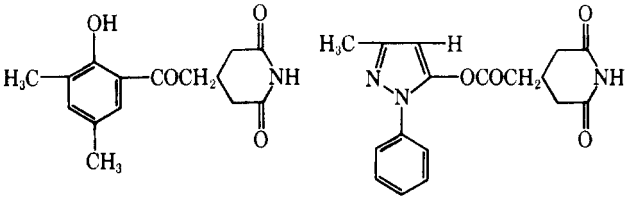
to give IIa and IIb, respectively. In the latter case, a second glutarimide derivative III was also isolated.

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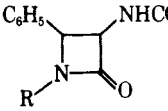
Both penicillin and cephalosporin contain an acylamino group in the 3 position of the azetidinone moiety, in fact this group seems to be necessary for antibacterial activity.[2] Benzylpenicillin and cephaloram both contain a phenylacetamido group. Therefore it was proposed that 1-substituted-3-phenylacetamido-4-phenyl-2-azetidinones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

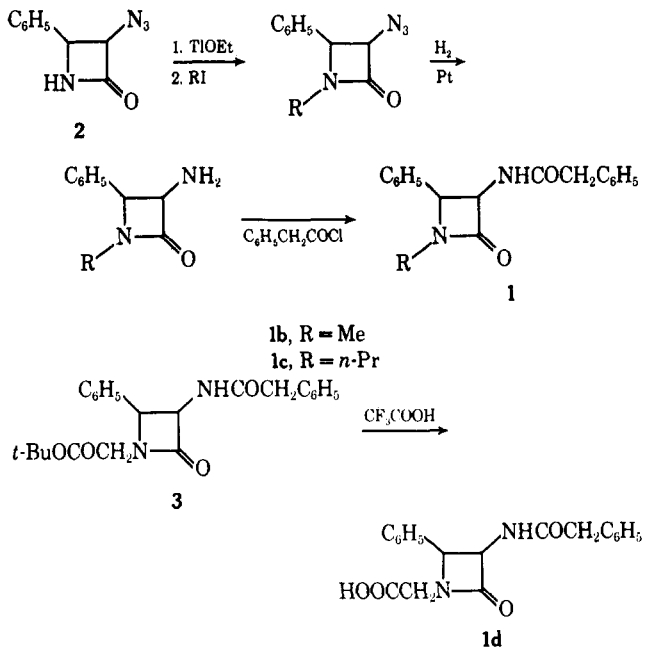
(4) J. N. Wells and R. E. Lee, *J. Org. Chem.*, **34**, 1477 (1969).

(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.



this series. Alkylation of **2** with thallous ethoxide and *tert*-butyl α-bromoacetate followed by reduction of the 3-azido group and acylation with phenylacetyl chloride gave 1-(*tert*-butoxycarbonylmethyl)-3-phenylacetamido-4-phenyl-2-azetidinone (**3**).

When **3** was treated with an excess of F_3CCO_2H[9] at 0° for 3 hr the *tert*-Bu group was removed and 1-(carboxymethyl)-3-phenylacetamido-4-phenyl-2-azetidinone (**1d**) was obtained in good yield. This reaction avoided the extensive decomposition which was characteristic of other conditions.[10-12]

Biological Activities.—Antibacterial activity of **1a,b,c,d** was evaluated by the cylinder-plate method against *Sarcina lutea* ATCC 9341, *Bacillus subtilis* ATCC 6633, *B. cereus* ATCC 9634, *Staphylococcus epidermidis* ATCC 12228, *Micococcus flauus* ATCC 10240, *Escherichia coli* B, and *E. coli* K12 at 1 mg/ml. The only compound which showed antibacterial activity was 1-methyl-3-phenylacetamido-4-phenyl-2-azetidinone (**1b**) which showed a slight zone of inhibition against *E. coli* B.

The lack of biological activity is not surprising in light of the fact that desthiobenzylpenicillin is inactive as an antibacterial.[13] In fact the inactivity of **1a,b,c,d** would lend credence to the supposition that the fused S heterocycle is requisite for antibacterial activity.

Experimental Section[14]

3-Phenylacetamido-4-phenyl-2-azetidinone (1a).—3-Amino-4-phenyl-2-azetidinone[5] (3.24 g, 20 mmoles) and Et_3N (2.02 g, 20 mmoles) were combined in 300 ml of dry CH_2Cl_2 and stirred at 0° while 3.08 g (20 mmoles) of phenylacetyl chloride dissolved in 60 ml of CH_2Cl_2 was added over a 2- to 3-hr period. The reaction mixt was stirred at 0° for 2 hr, allowed to warm to room temp, stirred for 12 hr, and then refluxed for 3 hr. The reaction mixt, when cool, was poured into 500 ml of H_2O. The CH_2Cl_2 was sepd and the aq phase was extd several times with $CHCl_3$. The organic exts were combined and the dried org solvents were removed *in vacuo* to give 3.5 g of solid which was recrystd from EtOH to give 2.1 g (77.5% yield) of **1a**; mp 185.5–186.0°. *Anal.* ($C_{17}H_{16}N_2O_2$) C, H.

Alkylation of 3-Azido-4-phenyl-2-azetidinone (2).—3-Azido-4-phenyl-2-azetidinone (**2**) (3.74 g, 20 mmoles) was dissolved in 50 ml of freshly distilled DMF and stirred at room temp while thallous ethoxide (5.0 g, 20 mmoles) was added in one portion. The thallous salt of the azetidinone formed at once and 20 mmoles of the appropriate alkyl halide in 10–20 ml of DMF was added over a 5-min period. The reaction mixt was stirred at room temp for 1 hr and the pptd halide was removed *via* filtration. The DMF filtrate was poured into 1000 ml of H_2O. The H_2O was extd several times with Et_2O and then the Et_2O exts were washed repeatedly with H_2O to remove all traces of DMF. After drying, the EtO was removed *in vacuo* to give the alkylated azetidinone as an oil which was reduced catalytically without further purification.

Reaction with MeI gave 1.8 g (44.5% yield) of 1-methyl-3-azido-4-phenyl-2-azetidinone.

Reaction with *n*-PrI gave 1.6 g (35% yield) of 1-*n*-propyl-3-azido-4-phenyl-2-azetidinone.

Reaction with *tert*-butyl α-bromoacetate gave 3.07 g (50% yield) of 1-(*tert*-butoxycarbonylmethyl)-3-azido-4-phenyl-2-azetidinone.

Catalytic Reduction of 1-Substituted-3-azido-4-phenyl-2-azetidinones.—The oily 1-substituted-3-azido-4-phenyl-2-azetidinone was dissolved in 100 ml of EtOH and reduced over Pt at 3.9 kg/cm² of H_2 for 48 hr. The Pt was removed by filtration and the EtOH was removed *in vacuo* to give the 1-substituted-3-amino-4-phenyl-2-azetidinone as an oil which was acylated without further purification.

Catalytic reduction of 1.8 g of 1-methyl-3-azido-4-phenyl-2-azetidinone gave 1.48 g (95%) of 1-methyl-3-amino-4-phenyl-2-azetidinone.

Catalytic reduction of 1.6 g of 1-*n*-propyl-3-azido-4-phenyl-2-azetidinone gave 1.5 g (100% yield) of 1-*n*-propyl-3-amino-4-phenyl-2-azetidinone.

Catalytic reduction of 3.07 g of 1-(*tert*-butyoxycarbonylmethyl)-3-azido-4-phenyl-2-azetidinone gave 2.22 g (79.5% yield) of 1-(*tert*-butoxycarbonylmethyl)-3-amino-4-phenyl-2-azetidinone.

Acylation of 1-Substituted-3-amino-4-phenyl-2-azetidinone. 1-Methyl-3-phenylacetamido-4-phenyl-2-azetidinone (1b).—1-Methyl-3-amino-4-phenyl-2-azetidinone (1.48 g, 8.4 mmoles) was dissolved in 100 ml of dry CH_2Cl_2 and cooled to 0°. Et_3N (0.90 g, 8.9 mmoles) was added in one portion. To this stirred mixture was added, at 0°, over 30 min, 1.38 g (8.9 mmoles) of $PhCH_2COCl$ dissolved in 40 ml of dry CH_2Cl_2. The reaction mixt was stirred at 0° for 30 min, then allowed to warm to room temp and stirred another 30 min. It was poured into 500 ml of H_2O, the CH_2Cl_2 phase was sepd, and the aq phase was extd several times with $CHCl_3$. The CH_2Cl_2 and $CHCl_3$ exts were combined and washed several times with H_2O. Evapn of the dried solvents *in vacuo* gave a white solid which was recrystd from EtOH to give 1.35 g (54.5% yield) of product; mp 180.5–181.5°. This represents a 23% yield for the reaction series starting with 3-azido-4-phenyl-2-azetidinone (**2**). *Anal.* ($C_{18}H_{18}N_2O_2$) C, H.

1-*n*-Propyl-3-phenylacetamido-4-phenyl-2-azetidinone (1c).—Reaction of 1.5 g (7.35 mmoles) of 1-*n*-propyl-3-amino-4-phenyl-2-azetidinone under the above conditions gave 1.31 g (55.5% yield) of 1-*n*-propyl-3-phenyl-acetamido-4-phenyl-2-azetidinone (**1c**). Recrystn from PhH–hexene gave 1.0g (42.3% yield) of product; mp 109.0–109.5°. *Anal.* ($C_{20}H_{22}N_2O_2$) C, H.

1-(*tert*-Butoxycarbonylmethyl)-3-phenylacetamido-4-phenyl-2-azetidinone (3).—Reaction of 1-(*tert*-butoxycarbonylmethyl)-3-amino-4-phenyl-2-azetidinone (2.22 g, 8.03 mmoles) under the above conditions gave an oil. Upon treatment with Et_2O the oil crystallized to give 1.83 g (58.3% yield) of product; mp 140–142°; spectra as expected.

1-(Carboxymethyl)-3-phenylacetamido-4-phenyl-2-azetidinone (1d).—1-(*tert*-Butoxycarbonylmethyl)-3-phenylacetamido-4-phenyl-2-azetidinone (**3**) (1.3 g, 3.3 mmoles) was dissolved in 25

(9) H. C. Beyerman and J. S. Bontekoe, *Recl. Trav. Chim. Pays-Bas*, **81**, 691 (1962).

(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol I, New York, N. Y., 1967, p 524.

(11) B. Loev, *Chem. Ind. (London)*, 193 (1964).

(12) T. Y. Shen, U. S. Patent 3,161,654 (1964) through "Basic Patents for Major Drugs," Sec. II, Noyes Development Corp., Park Ridge, N. J., 1969, p 896.

(13) E. Kaczka and K. Folkers, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 256.

(14) Melting points were determined using a Büchi capillary melting point apparatus with open capillary tubes and are uncorrected. Ir, nmr, and mass spectra were consistant with the structures assigned. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

ml of CF_3COOH and stirred at 0° for 3 hr. The CF_3COOH was removed *in vacuo* to yield a yellow oil which was then dissolved in slightly basic aq soln. The aq phase was extd several times with $CHCl_3$ to remove any unreacted starting material. The aq soln was made slightly acidic and the org acid which pptd was removed by filtration and dried to give 0.90 g (81% yield) of white solid. Recrystn from PhH–Me_2CO gave 0.86 g of product; mp 180.0–180.5°. *Anal.* ($C_{19}H_8N_8O_4$) H, N; Calcd C, 67.45; found, 68.08.

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Synthetic Biologically Active Polymers. 7. Antibacterial Activity of Some Sulfonamide–Formaldehyde Copolymers

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Chemistry.—In previous publications[2] we have described the preparation and certain biological activities of a number of synthetic biologically active polymers. Activities dealing with antimalarial properties of some sulfonamide–formaldehyde copolymers were among these reports.[2c-e] Since these latter reports, we have begun to screen the same or analogous copolymers more broadly. This report concerns the antibacterial activity of three sulfonamide–formaldehyde copolymers (see Table I) and a sulfone–formaldehyde copolymer. The copolymers were prepared by methods reported earlier.[2c-e]

Biological Activity.—As can be seen from Table I, in most tests, the monomer and the polymer had approximately equivalent antibacterial activity under the test conditions employed with a general tendency for the monomer activity to be higher. Thus, it continues to appear that polymerization of drugs may be useful as a method to prepare novel drug systems.

Employing three samples of the 4,4′-diaminodiphenylsulfone–formaldehyde copolymer of differing molecular weights[2e] in the antibacterial testing gave results (see Table I) which indicated that in this copolymer system, only a very minor indication of variation of activity with molecular weight was observed.

Experimental Section

All formaldehyde copolymers were prepared and characterized as reported earlier.[2c-e]

Antibacterial screening was carried out by seeding Mueller–Hinton agar with the test organisms and adding antibiotic assay cylinders to each petri dish. Each compound tested was added to the cylinders as a 1% solution in DMF. Each monomeric sulfonamide drug and the corresponding formaldehyde copolymer were tested at the same time. After overnight incubation at 37°, the zones of inhibition were measured. They were generally of the order of magnitude of 20–30 mm, even though the total lowest value observed was 10 mm and the highest 35 mm.

TABLE I

RELATIVE ANTIBACTERIAL ACTIVITY OF SOME SULFONAMIDE DRUGS (M) AND THE FORMALDEHYDE COPOLYMERS (P) THEREOF

Sulfonamide system	Test organism	Relative activity M	P	
Sulfapyridine	*Staphylococcus pyogenes*	1.1	1.0	
	Escherichia coli	1.7	1.0	
	Aerobacter aerogenes	1.1	1.0	
	Pseudomonas aeruginosa	1.1	1.0	
Sulfabenzamide	*Staph. pyogenes*	1.5	1.0	
	E. coli	1.0	1.0	
	A. aerogenes	1.4	1.0	
Sulfanilamide	*Staph. pyogenes*	1.2	1.0	
	E. coli	1.2	1.0	
	A. aerogenes	1.1	1.0	
	Ps. aeruginosa	1.8	1.0	
4,4′-Diaminodiphenylsulfone	*Staph. pyogenes*	1.4	1.0	($\bar{m}_w$ = 4700)[a]
		1.7	1.0	($\bar{m}_w$ = 7600)
		1.3	1.0	($\bar{m}_w$ = 10,000)

[a] $\bar{m}_w$ = weight average molecular weight ± 10%.[2e]

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New Thiocarboxamides Derivatives with Specific Gastric Antisecretory Properties

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Atropine-like drugs with their troublesome systemic side effects were, for a long time, the only products available for gastric antisecretory properties in ulcer therapy. During the past few years attempts have been made to find specific gastric antisecretory products acting by a nonanticholinergic pathway.

A well-documented review has just been published on this subject.[1] Among newly described chemicals, the most studied, 2-phenyl-2-(2-pyridyl)thioacetamide (PPT),[2] although not possessing really specific antigastrin properties,[3] seems to be the most available. Surprisingly, very few derivatives of this structure have been described. In the course of a research program on antiulcer compounds, we therefore synthesized some thiocarboxamides. Although completely devoid of anticholinergic activity, most of these compounds pos-

(1) Taken in part from the thesis to be submitted by Mr. John Razzano in partial fulfillment of the requirements for the Ph.D. degree.

(2) (a) R. J. Cornell and L. G. Donaruma, *J. Polym. Sci.*, **3A**, 827 (1965). (b) R. J. Cornell and L. G. Donaruma, *J. Med. Chem.*, **8**, 388 (1965). (c) L. G. Donaruma and J. Razzano, *ibid.*, **9**, 258 (1966). (d) J. R. Dombroski, L. G. Donaruma, and J. Razzano, *ibid.*, **10**, 963 (1967). (e) J. R. Dombroski, L. G. Donaruma, and J. Razzano, *ibid.*, **10**, 964 (1967).

(1) D. E. Butler, R. A. Purdon, and P. Bass, *Amer. J. Digest. Diseases*, **15** 157 (1970).

(2) D. L. Cook and R. G. Bianchi, *Life Sci.*, **6**, 1381 (1967).

(3) G. Gillespie, V. I. McCusker, B. S. Bedi, H. T. Debas, and I. E. Gillespie, *Gastroenterology*, **55**, 81 (1968).