218–222°. An anal. sample was obtained by recrystn from MeOH, mp 228–229°. *Anal.* ($C_{18}H_{16}NClO_6$): C, H, Cl, N.

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Synthesis and Biological Response of Some 3-Iminoprogestins

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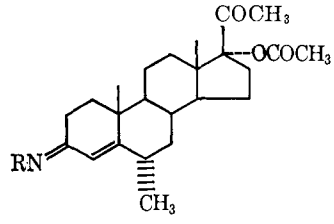
In a recent study[1] it was observed that the introduction of a 6α-Me group onto 17α-acetoxyprogesterone oxime enhanced the progestational response tenfold. At the same time introduction of a long-chain fatty ester at C-17 decreased the activity precipitously. The present study was initiated with 6α-methyl-17α-acetoxyprogesterone oxime to ascertain if varying the basicity at C-3 molecular modification would effect the progestational response.

The compounds listed in Table I were synthesized

TABLE I
3-OXIMINO ESTERS



Compound[a] No.	R	Recrystal[b] solvent	Mp, °C	Formula[c]
1	CH_3COO	M–W	104–107	$C_{26}H_{37}NO_5$
2	C_2H_5COO	M–W	81–85	$C_{27}H_{39}NO_5$
3	$CH_3[CH_2]_4COO$	M–W	105–108	$C_{30}H_{45}NO_5$
4	C_6H_5COO	M	190–193	$C_{31}H_{39}NO_5$
5	C_6H_5	H	133–135	$C_{30}H_{39}NO_3$
6	C_6H_5NH	M	154–157	$C_{30}H_{40}N_2O_3$
7	NH_2CONH	A	246–248	$C_{25}H_{37}N_3O_4$

[a] All compds showed uv absorption around 240 nm. [b] A = Me_2CO; H = hexane; M = MeOH; W = H_2O. [c] Acceptable C, H, N values were obtained for all compds.

according to the procedure outlined in the Experimental Section. The spectral data and elemental analyses confirm the structural assignments. These compounds were studied for their *in vivo* progestational response as well as their ability to bind *in vitro* to a specific progesterone receptor site.[2]

The data for the Clauberg test[3] are shown in Table II as the McPhail index.[4] It is apparent from the response of **1**, **2**, **3**, and **7** that decreasing the polarity of the parent molecule or increasing the basicity did not significantly alter the McPhail index. Interestingly

TABLE II
PROGESTATIONAL RESPONSE OF RABBIT UTERUS

Compound No.	Dose, mg/kg	McPhail index
1	0.5	3.2
2	0.5	2.9
3	0.5	3.1
4	1.0	3.3
5	1.0	3.2
6	1.0	3.2
7	0.5	3.45

4, **5**, and **6**, having a bulky Ph group in common, require twice the dose for similar response.

Binding studies of these compounds to uterine progestin receptor were carried out according to the method outlined in the Experimental Section. McGuire and DeDella[2] have published data suggesting the existence of a specific progestin receptor in the rabbit uterus. All of the compounds from Table I were studied for their ability to bind to this receptor by identical techniques. The binding response as tabulated in Table III represents the displacement of progesterone-*t* from the receptor by the compound. It is evident that all compounds bind very strongly to the progesterone receptor site except **7**. The discrepancy between the *in vivo* Clauberg test for **7** and the *in vitro* receptor binding response may be due to metabolism of **7**, or the C-3 terminal amino group may offset the binding dimensions.

TABLE III
UTERINE PROGESTIN RECEPTOR BINDING RESPONSE

Compound No.	Binding response[a]
1	+++
2	+++
3	+++
4	+++
5	+++
6	+++
7	+

[a] (+++) strong binder; (++) medium binder; (+) poor binder.

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The uv and ir data were obtained on a Cary Model 11 and Beckmann IR-5 spectrophotometers, respectively. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements (Table I), analytical results obtained for these elements were within ±0.4% of the theoretical value.

General Procedure for 1, 2, 3, and 4. 3,17α-Diacetoxy-6α-methylpregn-4-ene-3,20-dione 3-Oxime (1).—A soln contg 0.5 g of 17α-acetoxy-6α-methylpregn-4-ene-3,20-dione 3-oxime in 1.5 ml of Ac_2O and 0.7 ml of C_5H_5N was stirred for approx 10 min and poured over ice water. The crude crystals thus formed were collected by filtration and recrystd from MeOH–H_2O. The yield of **1**, mp 104–107, was 88%.

3-Iminobenzene-17α-acetoxy-6α-methylpregn-4-en-20-one (5).—17α-Acetoxy-6α-methylprogesterone (1 g) was treated with 10 ml of $PhNH_2$ and refluxed for 24 hr. Excess aniline was removed under reduced pressure and the residue was extd with boiling hexane. On cooling the hexane layer deposited yellowish crystals of **5**, mp 133–135°

General Procedure for 6 and 7. 17α-Acetoxy-6α-methylpregn-4-ene-3,20-dione 3-Phenylhydrazone (6).—17α-Acetoxy-6α-methylprogesterone (1 g) was treated with 250 mg of phenyl-

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(2) J. L. McGuire and C. DeDella, *Endocrinology*, in press.
(3) C. Clauberg, *Zentralbl. Gynaekol.*, **54**, 2757 (1930).
(4) M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1935).

hydrazine·HCl, 250 mg of NaOAc, and 1.0 ml of AcOH and refluxed for 40 min. The mixt was poured over a large amount of ice water and the ppt formed was collected by filtration. Recrystn from MeOH yielded 900 mg of **6**, mp 154–157°.

Receptor Binding Studies.—Uteri from 10 immature rabbits weighing less than 2 kg were removed, minced, and washed several times with buffer to rid the tissue of blood. Uteri were then homogenized in 0.4 vol of buffer (0.01 *M* Tris-HCl buffer, pH 8.0, contg 0.001 *M* EDTA and 0.25 *M* sucrose) at 4°. The homogenates were first centrifuged at 12,000*g* for 30 min, followed by 273,000*g* for 1.0 hr. Reaction mixts consisting of (a) 0.2 ml of buffer (0.01 *M* Tris-HCl, pH 8.0, contg 0.001 *M* EDTA, 0.25 *M* sucrose, and 25,000 cpm of progesterone-*t*/ml), (b) nonradioactive compds reported in this paper at a concn of 100 ng/ml, and (c) 50 μl of uterine cytosol were incubated at 4° for 16 hr. After incubation bound *vs.* unbound steroids were sepd as earlier reported, and the amt of bound progesterone-*t* was determined.

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β-Lactam Antimicrobial Agents Which Possess Antifungal Activity

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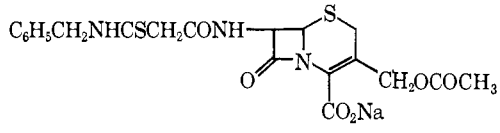
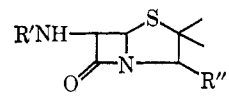
Although the cell walls of bacteria and fungi differ widely in their mucopeptide and mucopolysaccharide arrangement, we thought that it would be interesting to prepare some β-lactam-containing semisynthetic compounds and test them against certain fungi. Unexpectedly, we have found that a few of these antibiotics inhibit the growth of some pathogenic fungi *in vitro*.



I (**14**)



II (**15**), R′ = $C_6H_5OCH(CH_3)CO$; R″ = COSK
III (**16**), R′ = $C_6H_5OCH_2CO$; R″ = CHO

Chemistry.—The compounds listed in Tables I and II were prepared by two procedures unless otherwise noted. All of the thiocarbamoylmercaptomethylcephalosporanic acids were prepared by direct acylation of 7-aminocephalosporanic acid (7-ACA) with the *S*-carboxymethyl dithiocarbamate–carboxylic mixed anhydride (method A). The carbamoylmercaptomethylcephalosporins were prepared from the *S*-carboxymethyl *N*,*N*-disubstituted dithiocarbamates and 7-ACA in the presence of I_2 and NaI (method B).[1,2] *N*-Benyzlthiocarbamoylmercaptoacetamidocephalosporanic acid (I) (**14**) was prepared from sodium 7-(2-bromoacetamido)cephalosporanate[3] and potassium *N*-benzyldithiocarbamate. Potassium 6-[(−)-α-phenoxypropionamido]thiopenicillanate (II) (**15**)[4] and 6-phenoxyacetamidopenicillanal (III) (**16**)[5] were prepared by published procedures.

Antifungal Activity.—Results of the tests are summarized in Table I. As can be seen, the most active compound is sodium (*N*-benzyldithiocarbamoylacetamido)cephalosporanate (I) (Table I, **14**). It is noteworthy that this cephalosporin showed two- to fourfold greater antifungal activity than the antifungal acid **17**[6] from which it was derived. It is also of interest that the penicillin aldehyde III (**16**) which is virtually without activity *in vitro* aganist bacteria, showed antifungal effects. Compound **14** was tested in an experimental systemic *Cryptococcus neoformans* infection of mice but was found to case no prolongation of survival time. Thus, the probability exists that, although these compounds are active *in vitro*, they are not present in an active form in animal tissues at high enough concentrations to give protection against systemic fungal infections.

Experimental Section[7]

Sodium 7-(*N*,*N*-Dimethyldithiocarbamoylacetamido)cephalosporanate (Table I, 1) (Method A).—To a soln of 1.8 g (0.01 mole) of *S*-carboxymethyl *N*,*N*-dimethyldithiocarbamate and 1 g (0.01 mole) of Et_3N in 50 ml of THF at 0° was added 1.2 g (0.01 mole) of isovaleryl chloride. The mixt was stirred for 10 min and a soln of 2.8 g (0.01 mole) of 7-ACA and 1.1 g (0.11 mole) of Et_3N in 25 ml of H_2O was added all at once. The soln was stirred for 0.5 hr and the THF was evapd under reduced pressure at 30° (15 mm). The aq residue was acidified with 1:1 H_3PO_4 and extd with EtOAc. The exts were washed with H_2O and dried (Na_2SO_4). The soln was treated with sodium 2-ethylhexanoate and the white cryst salt was collected and recrystd three times from aq *n*-BuOH to give 2.5 g of product (see Table II).

Sodium 7-(*N*-Benzyldithiocarbamoylacetamido)cephalosporanate (14).—To a soln of 11.7 g (0.03 mole) of sodium 7-(2-bromoacetamido)cephalosporanate[3] and 2.5 g of $NaHCO_3$ in 200 ml of H_2O at 10° was added, with vigorous stirring, 6.6 g (0.03 mole) of potassium *N*-benzyldithiocarbamate.[6] The soln was stirred in the cold for 1 hr as the pH was kept around 7 with 2 *N* $NaHCO_3$ soln. The soln was washed with Et_2O, layered with 100 ml of EtOAc, and acidified to pH 4 with 42% H_3PO_4. The org layer was sepd, and the aq phase was again extd with EtOAc. The exts were washed with H_2O, dried (Na_2SO_4), and evapd to an oil under 15 mm pressure at 35°. The residue, after trituration with dry Et_2O was collected by filtration and was dried over

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(2) W. J. Gottstein, A. H. Eachus, and L. C. Cheney, *J. Org. Chem.*, **35**, 1693 (1970).

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(7) Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. Ir spectra were recorded on a Beckman IR 9 spectrometer, nmr spectra on a Varian A-60 spectrometer at a sweep width of 500 cps using D_2O as a solvent. All spectra were consistent with structure. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The authors wish to thank Mr. R. M. Downing and Mr. D. F. Whitehead for the microanalytical and spectral data, respectively.