Journal of Medicinal Chemistry

VOLUME 16, NUMBER 4 APRIL 1973

Antiarrhythmic Agents. Synthesis and Biological Activity of Some Tetrazole and Oxadiazole Analogs of 4-Dialkylamino-2,2-diarylbutyramides

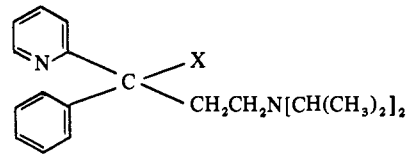
Gilbert W. Adelstein

Department of Chemical Research, Searle Laboratories, Chicago, Illinois 60680. *Received September 25, 1972*

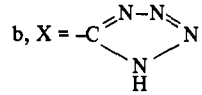
Analogs of the known antiarrhythmic 4-dialkylamino-2,2-diarylbutyramides were prepared where the carboxamide group was replaced by tetrazole or oxadiazole moieties. The oxadiazoles were synthesized from the corresponding acyl tetrazoles by cyclization of the 1,5 dipole formed from thermal elimination of nitrogen. Several unusual synthetic transformations are discussed. In general, modification of the carboxamide group resulted in a loss or considerable decrease in antiarrhythmic activity.

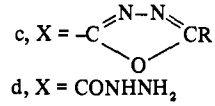
Much effort has been expended in these laboratories seeking an improved quinidine-type antiarrhythmic agent. From this effort, 4-diisopropylamino-2-phenyl-2-(2-pyridyl)-butyramide (**1a**, disopyramide)† emerged as a compound possessing superior therapeutic activity as an antiarrhythmic agent following myocardial infarct, yet devoid of much of the toxicity associated with quinidine therapy.[1]

This report describes attempts to further enhance the therapeutic activity of **1a** by substituting the carboxamide function by a 5-substituted tetrazole **1b** or a 2-substituted 1,3,4-oxadiazole **1c** group. In addition, tetrazole and oxadiazole derivatives of selected ring and side-chain analogs of **1a** were prepared and evaluated for antiarrhythmic activity.



1a, X = $CONH_2$

b, X = 

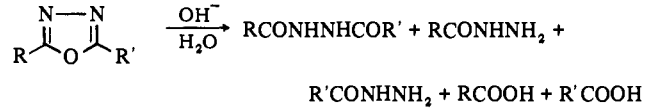
c, X = 

d, X = $CONHNH_2$

Chemistry. Tetrazoles (Table I) were prepared by the reaction of the corresponding nitriles with NaN_3 and NH_4Cl in DMF.[2] 1,3,4-Oxadiazoles (Table II) were prepared from the corresponding tetrazoles by reaction with Ac_2O in refluxing pyridine until gas evolution was no longer apparent. The mechanism for the reaction has been described by Huisgen.[3]

Although the conversion of tetrazoles to oxadiazoles by this route has not been significantly utilized in synthesis, the more conventional method of preparing 1,3,4-oxadiazoles *via* dehydration of diacyl hydrazides was not applicable to this series, the requisite hydrazide **1d** having only recently been prepared.‡ Prior to the availability of **1d**, it seemed likely that hydrolysis of oxadiazole **1c** might afford the hydrazide, or at least its acylated derivative, since alkaline hydrolysis of oxadiazoles has been utilized for such purposes.[4] The only drawback to this approach is the fact that the product of such reactions is frequently a mixture of diacylhydrazine and mixtures of hydrazides and the corresponding acids (Scheme I).

Scheme I



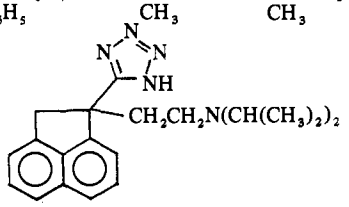
It seemed likely that if R′ = OH, then the number of possible products would be reduced to the desired hydrazide and its corresponding acid, since the alternative hydrazide and acid would decompose spontaneously. In fact, the acid **1** (X = COOH) has been obtained in these laboratories but is extremely unstable and rapidly undergoes decarboxylation to afford the diarylpropylamine **1** (X = H).‡

To test this hypothesis, model experiments were conducted using diphenylmethyltetrazole **6a**. Reaction of **6a** with carbobenzoxy chloride (CbzCl) gave crystalline carbobenzoxytetrazole **7a**, which was smoothly converted to benzyloxyoxadiazole **8a**. Debenzylation of **8a** occurred smoothly, the resulting product being oxadiazolinone **9a**. Mild alkaline treatment of **9a** (1% KOH-MeOH) served only to deprotonate it, while more vigorous treatment (10% KOH-MeOH, reflux) gave diphenylacetic acid as the only isolable product. On the other hand, similar alkaline treatment of **8a** gave a mixture of products, as determined by tlc. Subsequently, it was found that treatment of **8a** with con-

†Norpace.

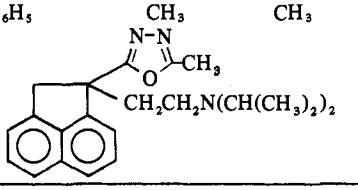
‡C. H. Yen, personal communication, G. D. Searle & Co., 1971.

Table I. Ar(Ph)(5-tetrazolyl)$CCH_2CH(R)NR^1_2$

Compd	Ar	R	R^1	Salt	Crystn solvent[a]	Yield, %	Mp, °C	Analyses
1b	2-C_5H_4N	H	$CH(CH_3)_2$		B	51	225 dec	C, H, N
2a	C_6H_5	H	$CH(CH_3)_2$	HCl	A	34	272–274 dec	C, H, N
3a	*p*-F-C_6H_4	H	$CH(CH_3)_2$	HCl	A	54	242 dec	H, N, F, Cl; C[b]
4a	C_6H_5	CH_3	CH_3	H_2O	A	79	281–281 dec	C, H, N
5a				HCl	A	11	235–242 dec	C, H, N

[a]A, precipitation from an alkaline solution with dilute HCl; B, H_2O–An. [b]C: calcd, 63.22; found, 62.05.

Table II. Ar(Ph)(2-methyl-1,3,4-oxadiazol-5-yl)$CCH_2CH(R)NR^1_2$

Compd	Ar	R	R^1	Salt	Crystn solvent[a]	Yield, %	Mp, °C	Analyses
1c	2-C_5H_4N	H	$CH(CH_3)_2$		A	62	76–78	C, H, N
2b	C_6H_5	H	$CH(CH_3)_2$		B	63	91–92	C, H, N
3b	*p*-F-C_6H_4	H	$CH(CH_3)_2$		A	29	99–101	C, H, N
4b	C_6H_5	CH_3	CH_3	HCl	C	9	198–204 dec	H, N; C[b]
5b				$HCl-H_2O$	D	12	296–297 dec	C, H, N

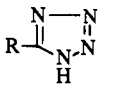
[a]A, Skellysolve B; B, PhH–Skellysolve B; C, Me_2CO–Et_2O; D, MeOH–Me_2CO. [b]C: calcd, 67.82; found, 66.92.

centrated NH_4OH briefly at 150° under pressure gave diphenylacetyl hydrazide in essentially quantitative yield.

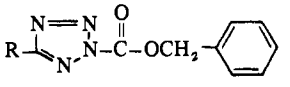
The benzyloxyoxadiazole **8b** was obtained as an oil. However, upon heating **8b** to 150° with concentrated NH_4OH, only oxadiazolinone **9b** and $(PhCH_2)_3N$ could be isolated. It is possible that traces of $PhCH_2OH$ in **8b** formed $PhCH_2NH_2$ or $(PhCH_2)_2NH$ during ammonolysis which served to debenzylate **8b** to yield **9b**. The structure of **9b** was confirmed by debenzylation of **8b** with HBr–HOAc and isolation of the product as the HBr salt.

In view of the fact that trifluoroacetamides are readily cleaved under basic conditions,[5] tetrazole **1b** was treated with trifluoroacetic anhydride in pyridine. Acylation of the tetrazole occurred readily at 10° and, upon warming to room temperature, gaseous evolution became vigorous. Work-up gave trifluoromethyloxadiazole **10c** as an oil, which was readily soluble in dilute aqueous KOH. Upon acidification, a colorless solid was obtained and characterized as the trifluoroacetyl hydrazide **11c**. The stability of the trifluoroacetyl hydrazide was surprising, and prolonged refluxing of a solution of **11c** in 5% KOH–MeOH afforded unchanged starting material on acidification.

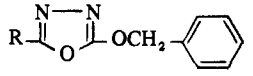
Due to the recent observation of Huisgen that tetrazoles



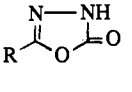
6



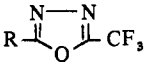
7



8



9



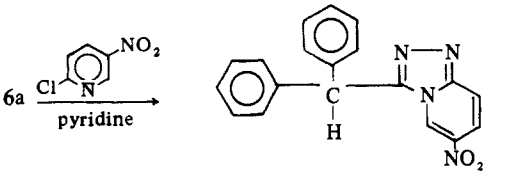
10c

$RCONHNHCOCF_3$

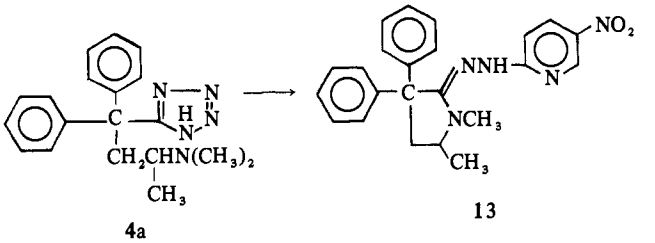
11c

a, R = Ph_2CH
b, R = 2-pyridyl(Ph)$CCH_2CH_2N(i\text{-}C_3H_7)_2$
c, R = $Ph_2CCH_2CH_2N(i\text{-}C_3H_7)_2$

react with suitably activated α-chloropyridines to form triazolopyridines,[6] **6a** was allowed to react with 2-chloro-5-nitropyridine in refluxing pyridine to afford **12** in modest yield. However, similar treatment of **1b** gave only a black water-soluble amorphous solid which was not characterized. When **4a** was allowed to react under similar conditions, a red crystalline product was obtained and subsequently characterized as the cyclic amidrazone **13**.§



12



4a 13

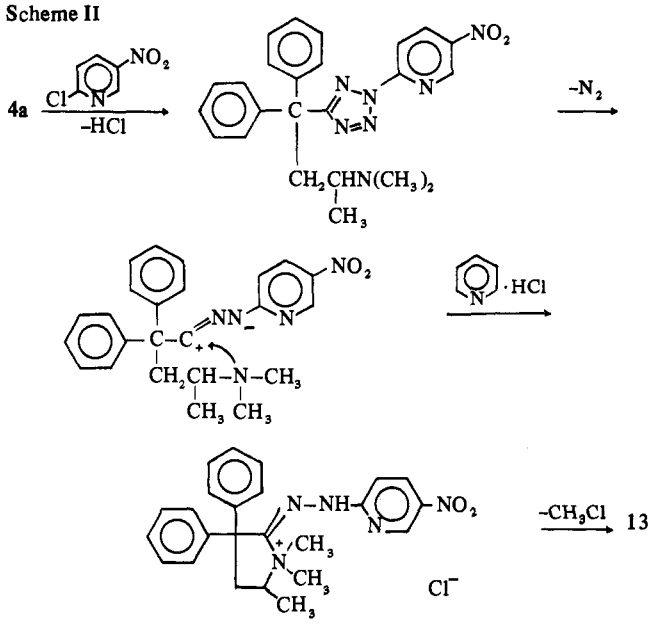
A possible mechanism for the formation of **13** is shown in Scheme II. Similar cyclizations have been observed during acid treatment of analogous nitriles to form iminopyrrolidines.[7]

Biology.# Compounds were assayed against aconitine-induced ventricular arrhythmia in the isolated rabbit heart. A compound was rated active if it caused a 50% or greater reduction in the ventricular rate for drug concentrations up

§The computer-generated theoretical nmr spectrum was superimposable with the actual spectrum of this compound.

#Biology data were furnished by Dr. D. L. Cook, Dr. R. R. Dean, and Mrs. E. Muir, Department of Biological Research, Searle Laboratories.

Scheme II



to 40 mg/l. Active compounds were then assayed against ouabain-induced ventricular arrhythmia in the intact anesthetized dog (rated active if return to normal sinus rhythm for a period of 15 min or more in half or more of dogs tested at a dose of 20 mg/kg or less) and/or ventricular arrhythmia induced by Harris two-stage coronary ligation[8] (rated active if 25% or greater reduction in ectopic beats for at least 10 min in half or more of dogs tested). The results are summarized in Table III.

Discussion

In general, modification of the carboxamide function of **1a** resulted in decreased antiarrhythmic activity. The tetrazoles **1b**, **2a**, **3a**, **4a**, and **5a** and oxadiazoles **2b**, **4b**, and **5b** were devoid of activity in all three tests. Only **1c** and **9b** showed significant activity but were relatively toxic.

Experimental Section**

5-[(3-Diisopropylamino-1,1-diphenyl)propyl]-1*H*-tetrazole Hydrochloride (2a). A suspension of 4-diisopropylamino-2,2-diphenylbutyronitrile (36.5 g, 0.1 mol), NaN_3 (9.75 g, 0.15 mol), NH_4Cl (7.95 g, 0.15 mol), and LiCl (0.15 g) in DMF (75 ml) was refluxed 12 hr. The solid which formed on cooling was removed by filtration, washed with a small amount of DMF, and purified by reprecipitation with dilute HCl from an aqueous alkaline solution of the crude product. *Anal.* ($C_{22}H_{19}N_5 \cdot HCl$) C, H, N.

In the case of **1b**, the product did not crystallize from the reaction mixture. The DMF was evaporated *in vacuo* and the residual oil, which crystallized on standing, was washed with H_2O and Me_2CO and dried. *Anal.* ($C_{21}H_{28}N_6$) C, H, N.

2-[[3-Diisopropylamino-1-(2-methyl-1,3,4-oxadiazol-5-yl)-1-phenyl]propyl]pyridine (1c). A solution of **1b** (11.8 g, 0.032 mol) and Ac_2O (35 ml) in pyridine (120 ml) was refluxed 2 hr until the evolution of gas was no longer evident. The dark mixture was cooled, H_2O (25 ml) was added to decompose the excess Ac_2O, and the solvents were removed by evaporation at reduced pressure. Et_2O was added to the residue and the resulting solution was washed with saturated $NaHCO_3$ solution, dried (anhydrous Na_2SO_4) and evaporated. The brown oil was eluted with PhH through a short column of alumina, and the colorless oil remaining after removal of solvent crystallized on standing. *Anal.* ($C_{23}H_{30}N_4O$) C, H, N.

2-Benzyloxy-5-diphenylmethyl-1,3,4-oxadiazole (8a). To a suspension of **6a** (25 g) in H_2O (200 ml) was added 10% NaOH solution dropwise until the solid had dissolved and the solution was distinctly alkaline. The solution was stirred in an ice bath while carbobenzoxy chloride (25 ml) was added dropwise. After stirring 2 hr, the gummy precipitate was collected, taken up in CH_2Cl_2, and dried (anhydrous Na_2SO_4). Evaporation of the solvent left an oil which crystallized from Et_2O affording 12.3 g of acylated tetrazole **7a**: mp 112°; ir ($CHCl_3$) 5.7 μ (C=O). A solution of this material in $PhCH_3$ (200 ml) was refluxed until evolution of gas was no longer evident (1.5 hr). Evaporation of solvent left an oil which crystallized from Et_2O affording 7.3 g of product, mp 95°. A second crop gave an additional 7.3 g of product. The combined fractions were recrystallized from CH_2Cl_2–EtO_2 affording pure material, mp 104–105°. *Anal.* C, H, N.

2-Diphenylmethyl-Δ^2-1,3,4-oxadiazolin-5-one (9a). A. Reaction of 9a with HBr. A solution of **8a** (1.0 g) in 32% HBr–HOAc (1 ml) was stirred at room temperature for 0.75 hr. H_2O was added and the precipitate filtered and dried, affording 0.7 g, mp 141–143°. Recrystallization of the crude product from Me_2CO–Skellysolve B gave 0.65 g of colorless material, mp 144.5–145.5°. *Anal.* ($C_{15}H_{12}N_2O_2$) C, H, N.

B. Hydrogenolysis of 8a. A mixture of **8a** (1.0 g) and 5% Pd/C (0.1 g) in EtOH was shaken in 1 atm of H_2 at 25° for 0.5 hr. Work-up in the usual way gave 0.6 g of product, mp 140–142°, identical in every respect with **9a**.

2[3-Diisopropylamino-1-(Δ^2-1,3,4-oxadiazolin-5-on-2-yl)-1-phenylpropyl]pyridine Hydrogen Bromide Hydrate (9b). A mixture of **6b** (7.3 g, 0.02 mol), K_2CO_3 (1.38 g, 0.01 mol), and H_2O (25 ml) was warmed until evolution of gas had ceased. $PhCH_3$ (150 ml) was added and the H_2O removed by azeotropic distillation. The suspension of the K^+ salt in $PhCH_3$ was stirred in an ice bath and carbobenzoxy chloride (4 ml, 0.024 mol) added dropwise. The reaction mixture was stirred 0.5 hr at room temperature and refluxed 1 hr. The mixture was cooled and filtered, and the solvent was evaporated leaving an oil. The oil was taken up in HOAc (10 ml) and cooled in an ice bath while 32% HBr–HOAc (6 ml) was added dropwise. The solution was stirred another 0.25 hr in the ice bath and 0.5 hr at room temperature. H_2O (100 ml) was added and the mixture extracted with Et_2O (2 × 50 ml). The aqueous solution was evaporated to 30 ml and partially neutralized with K_2CO_3(s). The solid that formed was collected and dried affording 2.1 g of crude product. Recrystallization of this material from Me_2CO–H_2O gave 1.3 g of hygroscopic material. *Anal.* ($C_{22}H_{28}N_4O_2 \cdot HBr \cdot 0.5H_2O$) C, H, Br, N.

3-Diphenylmethyl-6-nitro-*s*-triazolo[4,3-*a*]pyridine (12). A mixture of **6a** (23.6 g, 0.1 mol) and 2-chloro-5-nitropyridine (17.2 g, 0.11 mol) was refluxed in pyridine (120 ml) until the evolution of gas had ceased (*ca.* 3 hr). The pyridine was evaporated under reduced pressure; the residue was slurried in PhH and eluted through a column of alumina. Evaporation of the solvent gave a yellow oil which crystallized from Et_2O to give 30 g of solid. Recrystallization of this material from CH_2Cl_2–Et_2O gave 14.5 g of product. Pure material was obtained by column chromatography on silica gel, eluting with PhH–EtOAc (99:1), and washing the solid with Et_2O. *Anal.* ($C_{19}H_{14}N_4O_2$) C, H, N.

1-[4-Diisopropylamino-2-phenyl-2-(pyridyl)butyryl]-2-trifluoroacetylhydrazine (11c). A mixture of **1b** (7.3 g, 0.02 mol) in pyridine (75 ml) was stirred in an ice bath and trifluoroacetic anhydride (4.5 ml) added dropwise. When the addition was complete, the reaction mixture was allowed to warm to room temperature, during which time the evolution of gas was observed and a yellow solution resulted. After stirring at room temperature for 0.75 hr, the solvents were evaporated at reduced pressure at 40° and the resulting oil was eluted through a column of alumina with PhH (300 ml), affording 7.1 g of a light green oil. Attempts to crystallize this material were unsuccessful. The oily material (1.0 g) and KOH (0.2 g) in MeOH (10 ml) was refluxed 2 hr. H_2O was added, the MeOH evaporated

Table III. Activity Against Induced Ventricular Arrhythmias

Compd	Aconitine[a] (*n*)	Ouabain[b] (*n*)	Coronary ligation[b] (*n*)
1a	A (2)	6.6 (1)	7.5 (2)
1c	I (1)	20 (1)	5 (2)
3b	I (2)	15 (1)	
9b		5 (1)	7.5 (2)

[a] Rated active (A) or inactive (I) in isolated rabbit heart. [b] Activity expressed as minimum effective dose (mg/kg) in the intact dog.

**Nmr (Varian A-60D, $CDCl_3$ or DMSO-d_6, TMS standard) and ir (Beckman IR-12, $CHCl_3$ or Nujol mull) spectra were consistent with all structures and were determined by Mr. A. Damascus, Searle Spectroscopy Laboratory. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within 0.4% of the theoretical values and were determined by Mr. E. Zielinski, Department of Analytical Chemistry, Searle Laboratories. Melting points were determined in open capillary tubes in a bath and are uncorrected.

under reduced pressure, and the residue extracted into Et_2O. The aqueous solution was neutralized with HOAc and the solid which formed was filtered, washed with H_2O, and dried, affording 0.7 g of product. *Anal.* ($C_{23}H_{29}F_3N_4O_2$) C, H, F, N.

3,3-Diphenyl-1,5-dimethylpyrrolidin-2-one (5-Nitro-2-pyridyl)-hydrazone (13). A mixture of **4a** (9.9 g, 0.03 mol) and 2-chloro-5-nitropyridine (5.1 g, 0.032 mol) in pyridine (100 ml) was refluxed until evolution of gas had ceased. The pyridine was evaporated under reduced pressure; the residue was taken up in H_2O, acidified with dilute HCl, extracted into CH_2Cl_2, and dried (anhydrous Na_2SO_4). Evaporation of the solvent left a dark resinous oil (16.6 g) which was eluted through a column of silica gel with PhH–EtOAc (19:1), affording 6.0 g of a red crystalline product. Recrystallization of the crude material from PhH–Skellysolve **B** gave 2.0 g of product as red prisms. *Anal.* ($C_{23}H_{23}N_5O_2$) C, H, N.

Acknowledgments. I wish to express my sincere gratitude to Mr. Mark Wenger for supplying large quantities of **1b**, Mr. William Selby for hydrogenations, Mr. Robert Nicholson for column chromatography, Dr. Roy Bible, Miss Pat Green, and Miss Lydia Swenton for assistance in nmr interpretation, and Mrs. Judy Strauss and Mrs. Jeanette Martin for assistance in preparation of the manuscript.

References

(1) (a) C. M. Mokler and C. G. VanArman, *J. Pharmacol.*, **136**, 114 (1962); (b) R. R. Dean and D. M. Ferguson, *Arch. Int. Pharmacodyn. Ther.*, **190**, 183 (1971).
(2) G. W. Moersch, D. F. Morrow, and W. A. Nueklis, *J. Med. Chem.*, **10**, 149 (1967).
(3) R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Chem. Ber.*, **93**, 2106 (1960).
(4) A. Stempel, J. Zelauskas, and J. A. Aeschlimann, *J. Org. Chem.*, **20**, 412 (1955).
(5) E. Schroder and K. Lubke, "The Peptides," Vol. I, Academic Press, New York, N. Y., 1965, pp 6–9.
(6) R. Huisgen, H. J. Sturm, and M. Seidel, *Chem. Ber.*, **94**, 1555 (1962).
(7) P. Lucas and T. J. Slauson, *J. Amer. Chem. Soc.*, **71**, 2821 (1949).
(8) A. S. Harris, *Circulation*, **1**, 1318 (1950).

Nitrofuryltriazole Derivatives as Potential Urinary Tract Antibacterial Agents

Eva B. Åkerblom* and Dag E. S. Campbell

Department of Organic Chemistry, Pharmacia AB, Uppsala, Sweden. *Received May 25, 1972*

A series of 5-(5-nitro-2-furyl)-1,2,4-triazoles was synthesized and their activity as potential urinary tract antibacterial agents was tested. Many of the compounds showed a higher antibacterial activity than nitrofurantoin (XII) especially against gram-negative bacteria. After po administration in dogs only a few of the compounds were excreted in the urine in an antibacterially active form. All the compounds were less toxic than XII in mice. Five compounds were tested for emetic effect in cats and found less active than XII. The *in vitro* enzymatic degradation of different nitrofuryltriazoles showed no clear correlation to the excretion. Five compounds were tested for their excretion in man and 3-amino-5-(5-nitro-2-turyl)-1,-2,4-triazole (IVa) and 3-hydroxymethylamino-5-(5-nitro-2-furyl)-1,2,4-triazole (IVb) showed the highest excretion with 15% of given dose compared with 30% for XII. IVa was selected for further study. It was found active in experimental pyelonephritis in rats and showed a higher activity than XII in a test against 423 bacterial strains isolated from patients with urinary tract infection. A preclinical tolerance study in man showed that higher doses of IVa than of XII could be given without causing nausea and vomiting. However, four cases of suspected allergic reactions of drug fever type were reported for IVa. Two clinical studies showed that IVa had a therapeutic effect against urinary infections.

A new urinary tract antibacterial agent should fulfil the following basic criteria. It should have high antibacterial activity against microorganisms causing urinary tract infections, should be well absorbed perorally, and be excreted in the urine in amounts sufficient to give effective concentrations of the active substance.

Many nitrofuran derivatives have been synthesized and found to possess a good antibacterial activity *in vitro*, but only a few of these have been reported to be excreted in the urine in an antibacterially active form.[1,2] Nitrofurans are known to be inactivated rapidly in the body.[1]

Nitrofurantoin is a nitrofuran compound which largely fulfils the basic criteria for an effective urinary tract antibacterial agent and is indeed one of the clinically more important drugs. We have been searching for other nitrofuran derivatives with at least the same level of activity and broad antibacterial spectrum as nitrofurantoin and with less side effects. A series of 5-(5-nitro-2-furyl)-1,2,4-triazoles (Table I) was synthesized and subjected to the following screening tests: *in vitro* antibacterial activity against bacteria causing infections in the genitourinary tract, *in vivo* urinary excretion, acute toxicity, acute emetic effect, and metabolic susceptibility.

Chemistry. A number of the nitrofuran compounds in series I, II, and IV (Table I) were obtained by ring closure of furoylaminoguanidines to 3-amino-5-(2-furyl)-1,2,4-triazoles,[3] which were then acetylated and nitrated in a mixture of concentrated HNO_3 and H_2SO_4 (Scheme I). In later

Scheme I