomers. We have shown that the hydrogen atom on the asymmetric carbon of the cyclopentanone moiety is easily racemized in an acidic or basic medium with optical active compounds.[6] Compound **8b** is an oily substance; accordingly, compound **8b** was converted to the sodium salt **15**, which is a crystal of a 1:1 mixture of diastereoisomers. The resolution and biological properties of the optical isomers of **8b** will be reported elsewhere.

On the basis of the above screening data and the physical properties, **15** and **13b** were selected for additional evaluation in order to define their spectrum of antiinflammatory activity. The pharmacological results for **15** and **13b** are summarized in Table II. In terms of antiinflammatory activity as measured by the adjuvant arthritis procedure in rats, **15** was less active than indo-

methacin, while **13b** was more active. The analgesic activity examined by the Randall–Sellito and bradykinin pain models showed that both compounds were more active than indomethacin, with **15** being at least 20 times as active as indomethacin in both analgesic tests. The antipyretic activity was measured in the LPS-induced fever assay in guinea pigs, and both compounds showed very strong activity.

In conclusion, it was found that sodium 2-[4-[(2-oxocyclopentyl)methyl]phenyl]propionate (**15**) and 2-[4-[(2-oxocyclohexylidene)methyl]phenyl]propionic acid (**13b**) were highly active as antiinflammatory, analgesic, and antipyretic agents.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. The IR (KBr or Nujol) and NMR (CDCl$_3$) spectra of all new compounds were consistent with their structures. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.3% of their theoretical values.

General Method for the Synthesis of [4-[(2-Oxocycloalkyl)methyl]phenyl]acetic Acid Derivatives (8a–e). Method A. To a solution of KOH (0.8 mol) in DMF (580 mL) was added ethyl 2-oxocycloalkanecarboxylate (0.8 mol) at room temperature. After stirring for 0.5 h, ethyl [p-(chloromethyl)phenyl]acetate or propionate (0.8 mol) was added to the reaction mixture at 10 °C and stirred for 1 h at 50 °C. The reaction mixture was poured onto ice–water, neutralized (AcOH), and extracted with ether, and the extract was washed with H$_2$O, dried over Na$_2$SO$_4$, and evaporated to give **8**.

Method B. A solution of ethyl [p-(chloromethyl)phenyl]acetate or propionate (0.7 mol) and morpholinocycloalkene (1.4 mol) in xylene (700 mL) was heated under reflux for 10 h. After the mixture was cooled, 10% HCl (700 mL) was added to the reaction mixture. The reaction mixture was extracted with ether, washed with H$_2$O, dried over Na$_2$SO$_4$, and evaporated to give an oil. A mixture of the oil, KOH (0.2 mol), and 80% EtOH (200 mL) was heated under reflux for 2 h. The reaction mixture was poured into ice–water, acidified with HCl, and extracted with ether. The extracts were washed with H$_2$O, dried over Na$_2$SO$_4$, and evaporated to give **8**. Compound **8d** was recrystallized from ether–hexane.

2-[4-(Cyclopentylmethyl)phenyl]propionic Acid (10). A mixture of **8b** (0.5 g), Zn–Hg (20 g), concentrated HCl (25 mL), dioxane (50 mL), and H$_2$O (25 mL) was heated under reflux for 4 h. After cooling, the reaction mixture was poured into water and extracted with ether, and the extract was washed with H$_2$O, dried over Na$_2$SO$_4$, and evaporated to give **10** (0.3 g).

General Procedure for the Synthesis of [4-[[2-(Hydroxyimino)cycloalkyl]methyl]phenyl]acetic Acid Derivatives

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(6) S. Naruto and A. Terada, *Chem. Pharm. Bull.*, submitted.

(11a–e). A mixture of 8 (0.01 mol), $NH_2OH\cdot HCl$ (0.012 mol), CH_3COONa (0.025 mol), and 85% EtOH (20 mL) was heated under reflux for 1 h. After cooling, the reaction mixture was poured into H_2O and extracted with ether. The extracts were washed with H_2O, dried over Na_2SO_4, and evaporated to give the solid. Recrystallization from EtOH–hexane gave 11.

General Procedure for the Synthesis of 2-[4-[(2-Oxo-cycloalkylidene)methyl]phenyl]propionic Acid Derivatives (13a–c). Method C. A solution of 12 (0.5 mol) and 9 (1.0 mol) in xylene (500 mL) was heated under reflux for 24 h. After the solution was cooled, 6 N HCl (450 mL) was added to the reaction mixture and stirred for 5 h at room temperature. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, and evaporated to give an oil. This oil was dissolved in MeOH (1000 mL) and added to a solution of K_2CO_3 (0.75 mol) in H_2O (400 mL). The reaction mixture was kept at room temperature for 72 h. It was then acidified with HCl and extracted with ether, and the extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The crude product (13a,b) was recrystallized from ether–hexane.

Method D. To a solution of KOH (0.05 mol) in H_2O (30 mL) was added 14 (0.05 mol) and then 12 (0.05 mol) under ice cooling. The reaction mixture was heated under reflux for 3 h. After cooling, the reaction mixture was acidified with AcOH and extracted with EtOAc. The extracts were washed with H_2O, dried over Na_2SO_4, and evaporated. The reaction product was recrystallized from ether–hexane in the case of 13a,b and evaporated in the case of 13c.

Sodium 2-[4-[(2-Oxocyclopentyl)methyl]phenyl]-propionate Dihydrate (15). To a solution of 8b (2.46 g) in EtOH (10 mL) was added a solution of NaOH (0.38 g) in H_2O (5.0 mL) under ice cooling. After the solution was stirred for 2 h at room temperature, the solvent was removed under reduced pressure to give a solid. Recrystallization from aqueous EtOAc gave a colorless solid: yield 2.5 g; mp 194–198 °C. Anal. ($C_{15}H_{21}O_5Na$) C, H.

Pharmacology. Carrageenan-Induced Paw Edema.[7] The test compounds were administered orally in a 0.5% tragacanth suspension in doses of 100, 25, 6.3, 1.6, and 0.4 mg/kg to rats (Wister Imamichi, male, weighing about 120 g) that had been fasted for 16 h before the medication. Thirty minutes after drug administration, 0.05 mL of 1% carrageenan suspension in saline was injected subcutaneously into the plantar region of the hind paw. The volume of the paw was measured just before and 3 h after the carrageenan injection. ID_{50} values were calculated based on a regression line prepared from percent inhibition and dose by the least-squares method.

Scald-Induced Pain Test.[8] Male Wister Imamichi rats weighing about 100 g, fasted for 16 h, were scalded by dipping a hind paw into hot water at 57 °C for 6 s. Then the rats were given a second stimulus by dipping the scalded paw into warm water at 40 °C for 5 s, after which each rat was placed in a cage. Each animal had a tendency to keep the scalded paw off the floor. The sum of the time (seconds) showing such pain responses over a 30-s period after the second stimulus was referred to as the pain reaction time, which decreased as the pain was alleviated. The test compounds (dose: 58, 19, 6.3, 2.1, 0.7, and 0.23 mg/kg) suspended in 0.5% tragacanth were given orally 2 h after scalding, and the pain reaction time was determined 1 and 2 h after the medication. Analgesic activity was expressed as percent inhibition of the pain reaction time. The mean value of the 1- and 2-h estimation was used for calculation of percent inhibition and ID_{50} values.

Adjuvant Arthritis.[9] Lewis rats (female, weighing 160–200 g) were injected with 0.05 mL of complete Freund adjuvant (CFA) into the right hind paw. CFA was prepared by suspending heat-killed *Mycobacterium tuberculosis* (Defco) in liquid paraffin at a concentration of 1 mg/mL. The test compounds (dose: 5.0, 1.0, 0.2, and 0.04 mg/kg) were administered once a day from the

day (day 0) of adjuvant injection to day 20. The degree of arthritis was observed by measurement of the injected hind paw volume by using the water-displacement method. The swelled hind paw volume was expressed by the difference between values determined on the day before and on day 21 after the adjuvant injection. The efficacy of each drug was expressed as the percent inhibition of swelled foot volume relative to the untreated control mean. ID_{50} values were expressed as described in the carrageenan paw edema test.

Randall–Seltto.[10] This method was performed by the modification previously described by Winter and Flataker[11] of the original method of Randall and Sellito.[10] Fasted rats (Wister Imamichi, male, weighing 60–90 g) were injected with 0.1 mL of 20% Brewers yeast suspension into the right hind paw. Four hours later, rats that had been made hypersensitive to a pressure stimulus induced pain of less than 10×30 g in pain threshold were selected and administered the test compounds (dose: 50, 12.5, 3.1, 0.8, 0.2, and 0.05 mg/kg). According to Blane's method,[12] a test compound resulting in an increase in pain threshold more than twice as large as that of the unmedicated control was regarded as effective. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[13]

Bradykinin-Induced Pain Test. This method was performed in our laboratory by a modification of the method previously described by Deffenu et al.[14] and Blane,[12] using guinea pigs instead of rats. Guinea pigs (Hartley, female, weighing 350–400 g) were cannulated antidromically into the carotid artery under ether anesthesia. When a bradykinin solution (0.5 µg/mL) was injected through the cannula, animals showed rotation of their head, flexion of forelimbs, and squeaked. The test compounds (dose: 10, 5, 2.5, 1, 0.5, and 0.2 mg/kg) were administered to those guinea pigs that had shown good pain responses as described above. The bradykinin solution was injected 15, 30, 60, 90, and 120 min after the medication, and the pain response was observed each time. The drug was regarded as effective when more than two out of three signs of the responses disappeared. ED_{50} values were calculated by the Litchfield–Wilcoxon method.[13]

Antipyretic Activity. Effect on LPS-induced fever was tested by the method of Kobayashi and Takagi,[15] with a slight modification. Guinea pigs (Hartley, female, weighing 300–350 g) that had been fasted 16 h before the experiment were fevered by intravenous injection of a lipopolysaccharide (LPS from *E. coli*) solution (1 µg/mL) at a dose of 1 µg/kg. The rectal temperature of the test animals was measured 1 and 2 h after drug administration (dose: 6.3, 2.1, 0.7, and 0.23 mg/kg), and the mean of the two values was used for the estimation. ID_{50} values were expressed as described in the carrageenan paw edema test.

Gastric Lesion Activity. The irritative effect on gastric mucosa was tested by the method of Jahn and Adrian,[16] with a slight modification. The test compounds (dose: 20, 10, 7.5, 5, and 2.5 mg/kg) were administered to rats (Wister Imamichi, male, weighing about 120 g) that had been fasted for 16 h before administration of the medication. The rats were sacrificed by bleeding under ether anesthesia 3.5 h after dosing, and the stomachs were removed, opened by cutting along the greater curvature, and washed with physiological saline. The isolated stomachs were observed with a stereomicroscope and dark brown lesions with 0.5-mm length were counted. An animal with more than four erosions was regarded as positive (Hitchens et al.[17]). UD_{50} values were calculated by the Litchfield–Wilcoxon method.[13]

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Synthesis and Antimicrobial Activity of Clindamycin Analogues: Pirlimycin,[1,2] a Potent Antibacterial Agent

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The preparation of a series of analogues of clindamycin is described in which the naturally occurring five-membered cyclic amino acid amide portion of the molecule is replaced by a four-, six-, or seven-membered cyclic amino acid amide. The most interesting compound is pirlimycin (**7e**, U-57,930E), in which the (2S-trans)-4-n-propylhygramide portion of clindamycin is replaced by (2S-cis)-4-ethylpipecolamide. This structural modification results in significantly favorable changes in toxicity, metabolism, and antibacterial potency. Although the in vitro antibacterial activity of clindamycin and pirlimycin are nearly identical, the latter compound is 2–20 times more active than clindamycin when administered to mice experimentally infected with strains of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Bacteroides fragilis*, and *Plasmodium berghei*. Pirlimycin is absorbed in rats and mice following both subcutaneous and oral administration. It readily penetrates *B. fragilis* induced abscesses in mice and is sequestered within these abscesses. A drug concentration of at least 60 times the required inhibitory concentration is maintained for 6 h following a single subcutaneous dose of 200 mg/kg. Urinary excretion of total bioactivity consists only of intact pirlimycin with no other antibacterially active metabolites being detected. Pirlimycin is tolerated well in rats and mice at the administered levels.

The synthesis and structure of the antibiotic clindamycin (**1**; Chart I) and the potency and spectrum of its antibacterial activity were described in earlier communications from this laboratory.[3] Further investigation into the chemistry and biology of the lincomycin/clindamycin family of antibiotics resulted in changes in the sugar-ring portion of the molecule at C-1–C-4 and in replacement of the chlorine atom at C-7 of clindamycin by a nitrile group, as well as by several different sulfur- and oxygen-containing moieties.[3,4] Alterations introduced into the amino acid amide portion of clindamycin included variations in the length of the alkyl side chain and replacement of the methyl group attached to the nitrogen atom by a longer chain alkyl group, by a 2-hydroxyethyl function, and by a hydrogen.[5] A group of compounds was also prepared in which the cyclic amino acid amide portion of clindamycin was replaced by a noncyclic amino acid amide.[6]
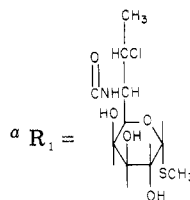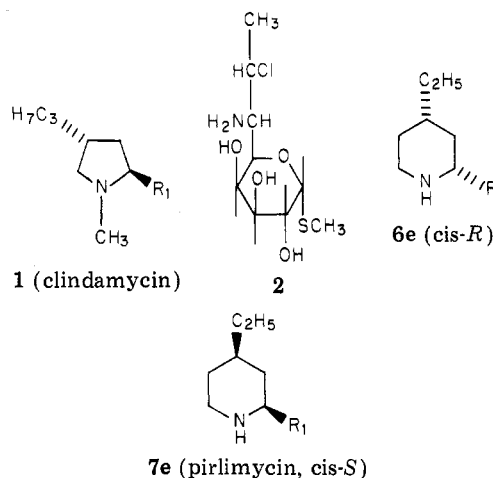
(1) A preliminary announcement of a portion of this work was presented earlier: (a) Birkenmeyer, R. D. *Abstr. 20th Intersci. Conf. Antimicrob. Ag. Chemother.* **1980**, abstr 65. (b) Lewis, C.; Stern, K. F.; Zurenko, G. E. *Ibid.* **1980**, abstr 66.
(2) Pirlimycin is the generic name for the (2S-cis)-4-ethylpipecolamide of methyl (7S)-7-chloro-7-deoxythiolincosaminide.
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Chart I[a]

1 (clindamycin)   **2**   **6e** (cis-R)

7e (pirlimycin, cis-S)

[a] R₁ =

This paper describes a further examination of the structure–activity relationships of a series of analogues in which the size of the cyclic amino acid amide portion of the molecule was increased or decreased by one, two, or three methylene groups. In the six-membered ring series, we also investigated the effect on antibacterial activity of changes in N-substitution and in the length, branching, and position of the alkyl side chain. Pirlimycin (**7e**, U-57,930E) was the most interesting compound prepared in this study.

Chemistry. The synthesis of amides of general structure **5** was carried out as shown in Scheme I. The amino acids **3a–c,l** were obtained from commercial sources, while **3d–j** were prepared by a modification of the method of