To test these analogs for antifertility activity, female Royal Hart rats, 210–230 g, were cohabited with proven breeders for 5 days. Starting on the fifth day, the females were dosed with compound for 10 days. The next day the rats were killed and examined for implantations, fetuses, and *corpora lutea*. Doses of 0, 50, 100, and 200 mg/kg/day (ip or subcutaneously) were used. In this test aminoglutethimide was active but all our analogs were found inactive. Thus it is concluded that the activity of 1 is very specific, as all of the changes made caused the activity to be lost.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, the results obtained for those elements were within ±0.4% of the theoretical values. The structures of all compounds were assigned on the basis of compatible ir and nmr spectra.

Ethyl (and Methyl) 4-Cyano-4-(*p*-nitrophenyl)-2-hexenoate (22). A solution of 28.5 g (0.15 mol) of 2-(*p*-nitrophenyl)butyronitrile[3,4] and 14.7 g (0.15 mol) of ethyl propiolate in 100 ml of dioxane was maintained at 60–80° under N_2 while 15 ml of benzyltrimethylammonium hydroxide (40% in methanol) was added dropwise. Upon completion of the addition, the dark solution was refluxed for 19 hr. The reaction mixture was distilled, accompanied by a great deal of decomposition, to give 20.9 g (48%) of a yellow oil, bp 188–192° (0.15 mm). While the elemental analysis was acceptable, partition chromatography showed at least three major products in roughly equal amounts. Identification by nmr showed them to be the cis and trans isomers of **22** and the *trans*-methyl ester analog of **22** (resulting from transesterification). Scaling up this reaction gave lower yields. *Anal.* ($C_{15}H_{16}N_2O_4$) C, H, N.

4-Ethyl-4-(*p*-nitrophenyl)glutaconimide (24). Because of the losses on distilling the starting material, crude ester **22** was used. A mixture of 141 g (0.50 mol in theory) of crude, black *cis*- and *trans*-ethyl and -methyl 4-cyano-4-(*p*-nitrophenyl)-2-hexenoate, 150 ml of EtOH, 40 g (1.0 mol) of sodium hydroxide in 200 ml of H_2O, and 100 ml of THF was stirred for 0.5 hr. Then 200 ml of H_2O was added and stirring continued for another 2.5 hr. Upon acidification with aqueous HCl, the mixture was extracted twice with Et_2O (the volume of Et_2O was noted as the interface was not visible). Filtration of the combined organic extracts through diatomaceous earth removed some solid matter. Next the product was extracted into aqueous $KHCO_3$ and the aqueous phase washed with EtOAc followed by acidification. After extraction with Et_2O, the solution of product was washed with brine, dried (Na_2SO_4), and evaporated to dryness. To the residual black oily acid was added 1000 g of polyphosphoric acid. The mixture was stirred and heated at 130–140° for 3 hr and then poured onto ice. Next, it was neutralized with aqueous concentrated KOH. A brown precipitate was collected and washed with H_2O, aqueous $KHCO_3$, and then H_2O. Air drying overnight gave 60.7 g (47%) of a dark brown solid. Four recrystallizations from ethanol and work-up of the mother liquors gave 19.4 g (15% from **21–24**) of yellow crystals, mp 175–178.5°. The nmr was consistent with the structure. *Anal.* ($C_{13}H_{12}N_2O_4$) C, H, N.

4-(*p*-Aminophenyl)-4-ethylglutaconimide (25). Heat was applied to a solution of 10.40 g (40 mmol) of 4-ethyl-4-(*p*-nitrophenyl)glutaconimide (**24**) in 50 ml (50 mmol) of 1 *N* NaOH, 20 ml of H_2O, and 14.8 g of wet (*ca.* 55 mmol) $Na_2S \cdot 9H_2O$ on a steam bath for 30 min. The resulting black solution was adjusted to pH 6 with aqueous HCl and cooled overnight. A brown precipitate was collected and leached twice with warm, dilute, aqueous HCl. Upon adjusting the pH of the extract to 6 with $NaHCO_3$ a tan precipitate appeared which was collected and dried to give 6.71 g (73%) of solid. Two recrystallizations from ethanol purified the product. Some unreacted starting material was recovered from the first brown precipitate which was recycled. A total of 4.09 g (44%) of colorless crystals, mp 200–202°, was obtained, whose nmr was consistent with the structure. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

Ethyl (and Methyl) 3-Methyl-4-cyano-4-(*p*-nitrophenyl)hexanoate (26). This was prepared similarly to **22** except the benzyltrimethylammonium hydroxide (40% in methanol) used was twice taken up in *t*-BuOH and concentrated *in vacuo* before use in this reaction. A 50% yield of product was obtained as a yellow oil, bp 188–191° (0.15 mm). The vpc showed two major and one minor peaks, while the nmr showed 83% ethyl ester and 17% methyl ester, both being 50–50 mixtures of epimers. *Anal.* ($C_{16}H_{20}N_2O_4$) C, H, N.

2-Ethyl-2-(*p*-nitrophenyl)-3-methylglutaramide (28). This reaction was carried out on **26** like the preparation of **24** to give an overall 27% yield of solid product (EtOH), mp 143–150°. The structure of the mixture of diastereomers was confirmed by nmr. *Anal.* ($C_{14}H_{16}N_2O_4$) C, H, N.

2-(*p*-Aminophenyl)-2-ethyl-3-methylglutarimide (29). This reduction was carried out similarly to **17–20**. The product was a yellow oil whose structure and solvation were confirmed by nmr. *Anal.* ($C_{14}H_{18}N_2O_2 \cdot 0.25EtOH$) C, H, N.

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Studies on β-Lactams. 35.[1] Antibacterial Activity of Monocyclic β-Lactams

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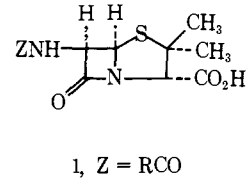
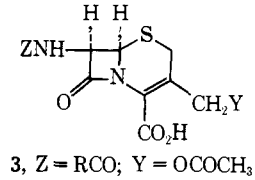
In recent years a large number of penicillins (**1**) and cephalosporins (**3**) have been prepared from 6-APA (**2**) and 7-ACA (**4**) in an effort to modify the antibacterial activity of these bicyclic β-lactams. From the literature on structure–activity correlation in the penicillin–cephalosporin field, it appears to be a generally held view that the following features are essential for therapeutically effective antibiotic activity:[2] an α-amido-β-lactam, cis stereochemistry of the fused β-lactam, and a free carboxy group in the non-β-lactam heterocycle part.



1, Z = RCO
2, Z = H



3, Z = RCO; Y = $OCOCH_3$
4, Z = H; Y = $OCOCH_3$

The various monocyclic β-lactams obtained by the scission of the thiazolidine ring in penicillins and subsequent transformations for obtaining cephalosporin derivatives appear to be without antibacterial activity.[3] We wish to report here the first examples of synthetic monocyclic β-lactams that have shown antibiotic activity.

In the course of a project on the total synthesis of diverse analogs of penicillins and cephalosporins, we have prepared variously substituted monocyclic β-lactams. The "acid chloride–imine" reaction[4] was used for the synthesis of the 1,3,4-trisubstituted 2-azetidinones described herein.

Table I. Antibiotic Activity of Monocyclic β-Lactams

Compd	Test organisms	MIC,[a] μ/ml
7	*Bacillus subtilis* ATCC 6633	100
9	*Streptococcus haemolyticus* A 266	100
	Diplococcus pneumoniae L 54	100
11	*Brucella melitensis* A 488 (gram-neg)	25
14	*Brucella melitensis* A 488 (gram-neg)	25
17	*Staphylococcus aureus* ATCC 6538 P(A 55)	100
	Staphylococcus aureus A 321	100
	Staphylococcus aureus A 355	100
	Staphylococcus aureus L 160a	100
18	*Staphylococcus aureus* ATCC 6538 P(A 55)	50
20	*Bacillus subtilis* ATCC 6333	50
	Staphylococcus aureus ATCC 6538 P(A 55)	50
22	*Brucella melitensis* A 488 (gram-neg)	50
24	*Brucella melitensis* A 488 (gram-neg)	50

[a] A stock solution of the test compounds at a concentration of 2000 μ/ml in 0.05 *M* phosphate buffer solution at a pH of 6.5 was prepared and twofold dilutions were made with sterile buffer. 1-ml quantities of each dilution were then incorporated into 19 ml of brain heart infusion agar in sterile petri dishes. The hardened surface was then inoculated with the test organisms and it was then incubated for 18 hr at 37°. The minimum inhibitory concentration (MIC) which is the least amount of compound completely inhibiting the test organism was determined in μ/ml.

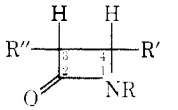
The Schiff base **6** was treated with the appropriate acid chloride **5** in the presence of triethylamine when β-lactams **7**, **8**, **11**, **12**, **15**, **19**, **21**, **23**, and **24** were formed in 60–80% yield. The nmr spectra of these β-lactams revealed cis stereochemistry (J = 4–6 Hz) of the protons at C_3 and C_4. The 3-azido-β-lactams **8** and **15** were reduced to the corresponding amino-β-lactams **9** and **16** by catalytic reduction using 10% Pd/C. The amino β-lactam **9** upon acylation with phenylacetyl chloride produced the α-amido-β-lactam **10**. In order to incorporate an amido side chain in the C_4 substituent on the azetidinone ring, the nitro-β-lactams **12** and **21** were reduced with 10% Pd/C to the amino-β-lactams **13** and **22**. The reaction of **13** with phenylacetyl chloride generated the amido-2-azetidinone **14**.

The β-lactam **19** was prepared by treating the Schiff base derived from ethyl anthranilate and furfuraldehyde and treating it with phenoxyacetyl chloride. The ester group in the β-lactam **19** could not be preferentially hydrolyzed to obtain the corresponding carboxy-β-lactam **20**. Neither acid nor base hydrolysis could be employed as the β-lactam ring is susceptible to cleavage under these conditions. Preferential ester cleavage was, however, accomplished by refluxing **19** with lithium iodide in anhydrous pyridine[5] when **20** was formed in 88% yield.

RCH_2COCl (**5**) $\qquad$ $R'CH{=}NR$ (**6**)

The β-lactams **7**–**24** were tested *in vitro* for antibacterial activity against a number of different gram-positive and gram-negative bacteria (see Table I). It is interesting to note that these 1,3,4-trisubstituted 2-azetidinones do not possess all the structural features that have until now appeared to be essential for antibiotic activity in penicillins and cephalosporins. Thus, the α-amido-β-lactam **9** is active but the corresponding α-(phenylacetamido)-β-lactam **10** has no activity; N-acylation of the inactive amino-β-lactam **13** has generated the antibacterial property in the amido-β-lactam **14** but the amido group in this compound is not α to the β-lactam carbonyl; the trans configuration in **20** has not eliminated antimicrobial activity. More importantly, the active β-lactams **4**, **8**, **14**, **17**, **18**, **20**, **22**, and **24** have a methoxy or a phenoxy group α to the β-lactam carbonyl instead of an amido group. 1-Phenyl-3-phenoxy-4-(*o*-aminophenyl)-2-azetidinone (**22**) is active against *Brucella melitensis*, whereas the corresponding 1-cyclohexyl compound **13** is inactive. Comparison of **19** and **20** shows that the presence of a free carboxylic acid is helpful (Chart I).

Chart I. Substituted β-Lactams[a]

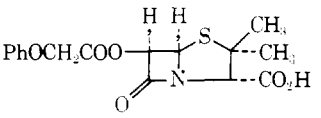


	R	R′	R″
7	*p*-$CH_3COC_6H_4$	*p*-$CH_3OC_6H_4$	OCH_3
8	Ph_2CH	*p*-$CH_3OC_6H_4$	N_3
9	Ph_2CH	*p*-$CH_3OC_6H_4$	NH_2
10	Ph_2CH	*p*-$CH_3OC_6H_4$	$NHCOCH_2Ph$
11	C_6H_{11}	*o*-$NO_2C_6H_4$	OCH_3
12	C_6H_{11}	*o*-$NO_2C_6H_4$	OPh
13	C_6H_{11}	*o*-$NH_2C_6H_4$	OPh
14	C_6H_{11}	*o*-$(NHCOCH_2Ph)C_6H_4$	OPh
15	*p*-$CH_3OC_6H_4$		N_3
16	*p*-$CH_3OC_6H_4$		NH_2
17[b]	*p*-$CH_3OC_6H_4$	*p*-$(CO_2H)C_6H_4$	OPh
18[b]	*p*-$(CO_2H)C_6H_4$	*p*-$CH_3OC_6H_4$	OPh
19	*p*-$(CO_2CH_3)C_6H_4$		OPh
20	*p*-$(CO_2H)C_6H_4$		OPh
21	Ph	*o*-$NO_2C_6H_4$	OPh
22	Ph	*o*-$NH_2C_6H_4$	OPh
23	Ph_2CH	*p*-$CH_3OC_6H_4$	OPh
24	Ph_2CH	*p*-$CH_3OC_6H_4$	OMe

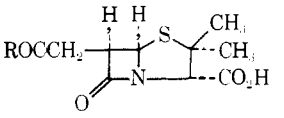
[a] The β-lactams **16** and **17** are of trans configuration; the rest are of cis stereochemistry. [b] See ref 12.

The number of compounds in this communication is too small to allow any generalization on structure–activity correlation at this stage. Their activity is of a lower order than most penicillins and cephalosporins; it is quite possible that different modes of action are involved. In this connection it is worth noting that wildfire toxin[6] isolated from *Pseudomonas tabaci* is a monocyclic β-lactam that shows various types of biological activity including antimicrobial activity.

Some monocyclic β-lactams had been reported previously by Testa, *et al.*, to have CNS activity.[7] Antiinflammatory activity was observed for some spiro-β-lactam synthesized by Bose and coworkers.[8,9] Levine and Narayanan[10] have reported that 1-adamantyl-2-azetidinone has antiviral activity. Recently Sheehan and coworkers[11] have shown that penicillin derivatives in which the amide side chain has been replaced by other functionalities as in **25** and **26** also exhibit antibacterial activity. These results



25



26a, R = Ph
b, R = CH_2OPh

Table II. Analytical and Spectral Data

Compd	Mp, °C	Formula	Analyses[a]	Spectral data
7	135–136 (CH_2Cl_2–*n*-hexane)	$C_{19}H_{19}NO_4$	C, H, N	Ir 1750 (β-lactam CO), 1685 cm^{-1}; nmr 7.5 (q, 4 H, J = 8 Hz), 7.01 (q, 4 H, J = 8 Hz), 5.2 (d, 1 H, J = 5 Hz, cis), 4.8 (d, 1 H, J = 5 Hz, cis); mass spectrum *m/e* 325, 253, 164, 97
8	107–109 (CH_2Cl_2–*n*-hexane)	$C_{23}H_{20}N_4O_2$	C, H, N	Ir 2110 (N_3), 1750 cm^{-1} (β-lactam CO); nmr 7.5–6.72 (m, 14 H), 5.6 (s, 1 H), 4.85 (d, 1 H, J = 5 Hz, cis), 4.63 (d, 1 H, J = 5 Hz, cis), 3.72 (s, 3 H)
9	140 (CH_2Cl_2 + *n*-hexane)	$C_{23}H_{22}N_2O_2$	C, H, N	Ir 3260 (NH_2), 1720 cm^{-1} (β-lactam CO); nmr 7.4–6.7 (m, 14 H), 5.7 (s, 1 H), 4.79 (d, 1 H, J = 6 Hz, cis), 4.41 (d, 1 H, J = 6 Hz, cis), 3.74 (s, 3 H), 2.21 (s, 2 H); mass spectrum M^+ at *m/e* 358
10	122 (CH_2Cl_2–*n*-hexane)	$C_{30}H_{28}N_2O_3$	C, H, N	Ir 3300 (NH), 1755 (β-lactam CO), 1675 cm^{-1} (amide CO); nmr 7.3–6.5 (m, 19 H), 5.65 (s, 1 H), 4.83 (m, 2 H), 4.13 (d, 1 H, J = 5 Hz), 3.74 (s, 3 H), 3.24 (s, 2 H)
11	95–96 (CH_2Cl_2–*n*-hexane–C_6H_6)	$C_{16}H_{20}N_2O_4$	C, H, N	Ir 1770 cm^{-1} (β-lactam CO); nmr 8.08–7.26 (m, 9 H), 5.01 (d, 1 H, J = 5 Hz, cis), 4.78 (d, 1 H, J = 5 Hz, cis), 3.16 (s, 3 H), 3.35 (b, 1 H), 1.5 (b, 10 H)
12	121–122 (C_6H_6–*n*-hexane)	$C_{21}H_{22}N_2O_4$	C, H, N	Ir 1755 cm^{-1} (β-lactam CO); nmr 8.01–6.65 (m, 8 H), 5.7 (d, 1 H, J = 5 Hz, cis), 5.45 (d, 1 H, J = 5 Hz, cis), 3.48 (b, 1 H), 1.5 (b, 10 H)
13	163–164 (CH_2Cl_2 + *n*-hexane)	$C_{21}H_{24}N_2O_2$	C, H, N	Ir 3450 (–NH_2), 1745 cm^{-1} (β-lactam CO); nmr 6.5–7.4 (m, 9 H), 5.34 (d, 1 H, J = 5 Hz, cis), 5.0 (d, 1 H, J = 5 Hz, cis), 3.55 (b, 1 H), 1.5 (vb, 12 H); mass spectrum 336, 243, 211
14	116–118 (CH_2Cl_2 + *n*-hexane)	$C_{29}H_{30}N_2O_3$	C, H, N	Ir 3245 (–NH), 1765 (β-lactam CO), 1700 cm^{-1} (amide CO); nmr 7.5–6.35 (m, 15 H), 5.05 (b, 1 H), 4.75 (d, 1 H, J = 6 Hz, cis), 3.7 (s, 2 H), 3.35 (b, 1 H), 1.5 (vb, 10 H); mass spectrum 454, 361, 330, 321, 134
15	68–70 (C_6H_6–*n*-hexane)	$C_{14}H_{12}N_4O_3$	C, H, N	Ir 2100 (N_3), 1740 cm^{-1} (β-lactam CO); nmr 7.48–6.40 (m, 7 H), 5.11 (d, 1 H, J = 5 Hz, cis), 4.88 (d, 1 H, J = 5 Hz, cis), 3.7 (s, 3 H); mass spectrum *m/e* 283, 255, 200, 149, 143
16	129–131 (CH_2Cl_2 + *n*-hexane)	$C_{14}H_{14}N_2O_3$	C, H, N	Ir 3380, 3440 (NH_2), 1760 cm^{-1} (β-lactam CO); nmr 7.3–6.26 (m, 7 H), 5.22 (d, 1 H, J = 5 Hz, cis), 4.65 (d, 1 H, J = 5 Hz, cis), 3.78 (s, 3 H), 1.36 (b, 2 H)
19	120 (CH_2Cl_2–*n*-hexane)	$C_{21}H_{17}NO_5$	C, H, N	Ir 1755 (β-lactam CO), 1725 cm^{-1} (ester CO); nmr 8.16–6.4 (m, 12 H), 5.5 (d, 1 H, J = 2 Hz, trans), 5.17 (d, 1 H, J = 2 Hz, trans), 3.87 (s, 3 H); mass spectrum *m/e* 363, 332, 229, 186
20	199–200 (CH_2Cl_2 + *n*-hexane)	$C_{20}H_{15}NO_5$	C, H, N	Ir 1785 (β-lactam CO), 1690 cm^{-1} (acid CO); nmr 8.1–6.33 (m, 12 H), 5.44 (d, 1 H, J = 2 Hz, trans), 0.9 (b, 1 H); mass spectrum M^+ at *m/e* 349
21	125–126 (C_6H_6–*n*-hexane)	$C_{21}H_{16}N_2O_4$	C, H, N	Ir 1775 cm^{-1} (β-lactam CO); nmr 8.28–6.77 (m, 14 H), 6.12 (d, 1 H, J = 5 Hz, cis), 5.66 (d, 1 H, J = 5 Hz, cis); mass spectrum *m/e* 360, 226, 241, 119
22	223–224 (CH_2Cl_2 + *n*-hexane)	$C_{21}H_{16}N_2O_2$	C, H, N	Ir 3360, 3200 (–NH_2), 1685 cm^{-1} (β-lactam CO); nmr 7.5–5.9 (m, 14 H), 5.0 (m, 2 H), 3.32 (s, 2 H); mass spectrum *m/e* 330, 237, 196, 93
23	122–124 (CH_2Cl_2 + *n*-hexane)	$C_{29}H_{25}NO_3$	C, H, N	Ir 1750 cm^{-1} (β-lactam CO); nmr 7.5–6.6 (m, 19 H), 5.75 (s, 1 H), 5.42 (d, 1 H, J = 4.7 Hz, cis), 5.26 (d, 1 H, J = 4.7 Hz, cis), 6.68 (s, 3 H); mass spectrum M^+ at *m/e* 436
24	93–95 (CH_2Cl_2 + *n*-hexane)	$C_{24}H_{23}NO_3$	C, H, N	Ir 1730 cm^{-1} (β-lactam CO); nmr 7.3–6.61 (m, 14 H), 5.7 (s, 1 H), 4.65 (s, 2 H), 3.75 (s, 3 H), 3.1 (s, 3 H). The signal at δ 4.65 was resolved into a quartet with J = 4.5 Hz (cis) in a 100-MHz nmr spectrum

[a] Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

coupled with our own findings on the antimicrobial action of some monocyclic β-lactams point to the possibility of a wider field of search for β-lactam antibiotics.

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord spectrometer. The nmr spectra were recorded on a Varian A-60A spectrometer using TMS as an internal standard. The chemical shifts are shown in δ units (parts per million downfield from TMS). See Table II.

Preparation of Schiff Bases. The Schiff bases were prepared by refluxing a benzene solution of the appropriate amine and aldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid; a water separator was used to aid the completion of reaction. After removal of the solvent under reduced pressure the crude products were used as such for further work.

Schiff bases from cyclohexylamine were formed when anhydrous $ZnCl_2$ was employed instead of *p*-toluenesulfonic acid as the catalyst.

Preparation of β-Lactams. 1-(*p*-Acetylphenyl)-3-methoxy-4-(*p*-methoxyphenyl)azetidin-2-one (7). The Schiff base from *p*-methoxybenzaldehyde and *p*-aminoacetophenone (2.5 g) and triethylamine (1.01 g) were stirred in anhydrous CH_2Cl_2 (200 ml) under a nitrogen atmosphere while a solution of methoxyacetyl chloride (1.1 g) in dry CH_2Cl_2 (40 ml) was added dropwise. After addition was complete the mixture was stirred overnight. The resulting solution was washed with water (100 ml × 4) and dried ($MgSO_4$). Removal of the solvent gave the title compound.

The β-lactams 8, 11, 12, 15, 19, 21, 23, and 24 were prepared by the same general procedure using the appropriate acid chloride and Schiff base.

Preparation of α-Amido-β-lactams. 1-Benzhydryl-3-amino-4-(*p*-methoxyphenyl)-2-azetidinone (9). Platinum oxide (1 g) was added to a solution of 4 g of the azido-β-lactam 8 in ethyl acetate and the mixture hydrogenated at 40 psi overnight, filtered, and evaporated to give 9 (3.5 g).

1-Benzhydryl-3-phenylacetamido-4-(*p*-methoxyphenyl)-2-azetidinone (10). Phenylacetyl chloride (0.7 g) in dry methylene chloride (50 ml) was added dropwise over a period of 45 min to a stirred solution of 9 (1.5 g) and triethylamine (0.5 g) and stirred overnight. The resulting solution was washed with water (50 ml × 3) and dried ($MgSO_4$). Removal of the solvent gave a thick oily liquid which was chromatographed over Florisil to provide the amido-β-lactam 10.

The nitro-β-lactam 12 was reduced to the amino compound 13 using Adams catalyst and subsequently acylated to 14 with phenylacetyl chloride using similar conditions as described for the synthesis of 10.

1-(*p*-Carboxyphenyl)-3-phenoxy-4-furfuryl-2-acetidinone (20). A mixture of the carbomethoxy-β-lactam 19 (1.0 g) and LiI (2.5 g) in anhydrous pyridine (30 ml) was refluxed (12 hr) under nitrogen atmosphere. The golden yellow solution was cooled, diluted with $CHCl_3$ (100 ml), and poured into 150 ml of cooled (0°) concentrated HCl. The aqueous phase was extracted with $CHCl_3$ (4 × 100 ml); the combined organic phase was washed with cold water (3 × 50 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure provided 0.85 g of the carboxy derivative 20.

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Synthesis and Antiinflammatory Activity of a Series of 2-Aroyl-1,1a,2,6b-tetrahydrocycloprop[*b*]indole-1-carboxylic Acids

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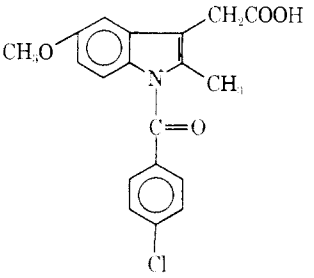
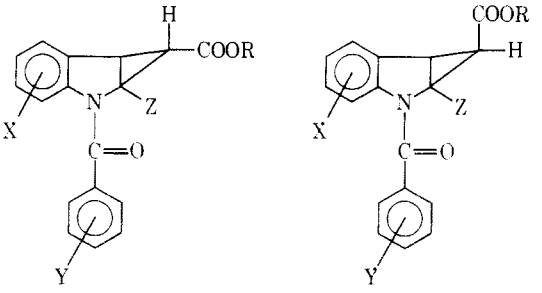
In an attempt to prepare an effective antiinflammatory agent and, at the same time, better define the hypothetical receptor proposed by Shen for antiinflammatory compounds related to indomethacin,[1] we have prepared a series of 2-aroyl-1,1a,2,6b-tetrahydrocycloprop[*b*]indole-1-carboxylic acids and esters, I and II, for structure–activity studies. This chemical modification provides structural rigidity without the addition of bulky substituents and allows a pharmacological comparison of the two diastereomers. In addition, the reduction in electron density brought about by expanding the 2,3 double bond into a cyclopropyl ring was expected to shed some light on the electronic requirements of the receptor.



indomethacin



Ia, R = C_2H_5
b, R = H

IIa, R = C_2H_5
b, R = H

X = H, Cl, OCH_3
Y = H, Cl, OCH_3, CF_3
Z = H, CH_3

Chemistry. Previous attempts to prepare the 1,1a,2,6b-tetrahydrocycloprop[*b*]indole ring system by the addition of ethyl diazoacetate to indoles have led to rearrangement products.[2] We have found that deactivation of the indole nucleus with a 1-aroyl group allows the insertion of a carbalkoxymethylene group into the 2,3 double bond without rearrangement. In our case, ethyl diazoacetate was added to a 1-aroylindole using CuCN as a catalyst to produce the desired ring system. The reaction conditions are critical for acceptable yields.

Nmr analysis of the reaction mixtures indicated the formation of a mixture of exo and endo isomers Ia and IIa, usually in the ratio of about 5:1. After separation by column chromatography, the structures were unequivocally assigned on the basis of characteristic nmr coupling constants for *cis*- and *trans*-cyclopropyl hydrogens[3] and the marked upfield shift (*ca.* 0.3 ppm) of the ethyl group signals in IIa relative to Ia, due to the shielding influence of the aromatic ring. (See paragraph at the end of the paper regarding supplementary material.)

Saponification of the esters Ia and IIa gave the corresponding acids Ib and IIb in good yields. The nmr spectra of the crude reaction mixtures showed that little or no rearrangement to an indoleacetic acid had taken place. The larger coupling constants (7–9 Hz) confirm the all-cis arrangement for the cyclopropyl protons in IIb. In the spectra of Ib, the smaller coupling constants (2–4 Hz) for *trans*-cyclopropyl protons are visible, in addition to the dramatic upfield shift (0.2–0.5 ppm), relative to IIb, of the proton α to the carboxyl group, due to shielding by the aromatic ring.