30% acetone in $CHCl_3$ as solvent. The product recrystallized from aqueous MeOH to afford **11** in a yield of 46%: mp 98–99°; nmr δ 0.81 (s, C-18 H's), 1.21 (s, C-19 H's), and 5.76 (s, C-4 H). *Anal.* ($C_{22}H_{34}O_4$) C, H.

17β-(3′-Hydroxypropyl)androst-4-en-3-one (12). Conditions similar to those used to prepare **7** were used to convert **13** to **12** in a yield of 91%. The product was recrystallized from aqueous acetone: mp 85–86°. *Anal.* ($C_{22}H_{34}O_3$) C, H.

17β-(3′-Hydroxypropoxy)androst-5-ene-3,2′-(1′,3′-dioxolane) (13). To a flask which contained 9-borabicyclo[3.3.1]nonane (0.219 g, 1.79 mmol) and which was cooled in an ice bath was added, under N_2, a solution of **3** (0.5 g, 1.34 mmol) in 10 ml of THF. The mixture was stirred at room temperature for 3 hr and under reflux for 1 hr. The solution was cooled to room temperature and a solution of 2 ml of H_2O, 2 ml of 3 *N* aqueous NaOH, and 2 ml of 30% H_2O_2 was added. The mixture was stirred until gas evolution ceased. The product was chromatographed over 17 g of neutral Al_2O_3 using benzene as solvent. Crystallization from aqueous EtOH or acetone gave **13** in a yield of 49%: mp 168–169°; nmr δ 0.80 (s, C-18 H's), 1.05 (s, C-19 H's), and 5.40 (m, C-6 H). *Anal.* ($C_{24}H_{38}O$) C, H.

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Substituted Pyrazolo Corticoids as Topical Antiinflammatory Agents

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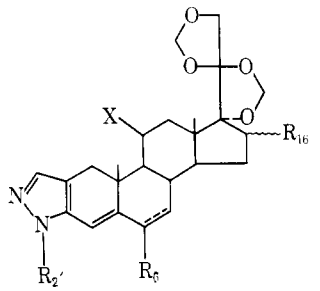
The synthesis of a series of substituted pyrazolo corticoids is described. Of these 11β,17α,21-trihydroxy-6,16α-dimethyl-4,6-pregnadieno[3,2-*c*]-2′-(4-pyridyl)pyrazole (**21**) shows an excellent separation of systemic to local activity in the model animal test. Compound **21** exhibits high vasoconstriction activity in human volunteers and is clinically effective in the treatment of psoriasis.

The discovery that certain heterocycles, especially pyrazoles containing 2′-aryl substituents, imparted enhanced antiinflammatory activity when fused to the corticoid nucleus at the 2,3 positions was reported some years ago by Hirschmann, *et al.*,[1a] and has been further explored by the Merck group[1,2] and by others.[3] The Merck findings have been reviewed.[1e]

To date, there have been no reports that such derivatization raises steroidal androgenic, progestational, or aldosterone antagonist potency. This implies potentially increased selectivity with respect to the antiinflammatory process. Furthermore, preliminary studies indicated that pyrazolo corticoids could be active antiinflammatory agents without requiring all of the typical corticoid functionality and that they could show a high local to systemic ratio relative to hydrocortisone. An early example was 17α,21-dihydroxy-20-oxopregn-4-eno[3,2-*c*]-2′-(4-fluorophenyl)pyrazole (**1**) which was 30 times as potent in the local granuloma test as hydrocortisone and which unexpectedly displayed 12 times greater local than systemic inhibition of granuloma formation in the same test system.

With this encouraging data, we initiated a search for an optimal topical antiinflammatory steroid among the pyrazolo corticoids using as criteria high local activity, low systemic activity, and good skin penetration.

Table I



R_2	R_6	X	R_{16}	Method	Mp, °C	Formula[a]
4-FC_6H_4[b]	H	H	H	A	221–225	$C_{30}H_{35}FN_2O_4$
$C_6H_5CH_2$	H	OH	α-CH_3	B	193–196	$C_{32}H_{40}N_2O_5$
4-FC_6H_4	H	OH	α-CH_3	*f*	154.5–155.5	$C_{31}H_{37}FN_2O_5$
4-ClC_6H_4	H	OH	α-CH_3	*g*	155–157	$C_{31}H_{37}ClN_2O_5$
4-HOC_6H_4	H	OH	α-CH_3	B	326–329 dec	$C_{31}H_{38}N_2O_6$
4-$CH_3CONHC_6H_4$[c]	H	OH	α-CH_3	B	199–202 dec	$C_{33}H_{41}N_3O_6$
4-$CH_3SC_6H_4$	H	OH	α-CH_3	B	225–231 dec	$C_{32}H_{40}N_2O_5S$
4-$CH_3SOC_6H_4$[d]	H	OH	α-CH_3		209–297	$C_{32}H_{40}N_2O_6S$
$CH_3CH_2CH_2$	H	OH	α-CH_3	B	183–186	$C_{28}H_{40}N_2O_5$
Cyclopropyl	H	OH	α-CH_3	B	Amorphous	$C_{28}H_{38}N_2O_5$
Cyclopentyl	H	OH	α-CH_3	B	Amorphous	$C_{30}H_{42}N_2O_5$
Cyclohexyl	H	OH	α-CH_3	B	Amorphous	$C_{31}H_{44}N_2O_5$
CH_3OOCCH_2	H	OH	α-CH_3	B	189–194	$C_{26}H_{36}N_2O_6$
$HOCH_2CH_2$	H	OH	α-CH_3	*g*	184–186	$C_{27}H_{38}N_2O_6$
2-Pyridyl	H	OH	α-CH_3	A	270–278 dec	$C_{30}H_{37}N_3O_5$
3-Pyridyl	H	OH	α-CH_3	A	230–235	$C_{30}H_{37}N_3O_5$
4-Pyridyl	H	OH	α-CH_3	A	278–284	$C_{30}H_{37}N_3O_5$
4-Piperidyl	H	OH	α-CH_3	B	Amorphous	$C_{30}H_{43}N_3O_5$
4-Pyridyl	CH_3-Δ^6	OH	α-CH_3	B	279–285	$C_{31}H_{37}N_3O_5$
4-$CH_3CONHC_6H_4$	CH_3-Δ^6	OH	α-CH_3	B	199–202	$C_{34}H_{41}N_3O_6$
4-Pyridyl[e]	CH_3-Δ^6	OH	β-CH_3	*e*	291–295	$C_{31}H_{37}N_3O_5$

[a] Analytical results were within 0.4% of the theoretical values. [b] 2′ isomer: 58% yield; mp 221–225°; λ_{max} 262 nm (ε 16,520); $[\alpha]^{25}D$ +17.6°. *Anal.* ($C_{30}H_{35}N_2O_4$) C, H, N. 1′ isomer: 11% yield; mp 282–286°; λ_{max} 294 nm (ε 28,470); $[\alpha]^{25}D$ −53.4°. *Anal.* ($C_{30}H_{35}N_2O_4$) C, H, N. [c] Made from 17α,20:20,21-bis(methylenedioxy)-2-hydroxymethylene-16α-methylpregn-4-ene-3,11-dione[1c] *via* pyrazole formation (method B) to yield the product, mp 221–225° [*Anal.* ($C_{33}H_{39}N_3O_6$) C, H, N], further reduced by $NaBH_4$-*i*-PrOH to yield the indicated compound. [d] Prepared from the 4-$CH_3SC_6H_4$ precursor by peracetic acid oxidation. [e] The required 17α,20:20,21-bis(methylenedioxy)-2-hydroxymethylene-6,16β-dimethyl-4,6-pregnadiene-3,11-dione was made in these laboratories by Dr. D. W. Graham and characterized by mp 235–247°; λ_{max} 292 nm (ε 15,300). *Anal.* ($C_{26}H_{32}O_7$) C, H from 17α,20:20,21-bis(methylenedioxy)-11β-hydroxy-6α,16β-dimethylpregn-4-en-3-one (to be published). 17α,20:20,21-Bis(methylenedioxy)-6,16β-dimethyl-11-oxopregna-4,6-dieno[3,2-*c*]-2′-(4-pyridyl)pyrazole was prepared by method A and melted at 315–325° dec. *Anal.* ($C_{31}H_{35}N_3O_5$) C, H, N. It was further reduced by $NaBH_4$-*i*-PrOH to yield the compound indicated in this table. [f] See ref 1a. [g] See ref 1c.

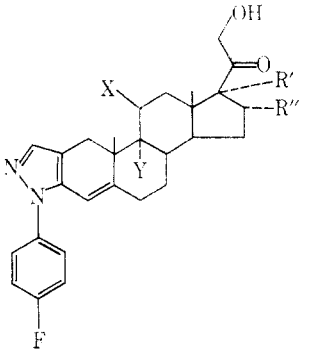
Chemistry. Methods for the synthesis of substituted pyrazolo corticoids were developed by Hirschmann, *et al.*[1a,b] In this investigation we used two procedures for pyrazole formation from the 2-hydroxymethylene-3-keto intermediates. Both are quite broadly applicable although the glacial acetic acid method was not satisfactory in the case of the pyridylpyrazoles. Characterization data for the intermediate, BMD-protected pyrazolo corticoids appear in Table I. Assignments as the desired 2′ isomers were based on characteristic uv differences between the 2′ and 1′ isomers. Only in the case of the 11-desoxy compound **1** was a substantial proportion (11%) of the inactive 1′ isomer formed.

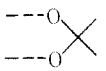
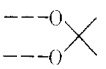
Results

Summary data on several of the pyrazolo corticoids made initially in this project appear in Table II. The intent was to investigate the applicability of the 16,17-acetonide function and the possible usefulness of the 11-desoxy function in reducing systemic effects. Although high potencies and encouraging local/systemic ratios were obtained in the model system, the potency of these steroids did not extrapolate to the vasoconstriction test using human subjects. Perhaps poor dermal penetration was a limiting factor. In any event, it was evident that vasoconstriction activity would have to be an important early criterion in addition to potency and ratio as determined in the rat granuloma systems.

Table III summarizes variations of the 2′ substituent on the pyrazole of 16α-methylhydrocortisone, expanding the work of Hirschmann, *et al.*, in which high systemic activity with 2′-phenyl and 2′-(4-fluorophenyl) substituents was found. Despite its mediocre potency in the granuloma assays, surprisingly high vasoconstriction activity was observed with the 4-acetamidophenyl analog. Good local to systemic activity ratios were apparent for the benzyl, cyclohexyl, and 4-pyridyl derivatives, with the latter appearing to be the most promising in respect to the three preclinical criteria mentioned above. The 2′-(4-pyridyl)- and 2′-(4-acetamido)-[3,2-*c*]pyrazole functions were accordingly combined with other potency enhancing groups in the cortical steroid series. Some of the data which were obtained are summarized in Table IV. It was concluded that compound **21** held special promise for further studies based on both the granuloma and vasoconstriction data. Confirmation was obtained in recent multiclinic studies in

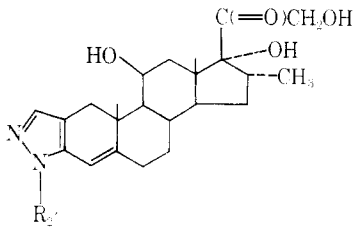
Table II



No.	X	Y	R′	R″	Formula	Mp, °C	Rat granuloma assay[a] (potency × hydrocortisone) Local	Rat granuloma assay[a] (potency × hydrocortisone) Systemic	Vasoconstriction,[b] rel potency at ED_{50}
1[c]	H	H	OH	H	$C_{28}H_{33}FN_2O_3$	226–238 dec	30	2.5	
2	H	H			$C_{31}H_{37}FN_2O_4$	215–221	110	7	<1
3[d]	H	F			$C_{31}H_{36}F_2N_2O_5$	244–258 dec	2000–3000	300	40
Fluocinolone acetonide							100–150	150	100

[a]Inhibition of granuloma was measured in the rat cotton pellet assay.[4] For a local test the steroid was absorbed onto the pellet from a 95% ethanol solution, dried *in vacuo*, and implanted. Systemically, the steroid was administered in the diet. [b]Vasoconstriction was estimated under occlusion on human volunteers using fluocinolone acetonide as the standard (100).[5] The steroids were applied using dilutions of a 95% ethanol solution to groups of ten subjects. Effective dose 50% response was measured graphically from a plot of number of patients responding against −log dilution over a range of 1/10,000 to 1/6,250,000. All compounds were submitted for assay under a code number rather than identified by structure. We are grateful to Dr. R. B. Stoughton, Scripps Clinic and Research Foundation, La Jolla, Calif., for these determinations conducted under a grant-in-aid from the Merck Sharp & Dohme Research Laboratories. [c]2′ isomer: mp 226–238° dec; λ_{max} 260 nm (ε 16,540); $[\alpha]^{27}D$ +115.2°. *Anal.* ($C_{28}H_{33}FN_2O_3$) C, H, N. 1′ isomer: mp 224–235° dec; λ_{max} 295 nm (ε 29,260); $[\alpha]^{25}D$ +46.8°. *Anal.* ($C_{28}H_{33}FN_2O_3$) C, H, N. [d]See ref 3c.

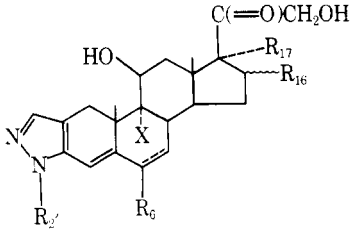
Table III



No.	$R_{2'}$	Formula[c]	Mp, °C	Rat granuloma assay[a] (potency × hydrocortisone) Local	Rat granuloma assay[a] (potency × hydrocortisone) Systemic	Vasoconstriction,[b] rel potency at ED_{50}
4	C_6H_5[d]	$C_{29}H_{36}N_2O_4$	143–145 dec	100	60	
5	$C_6H_5CH_2$	$C_{30}H_{38}N_2O_4$	180–185	50–70	2–3	2
6	4-FC_6H_4	$C_{29}H_{35}FN_2O_4$	240–248	100–200	110	15
7	4-ClC_6H_4	$C_{29}H_{35}ClN_2O_4$	243–252 dec	40	15	
8	4-HOC_6H_4	$C_{29}H_{36}N_2O_5$	259–263	10–20	3	1
9	4-$CH_3CONHC_6H_4$	$C_{31}H_{39}N_3O_5$	221–222	5–10	4–5	49
10	4-$CH_3SOC_6H_4$	$C_{30}H_{38}N_2O_5S$	245–248		<4	1
11	$CH_3CH_2CH_2$	$C_{26}H_{38}N_2O_4$	198–204	20		4
12	Cyclopropyl	$C_{26}H_{36}N_2O_4$	207–209	3–10		6
13	Cyclohexyl	$C_{29}H_{42}N_2O_4$	179–183	50	8	17
14	Cyclopentyl	$C_{28}H_{40}N_2O_4$	177–180	200–250	50–70	21
15	CH_3OOCCH_2	$C_{26}H_{36}N_2O_6$	118–120	<4	<2	<1
16	$HOCH_2CH_2$	$C_{25}H_{36}N_2O_5$	195–199	20 or >		<1
17	4-Pyridyl	$C_{28}H_{35}N_3O_4$	223–232	75–100	4	36
18	2-Pyridyl	$C_{28}H_{35}N_3O_4$	228–237 dec	5–10		2
19	3-Pyridyl	$C_{28}H_{35}N_3O_4$	259–265	75–100	80	7
20	4-Piperidyl	$C_{28}H_{41}N_3O_4$	Amorphous	5–7	<2	<1

[a,b]See Table II. [c]Analytical results for C, H, and N were within 0.4% of the theoretical value. [d]See ref 1c.

Table IV



No.	$R_{2'}$	R_6	X	R_{16}	R_{17}	Formula[c]	Mp, °C	Rat granuloma assay[a] (potency × hydrocortisone) Local	Rat granuloma assay[a] (potency × hydrocortisone) Systemic	Vasoconstriction,[b] rel potency at ED_{50}
20	4-Pyridyl	6-CH_3-Δ^6	H	β-CH_3	OH	$C_{29}H_{35}N_3O_4$	214–218	20–30	2–3	2
21	4-Pyridyl[d]	6-CH_3-Δ^6	H	α-CH_3	OH	$C_{29}H_{35}N_3O_4$	209–213	1000–1500	40–50	74
22	4-Pyridyl	H_2	F	---O ---O		$C_{30}H_{36}FN_3O_5$	285–290	300–350	20	2
23	4-$CH_3CONHC_6H_4$	H_2	F	---O ---O		$C_{33}H_{40}FN_3O_6$	200–205		<10	<1

[a,b] See Table II. [c] See Table III. [d] Compound 21 showed no progestational activity at 0.2 and 1.0 mg/kg in the Clauberg-McPhail assay. (We are indebted to Dr. J. R. Brooks of the Merck Institute, Rahway, N.J., for these determinations.) The topical antiinflammatory corticoids fluocinolone 16,17-acetonide and bethamethasone 17-valerate are reported[6] to be progestagens 50.3 and 7.2 times as active as progesterone, respectively.

which a 0.1% concentration of compound 21 in an alcoholic gel vehicle was shown to be active in the treatment of psoriasis.

Experimental Section

Except where otherwise stated, uv spectra were measured in methanol, and rotations as approximately 1% solutions in chloroform. Where analyses are indicated only by symbols of the elements, results were within ±0.4% of the theoretical values.

Pyrazole Formation. Two sets of standard conditions were used.

17α,20:20,21-Bis(methylenedioxy)-11β-hydroxy-6,16α-dimethylpregna-4,6-dieno[3,2-c]-2′-(4-pyridyl)pyrazole (Method A). A solution of 4-pyridylhydrazine hydrochloride (0.380 g, 2.62 mmol) and KOAc (2.57 g, 2.62 mmol) in EtOH (10 ml)-H_2O (5 ml) was added to a solution of 17α,20:20,21-bis(methylenedioxy)-2-hydroxymethylene-11β-hydroxy-6,16α-dimethylpregna-4,6-dien-3-one[1d] (1.00 g, 2.18 mmol) in EtOH (25 ml) and the solution boiled under reflux for 4 hr. Distillation of part of the solvent (10 ml) induced crystallization which was completed by slow addition of water (20 ml) to the hot slurry. The crude product was filtered off and crystallized from EtOH to give 700 mg, mp 279–285°. Chromatography of the mother liquors on silica gel yielded an additional 176 mg. The analytical sample melted at 279–285°: λ_{max} 228, 282.5, 331 nm (ε 8,600, 24,300, 15,800); λ_{max} (MeOH + H^+) 223, 310, 375 nm (ε 10,200, 44,800, 6,300); $[\alpha]^{25}D$ −114.2°. *Anal.* ($C_{31}H_{37}N_3O_5$) C, H, N.

17α,20:20,21-Bis(methylenedioxy)-11β-hydroxy-16α-methylpregn-4-eno[3,2-c]-2′-(*n*-propyl)pyrazole (Method B). A suspension of 17α,20:2,21-bis(methylenedioxy)-2-hydroxymethylene-11β-hydroxy-16α-methylpregn-4-en-3-one[1c] (446 mg, 1.0 mmol), *n*-propylhydrazine oxalate (328 mg, 2.0 mmol), and KOAc (196 mg, 2.0 mmol) in HOAc (15 ml) was stirred at room temperature for 3 hr. The addition of H_2O (50 ml) precipitated an oil which was extracted by $CHCl_3$, purified by preparative tlc on silica ($CHCl_3$–4% MeOH), and crystallized from EtOH to give 188 mg: mp 183–186°; λ_{max} 214, 220, 248, 258, 277 nm (ε 11,830, 12,300, 6,900, 7,700, 11,600); $[\alpha]^{25}D$ +34.8°. *Anal.* ($C_{28}M_{40}N_2O_5$) C, H, N.

11β,17α,21-Trihydroxy-6,16α-dimethyl-20-oxopregna-4,6-dieno[3,2-c]-2′-(4-pyridyl)pyrazole (21) (BMD Reversal Conditions). A solution of 0.365 g of 17α,20:20,21-bis(methylenedioxy)-11β-hydroxy-6,16α-dimethylpregna-4,6-dieno[3,2-c]-2′-(4-pyridyl)-pyrazole in 7 ml of aqueous 60% formic acid was heated on the steam bath for 25 min. The mixture was then cooled in ice and made alkaline with aqueous sodium hydroxide. The suspension containing product was extracted with ethyl acetate. The crude product (0.375 g) after crystallization from methylene chloride displayed mp 209–213°: $[\alpha]^{25}D$ −27.5°; λ_{max} 232.5, 282.5, 330 nm (ε 9,300, 24,400, 15,765). *Anal.* ($C_{29}H_{35}N_3O_4$) C, H, N.

16α,17α,21-Trihydroxy-20-oxopregn-4-eno[3,2-c]-2′-(4-fluorophenyl)pyrazole 16,17-Acetonide (2). To a stirred suspension of 1.289 g of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16,17-acetonide in 2.68 g of dihydropyran at room temperature was added 64 mg of *p*-toluenesulfonic acid monohydrate in 1 ml of ether. After 15 min 0.2 ml of pyridine and 50 ml of ether was added and the combined solvents were washed with water, dried, and removed to leave 1.25 g of crude tetrapyranyl ether. This was dissolved in 20 ml of dry benzene, and 1.18 g of 52.7% NaH oil dispersion and 0.1 ml of MeOH were added to the stirred mixture. Two additions of ethyl formate (1.05 ml) were made at 15 and 45 min. Work-up after 18 hr was by aqueous extraction and then back extraction into ethyl acetate from saturated NaH_2PO_4. The yield of 2-hydroxymethylene ketone was 995 mg of yellow foam: λ_{max} 250 nm ($E_{1\ cm}^{1\%}$ 205), 307 nm ($E_{1\ cm}^{1\%}$ 90) in methanol shifted with base to λ_{max} 242 nm ($E_{1\ cm}^{1\%}$ 259), 358 nm ($E_{1\ cm}^{1\%}$ 163).

Pyrazole formation was according to method A and the dihydropyran removal with concentrated HCl in MeOH under reflux for 15 min. The product displayed mp 215–221° (EtOAc): $[\alpha]^{25}D$ +135°; λ_{max} 263 nm (ε 16,660). *Anal.* ($C_{31}H_{37}FN_2O_4$) C, H, N.

The following compounds were prepared by the same process starting with 11β,16α,17α,21-tetrahydroxy-9α-fluoropregn-4-ene-3,20-dione 16,17-acetonide.

(a) **11β,16α,17α,21-Tetrahydroxy-9α-fluoro-20-oxopregn-4-eno[3,2-c]-2′-(4-fluorophenyl)pyrazole 16,17-acetonide (3):** mp 244–258° dec (MeOH–CH_2Cl_2); $[\alpha]^{27}D$ +109.2°; ε 262 nm (ε 16,250). *Anal.* ($C_{31}H_{36}F_2N_2O_5$) C, H, F, N.

(b) **11β,16α,17α,21-Tetrahydroxy-9α-fluoro-20-oxopregn-4-eno[3,2-c]-2′-(4-pyridyl)pyrazole 16,17-acetonide (22):** mp 285–290° (MeOH–CH_2Cl_2); λ_{max} 212, 269 nm (ε 15,180, 22,150); λ_{max} (MeOH + H^+) 223, 268, 301 nm (ε 10,800, 12,380, 32,400). *Anal.* ($C_{30}H_{36}FN_3O_5$) C, H, N.

(c) **11β,16α,17α,21-Tetrahydroxy-9α-fluoro-20-oxopregn-4-eno[3,2-c]-2′-(4-acetamidophenyl)pyrazole 16,17-acetonide (23):** mp 200–205° (MeOH–H_2O); $[\alpha]^{25}D$ +86.4°. *Anal.* ($C_{33}H_{40}FN_3O_6$) C, H, N.

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Preparation, Hydrolysis, and Oral Absorption of α-Carboxy Esters of Carbenicillin

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Twelve α-carboxy esters of carbenicillin, a parenteral broad spectrum semisynthetic penicillin, were synthesized and examined as potential oral carbenicillin derivatives. The rates at which the esters were hydrolyzed *in vitro* to carbenicillin by animal and human tissues were compared and the carbenicillin serum levels arising after oral administration of the esters were measured in squirrel monkeys and human volunteer subjects. The α-carboxyphenyl ester of carbenicillin [carfecillin (British Pharmacopoeia approved name), BRL 3475] was selected for further study and is presently undergoing clinical trial.

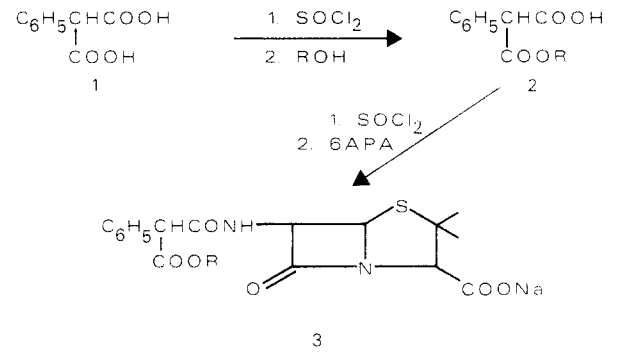
Carbenicillin (α-carboxybenzylpenicillin) has a broad spectrum of antibacterial activity and has been shown to be effective in the treatment of serious infections caused by *Pseudomonas aeruginosa* and other gram-negative bacteria. However, the compound is poorly absorbed from the gastrointestinal tract after administration by the oral route and its use is limited to parenteral administration. It has been found that certain α-carboxy esters of carbenicillin are absorbed by the oral route and undergo hydrolysis in the body to liberate carbenicillin.[1] One such ester (carbenicillin indanyl sodium) has been described in detail.[2]

Carbenicillin α-carboxy esters (that is, the ester group is in the side chain) possess a free thiazolidine carboxyl group and, hence, can be expected to demonstrate antibacterial activity *per se*. In general, we and others have found that the unhydrolyzed ester is more active than carbenicillin against gram-positive bacteria but shows a lesser degree of activity against most gram-negative bacilli.[3] However, the antibacterial spectrum shown by this class of compound will depend upon the extent of hydrolysis to carbenicillin that occurs in the course of the antibacterial test. Esters that are hydrolyzed rapidly to carbenicillin show an antibacterial spectrum similar to that of carbenicillin while esters with a slow rate of hydrolysis demonstrate activity primarily against gram-positive bacteria. In practice carbenicillin esters are of clinical interest only as a means of providing carbenicillin activity in the body after oral administration and in this context their intrinsic activity may be disregarded.

This report describes the preparation, *in vitro* hydrolysis rates, and oral absorption characteristics of a group of 12 α-carboxy esters of carbenicillin.

Chemistry. Scheme I illustrates the general route used to prepare α-carboxy esters of carbenicillin.[4] Phenylmalonic acid (1) was converted to its monoacid chloride by treatment with 1 equiv of thionyl chloride. The crude product was allowed to react with 1 equiv of alcohol or phenol (ROH) to afford the half-esters **2** described in Table I. The crystalline half-esters **2** were converted to their acid chlorides with excess thionyl chloride at 70° (higher temperatures caused degradation) and coupled directly to 6-aminopenicillanic acid (6-APA) in aqueous acetone. The penicillins **3** were isolated as their sodium salts and are described in Table II. A variation of this procedure has also been used to prepare penicillins of this type.[5]

Scheme I



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The α-carboxy esters, listed in Table II, as in the case of carbenicillin, contain an asymmetric center in their side chains and in solution their nmr spectra (Table III) suggested an approximately 1:1 mixture of epimers. However, in a number of instances (Table II) it was possible to obtain the penicillin sodium salts crystalline and these compounds were considered on nmr evidence to be single epimers in the solid state. Thus the nmr spectrum for the crystalline phenyl ester showed initially a singlet for the thiazolidine C-3 proton which rapidly changed to two singlets of equal intensity, consistent with racemization at the side-chain chiral center.†

Biological Properties. The 12 α-carboxy esters of carbenicillin, described in Table II, were examined for rates of hydrolysis to carbenicillin in aqueous solution and in the presence of isolated tissue homogenates. The 12 esters were also orally administered to both squirrel monkeys and human volunteers and levels of carbenicillin in blood and urine were measured. Details of these procedures are described in the Experimental Section. The results are discussed below.

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