Biological Data.—None of the compounds screened showed significant activity when tested orally for anti-inflammatory effects using the carrageenin-induced foot edema method in the rat.[6] All of the compounds were examined for estrogenic activity and for their effect

TABLE III
ESTROGENIC, ANTIESTROGENIC, ANTIFERTILITY, AND HYPOCHOLESTEREMIC ACTIVITIES

Compd	Estrogenic[a]	Antiestrogenic[b]	Anti-fertility[c]	Hypo-cholesteremic[d]
23	Inact	Inact	−	160
24	100	50	±	100
25	50	50	±	256
26	50	50	+	>256
27	50	50	+	120
28	50	50	+	>256
29	10	10	+	>256
30	50	50	+	Inact
31	10[e]	10[e]	+	>256

[a] Dose (sc mg/kg per day × 3) which produced minimal but significant increase in the wt of the uterus. [b] Dose (sc mg/kg per day × 3) which significantly inhibited the uterothrophic responsiveness to 17β-estradiol (sc, 0.002 mg/kg per day × 3). [c] Extent of effect of 50 mg/kg × 6 sc dose in preventing pregnancy; (+) completely, (±) partly, (−) ineffective. [d] ED_{33}, po mg/kg per day × 4. [e] po.

on fertility in female rats. The effects on serum cholesterol levels in the rat were also determined; the results of active compounds are tabulated in Table III. In general, these compounds were both estrogenic and antiestrogenic, the dose of each compound producing a minimal but significant increase in the weight of the uterus also inhibiting the uterotrophic response to estradiol.

Experimental Section[7]

General syntheses for compounds in Table I and II are as follows.

2-Aryl-3-(*p*-hydroxyphenyl)phthalimidine.—A mixt of 3-(*p*-hydroxyphenyl)phthalide and 2 molar equiv of arylamine was heated in an oil bath at 170–180°. H_2O which was formed during the reaction was swept out in a slow stream of N_2. After 5–6 hr, the mixture was cooled to 90° and dild with 2–3 vol of PhMe. The resulting precipitate was filtered off and recrystd from an appropriate solvent (Table I).

2-Alkyl-3-(*p*-hydroxyphenyl)phthalimidines.—A soln of 0.1 mole of 3-(*p*-hydroxyphenyl)phthalide and 0.2 mole of aliphatic amine was refluxed in 200 ml of xylene for 18–24 hr at which time 1 equiv of H_2O had been collected in an attached trap. On cooling, the product pptd out and was collected by filtration.

Alkylation of 3-(*p*-Hydroxyphenyl)-2-(substituted)phthalimidines.—A mixt of 0.1 mole of 2-aryl(or alkyl)-3-(*p*-hydroxyphenyl)phthalimidine, 100 g of powdered, anhyd K_2CO_3, 0.11 mole of alkyl halide (or dialkylaminoalkyl halide·HCl), and 300 ml of DMF was stirred under N_2 at 100–105° (oil bath) for 18–24 hr. The cooled mixt was filtered and the filtrate was evapd *in vacuo*. The residual oil which usually solidified on cooling was purified by crystn from an appropriate solvent (Table II).

Acknowledgment.—We are grateful to Dr. A. Arnold, Dr. G. Potts, and Mr. Z. Mielens for the biological data reported.

(7) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Analytical results for C, H, and N for all compounds cited were within 0.4% of the theoretical values.

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

Glutarimide Antibiotics. Analogs of Streptimidone

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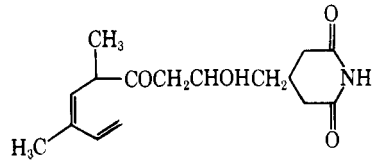
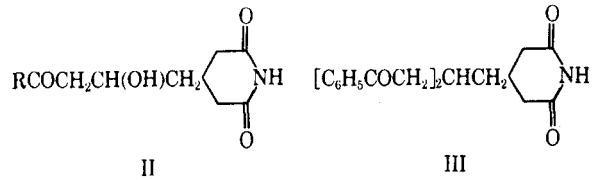
Numerous glutarimide antibiotics noted particularly for their antifungal activity have been isolated from various streptomycetes.[1] They have in common the β-(2-hydroxyethyl)glutarimide residue attached to a cyclic or acyclic ketone. Streptimidone (I) is produced[2] by *Streptomyces rimosus* forma *paramomycinus*. It is highly toxic[3] to certain species of yeast and filamentous fungi. It is effective against *Entamoeba histolytica* but not *Trichomonas vaginalis*. Toxicity against bacteria is poor; however, growth of *Brucella suis*, *Staphylococcus aureus*, and *Streptococcus pyogenes* are completely inhibited.

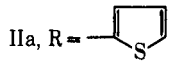


I

Analogs of I in which the 5-substituted 3-methyl-1,3-hexadiene moiety has been replaced by thiophene and benzene have been prepared.



II III



IIa, R =

IIb, R = C_6H_5

TABLE I
GLUTARIMIDE ANALOGS

Compound	% yield	Mp, °C	Formula[a]
IIa	34.0	169–170.5	$C_{13}H_{15}NO_4S$
IIb	14.3	130–132	$C_{15}H_{17}NO_4$
III	6.4	135–136.5	$C_{23}H_{23}NO_4$[b]
V	55.8	231–233	$C_{17}H_{17}N_3O_4$

[a] All compounds were analyzed for C, H, N. [b] C: calcd, 73.2; found, 74.1.

Glutarimide-β-acetaldehyde[4–6] was condensed with the Mg enolates of 2-acetylthiophene and acetophenone

(1) H. D. Sisler and M. R. Siegel, *Antibiotics*, **1**, 283.

(2) F. P. Frohardt, H. W. Dion, Z. L. Jakubowski, A. Ryder, J. C. French, and Q. R. Bartz, *J. Amer. Chem. Soc.*, **81**, 5500 (1959).

(3) D. L. Kohberger, M. W. Fisher, M. M. Galbraith, A. B. Hillegas, P. E. Thompson, and J. Ehrlich, *Antibiot. Chemother.*, **10**, 9 (1960).

(4) M. Suzuki, Y. Egawa, and T. Okuda, *Chem. Pharm. Bull.*, **11**, 589 (1963).

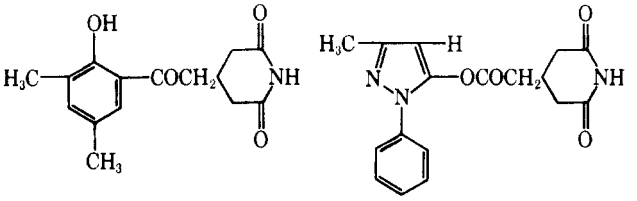
(5) B. C. Lawes, *J. Amer. Chem. Soc.*, **82**, 6414 (1960).

(6) F. Johnson, *J. Org. Chem.*, **27**, 3658 (1962).

to give IIa and IIb, respectively. In the latter case, a second glutarimide derivative III was also isolated.

Glutarimide-β-acetic acid, the precursor to the corresponding aldehyde intermediate, was best prepared[5] by pyrolysis of ammonium methanetriacetate. The synthesis of glutarimide-β-acetic acid by hydrolysis of diethyl 3-cyanomethylglutarate is reported[4] to proceed in 80% yield. In our hands, this method was erratic giving yields of under 20%.

In an attempt to prepare a heterocyclic analog of the glutarimide antibiotic actiphenol[7] (IV) the Na salt of 3-methyl-1-phenyl-2-pyrazolin-5-one was treated with glutarimide-β-acetyl chloride. The O-acylated product, 3-methyl-1-phenylpyrazol-5-ylglutarimide-β-acetate (V), was formed rather than the desired 4-(C)-acylated product.



IV V

Compounds IIa, IIb, III, and V were found to be inactive when screened against *Phytophthora infestans, Uromyces phaseoli, Erysiphe polygohi, Piricularia oryzae, Xanthomonas vesicatoria, Marmor tabaci,* and *Fusarium oxysporum f. sp. lycopersici.*

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are not corrected. The ir, nmr, and mass spectra are consistent with proposed structures.

3-[2-Hydroxy-3-(2-thenoyl)propyl]glutarimide (IIa).—A soln of 2-acetylthiophene (7.5 g, 0.059 mole) in 10 ml of anhyd THF was added under N_2 at 10–15° to a soln of *N*-methylanilinomagnesium chloride (0.067 mole) in a mixture of 15 ml of anhyd PhH and 15 ml of anhyd Et_2O. The mixt was stirred 15 min at ambient temperature, cooled to 0°, and treated with glutarimide-β-acetaldehyde (3.40 g, 0.022 mole) in 80 ml of anhyd THF. The soln was stirred for 1 hr at 0–5° and stored overnight at −10°. It was cooled to −40° and acidified with 7% HCl. The org layer was separated and the aq layer extd (EtOAc). The combined org exts were successively washed with 5% HCl, 5% $NaHCO_3$, and H_2O, dried (Na_2SO_4), and concd *in vacuo*. The residue was washed with EtOH giving 2.10 g (34%) of IIa, mp 169–170.5° after recrystn from EtOH. *Anal.* ($C_{15}H_{15}NO_4S$) C, H, N.

3-(2-Hydroxy-3-benzoylpropyl)glutarimide (IIb).—The reaction was run as above with the exception of storing the reaction mixture overnight utilizing 0.160 mole of *N*-methylanilinomagnesium chloride, 18.0 g of acetophenone (0.15 mole), and 9.35 g (0.060 mole) of glutarimide-β-acetaldehyde. The residue, 9.80 g, was chromatographed on 400 g of silica gel. Elution with PhH–Me_2CO, 7:3, gave 2.35 g (14.3%) of IIb, mp 130–132° after recrystn from EtOH. *Anal.* ($C_{15}H_{17}NO_4$) C, H, N.

3-(2,2-Diphenacylethyl)glutarimide (III).—Reaction run on 0.15 mole (7.75 g)of glutarimide-β-acetaldehyde as above with the reaction mixt being stored overnight at 0° after the aldehyde addition. Chromatography of the residue on silica gel gave, upon elution with PhH–Me_2CO, 3:1, 1.20 g (6.4%) of III, mp 134–136°. *Anal.* ($C_{23}H_{23}NO_4$) H, N, C, calcd 73.19; found, 74.09.

3-Methyl-1-phenylpyrazol-5-ylglutarimid-β-acetatee (V).—A soln of dry Me_2CO was added to the Na salt of 1-phenyl-3-methyl-2-pyrazolin-5-one (0.019 mole). The mixture was heated for 3 hr and the ppt collected and washed with H_2O giving 3.1 g (55.8%) of V. Successive recrystns from AcOH–H_2O and MeCN gave a product, mp 231–233°. *Anal.* ($C_{17}H_{17}N_3O_4$) C, H, N.

(7) R. J. Highet and U. V. Prelog, *Helv. Chim. Acta*, **43**, 1523 (1959).

1-Substituted-3-phenylacetamido-4-phenyl-2-azetidinones as Potential Antibacterials[1]

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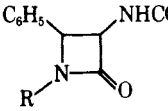
Both penicillin and cephalosporin contain an acylamino group in the 3 position of the azetidinone moiety, in fact this group seems to be necessary for antibacterial activity.[2] Benzylpenicillin and cephaloram both contain a phenylacetamido group. Therefore it was proposed that 1-substituted-3-phenylacetamido-4-phenyl-2-azetidinones (**1**) might possess antibacterial activity. An unsuccessful synthesis of 3-acylaminoazetidinones for this purpose has been published.[3]



1

1a, R = H
1b, R = Me
1c, R = *n*-Pr
1d, R = CH_2COOH

3-Azido-4-phenyl-2-azetidinone (**2**) appeared to be the most reasonable starting material for synthesis of these compounds. A recent publication from these laboratories[4] described the synthesis of **2** and a study of its chemical properties. Catalytic reduction of **2** resulted in 3-amino-4-phenyl-2-azetidinone[5] which was then treated with phenylacetyl chloride to produce 3-phenylacetamido-4-phenyl-2-azetidinone (**1a**).

Synthesis of the other analogs of this series of compounds required the alkylation of the amide N of **2** followed by reduction of the 3-azido group and acylation of the resulting amino group. Attempts to alkylate **2** using either Na or NaH and an alkyl halide resulted only in intractable mixtures. The alkylation of azetidinones by the reaction of Me_2SO_4 in alkaline medium has been reported.[6,7] However, these conditions did not suffice to convert 3-azido-4-phenyl-2-azetidinone (**2**) into 1-methyl-3-azido-4-phenyl-2-azetidinone.

The exclusive N-alkylation of 2-pyridone by the use of thallous ethoxide and an alkyl iodide has been described recently.[8] When these conditions were applied to 3-azido-4-phenyl-2-azetidinone (**2**) the 1-alkylazetidinone was obtained. By the use of this reaction the 1-Me and 1-*n*-Pr compounds were prepared; the azide group was reduced catalytically and then acylated with phenylacetyl chloride to prepare the potential antibacterial compounds, **1b** and **1c**.

Penicillin and cephalosporin both contain a carboxymethyl moiety on the azetidinone N, therefore it seemed germane to include 1-(carboxymethyl)-3-phenylacetamido-4-phenyl-2-azetidinone (**1d**, R = CH_2COOH) in

(1) Abstracted from the Ph.D. Thesis of O. R. Tarwater, Purdue University, Lafayette, Ind., Aug 1970.

(2) E. P. Abraham, "Topics in Pharmaceutical Sciences," Vol. I, D. Perlman, Ed., Interscience Publishers, New York, N. Y., 1968, p 4.

(3) B. G. Chatterjee, V. V. Rao, and P. N. Moza, *Tetrahedron*, **23**, 499 (1967).

(4) J. N. Wells and R. E. Lee, *J. Org. Chem.*, **34**, 1477 (1969).

(5) J. N. Wells and O. Reed Tarwater, *J. Pharm. Sci.*, in press.

(6) D. Borman, *Justus Liebigs Ann. Chem.*, **725**, 124 (1969).

(7) E. Testa and L. Fontanella, *ibid.*, **661**, 187 (1963).

(8) E. C. Taylor in "Reagents for Organic Synthesis," Vol. II, M. Fieser and L. F. Fieser, Ed., Wiley-Interscience, New York, N. Y., 1969, p 410.