1-(2,4-Dichlorobenzoyl)-3-(3,4-dichlorophenyl)urea.—To a stirred solution of 9.5 g (0.05 mole) of 2,4-dichlorobenazmide in 150 ml of PhMe, dried by azeotroping the mixture, was added 9.4 g (0.05 mole) of 3,4-dichlorophenyl isocyanate, the mixture then being heated under reflux for 20 hr. PhMe was distilled off and the residue was triturated with petroleum ether (bp 30–60°). The precipitated solid was filtered off and recrystallized from Me_2CO.

Minimum inhibitory concentrations for *S. aureus* ATCC 6538 were obtained by the agar streak dilution technique, in the presence of soap.[4] Three consecutive transfers of 24-hr broth cultures were made before testing.

Acknowledgment.—The authors are indebted to Mr. J. Brown, Jr., for the microbiological assays.

(4) D. R. Noel, R. E. Casely, M. W. Linfield, and L. A. Harriman, *Appl. Microbiol.*, **8**, 1 (1960).

Nitroheterocycles. I. Nitrofuryl-Substituted 3-Amino-1,2,4-oxadiazoles and 5-Amino-1,2,4-oxadiazoles

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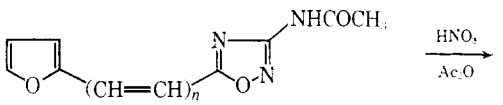
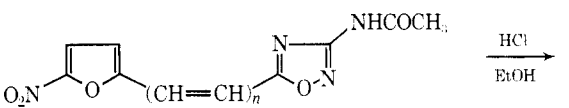
A novel synthesis of 5-substituted 3-amino-1,2,4-oxadiazoles has been developed in our laboratories.[1] Since the 5-nitrofuryl-2 group is present in a number of compounds showing antimicrobial activity, we decided to prepare a number of substituted 3-amino-1,2,4-oxadiazoles containing the 5-nitrofuryl-2 group and evaluate them for antimicrobial activity.

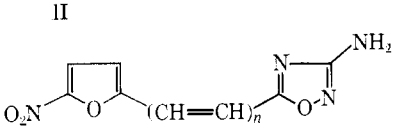
The furyloxadiazoles (I) were nitrated providing the 5-nitrofuryl-2 compounds (II) which could be cleaved to the final amino compounds (III) by warm ethanolic



I

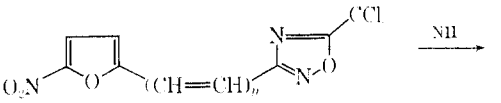


II

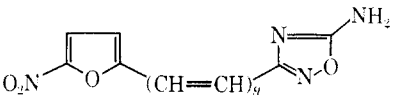


IIIa, $n = 0$
b, $n = 1$

HCl. The microbiological activities of these compounds are listed in Table I. The interesting antimicrobial spectrum of activity of these compounds prompted us to prepare the isomeric series of 3-substituted 5-amino-1,2,4-oxadiazoles. The reaction of the trichloromethyl compounds (IV) with NH_3, analogous



IV



Va, $n = 0$
b, $n = 1$

to the procedure of Eloy and Lenaers,[2] provided the 3-substituted 5-amino isomers (V).[3] Antimicrobial properties are listed in Table I. An examination of the data in Table I indicates that an ethylenic bridge enhances the intrinsic activity of these nitrofuryloxadiazoles; Vb appears to be the most interesting in view of its potent, broad antimicrobial spectrum, including activity against gram-negative and gram-positive bacteria as well as against fungi and protozoa.

Experimental Section

3-Amino-5-[2-(2-furyl)vinyl]-1,2,4-oxadiazole was prepared according to Wieland and Bauer[4] from dihydroxyguanidine hydrobromide and *β*-2-furanacryloyl chloride. An analytical sample, mp 137–138°, was obtained by crystallizing from EtOH. *Anal.* ($C_8H_7N_3O_2$) C, H, N.

3-Acetylamino-5-[2-(2-furyl)vinyl]-1,2,4-oxadiazole.—To a suspension of 5.8 g of 3-amino-5-[2-(2-furyl)vinyl]-1,2,4-oxadiazole in 120 ml of dry $CHCl_3$ and 3.2 g of pyridine was added dropwise with stirring 3.2 g of AcCl. The yield was 5 g (70%), mp 183–185°. *Anal.* ($C_{10}H_9N_3O_4$) C, H, N.

3-Acetylamino-5-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole.—To 60 ml of Ac_2O was added with stirring at −15°, 24 ml of HNO_3 (d = 1.51). At the same temperature 11.2 g of 3-acetylamino-5-[2-(2-furyl)vinyl]-1,2,4-oxadiazole was added in portions. The substance first went into solution and then fine crystals precipitated. When the last of the compound has been added a thick slurry had formed. The mixture was stirred for an additional 30 min, filtered, and washed (AcOH): yield 6.0 g (44%), mp 253° dec. The substance was recrystallized from AcOH. *Anal.* ($C_{10}H_8N_4O_5$) C, H, N.

3-Amino-5-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (IIIb). A solution of 1 g of 3-acetylamino-5-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole in 20 ml of 10% EtOH–HCl was refluxed, and then cooled. Bright yellow crystals were deposited. Filtration gave 0.6 g (71%) of IIIb, mp 232° dec. *Anal.* ($C_8H_6N_4O_4$) C, H, N.

3-Amino-5-(2-furyl)-1,2,4-oxadiazole could be prepared according to Wieland and Bauer[4] from dihydroxyguanidine hydrobromide and 2-furoyl-chloride. An analytical sample (mp 163°) was obtained from EtOH. *Anal.* ($C_8H_5N_3O_3$) C, H, N.

3-Acetylamino-5-(5-nitro-2-furyl)-1,2,4-oxadiazole.—To a mixture of 325 ml of Ac_2O, 130 ml of HNO_3 (d = 1.51), and 0.7 g of B_2O_3 was added at −20°, 50.7 g of 3-acetylamino-5-(2-furyl)-1,2,4-oxadiazole. This material, mp 151° [*Anal.* ($C_8H_5N_3O_4$) C, H, N], was prepared by acetylating 3-amino-5-(2-furyl)-1,2,4-oxadiazole with AcCl in pyridine. A solution formed upon stirring for 30 min. It was stirred for an additional 15 min at −10° and poured onto ice. The clear solution was adjusted to pH 4 with $NaHCO_3$ and kept overnight in the refrigerator, yielding 44.9 g (81%) of product, mp 181–182° dec. After recrystallization from dioxane, the substance melted at 182–183°. *Anal.* ($C_8H_6N_4O_5$) C, H, N.

3-Amino-5-(5-nitro-2-furyl)-1,2,4-oxadiazole (IIIa).—A solution of 10 g of 3-acetylamino-5-(5-nitro-2-furyl)-1,2,4-oxadiazole in 200 ml of 10% EtOH–HCl was refluxed for 3 hr. After cooling the crystalline precipitate was filtered, and a second crop was

(1) Details of the synthetic aspects of this work will be the subject of a future communication.

(2) F. Eloy and R. Lenaers, *Helv. Chim. Acta*, **49**, 1430 (1966).

(3) The *trans* nature of the vinyl group in Vb is shown by the nmr spectrum (DMSO-d_6), the coupling of the vinyl protons (τ 2.67, 2.91) being 16.5 Hz.

(4) H. Wieland and H. Bauer, *Chem. Ber.*, **40**, 1680 (1907).

TABLE I

		Min inhib concn,[a] μg/ml								
No.	Mp, C	S. a.[b]	S. s.	Ps. a.	P. v.	E. c.	C. a.	T. m.	F. b.	M. t.
IIIa	200–202	0.69	0.69	>50	18.7	4.2	>50	12.5		1.2
IIIb	232 dec	0.24	0.5	25.0	15.6	1.1	15.6	9.4	25.0	1.0
Va	231–233	9.4	0.12	37.5	>50	0.24	>50	>50	>50	2.3
Vb	290 dec	0.15	0.05	7.8	9.4	0.05	12.5	6.3	12.5	6.3

[a] The minimum inhibitory concentrations of each compound were determined by the twofold tube dilution assay using antibiotic assay broth (BBL). [b] S. a. = *Staphylococcus aureus*, S. s. = *Salmonella schottmuelleri*, Ps. a. = *Pseudomonas aeruginosa*, P. v. = *Proteus vulgaris*, E. c. = *Escherichia coli*, C. a. = *Candida albicans*, T. m. = *Trichophyton mentagrophytes*, F. b. = *Fusarium bulbigenum*, M. t. = *Mycobacterium tuberculosis*.

obtained by concentrating the filtrate. Crystallization from EtOH gave pure IIIa, mp 200–202°, in a yield of 7.2 g (88%). *Anal.* ($C_6H_4N_4O_4$) C, H, N.

5-Amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (Vb).—A solution of 3.2 g of 3-[2-(5-nitro-2-furyl)vinyl]-5-trichloromethyl-1,2,4-oxadiazole in 35–40 ml of liquid NH_3 was prepared by adding small portions of the solid with continuous stirring. A dark solution and later a thick crystalline slurry resulted. The NH_3 was permitted to evaporate and the residue crystallized from dioxane; yield 2 g (90%), mp 290° dec. *Anal.* ($C_8H_6N_4O_4$) C, H, N.

3-(5-Nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole was prepared by treating 1 mole of 5-nitro-2-furanamidoxime[5] in dioxane with 2 moles of trichloroacetyl chloride in the presence of 2 moles of pyridine, evaporation of the solvent, treating the residue with H_2O, and filtering the crystals, yield 90%, mp 106–108° (*i*-PrOH). *Anal.* ($C_7H_2Cl_3N_3O_4$) C, H, N.

5-Amino-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (Va).—3-(5-Nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole (10 g) was added portionwise with stirring to 100 ml of liquid NH_3. A dark solution was formed from which crystals separated. The NH_3 was allowed to evaporate, and the residue was treated with dilute HCl, yielding 6.3 g (95%) of product; recrystallization from Me_2CO provided pure material, mp 231–233°. *Anal.* ($C_6H_4N_4O_4$) C, H, N.

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(5) W. R. Sherman and A. Von Esch, *J. Med. Chem.*, **8**, 25 (1965).

Antimalarial Compounds Related to Diaminodiphenyl Sulfone

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The interest in preparing diaminodiphenyl sulfone derivatives was initiated in our laboratories from the work done on the nucleophilic displacement of activated fluorine in aromatic compounds.[1] The facile replacement of fluorine in 4,4′-difluorodiphenyl sulfone with one or two primary or secondary amines provided a versatile route for the preparation of many substituted derivatives which were not easily available by the methods previously used.[2–5]

Different amines showed different activity in replacing the fluorine atom. The replacement of the second fluorine atom was usually more difficult than the first. The dihydrazino derivative **6** served as a starting material for several compounds.

We had considerable difficulty in preparing 4-amino-4′-formamidodiphenyl sulfone. When prepared through the formylation of 4-amino-4′-nitrodiphenyl sulfone followed by catalytic reduction of the nitro to the amino group, the formyl group proved to be so labile that it was removed under the usual experimental conditions of purification. The same difficulty has been experienced by Heymann and Heidelberger.[4] An alternative route was tried to formylate diaminodiphenyl sulfone monohydrochloride in formic acid, because a monoprotonated diaminodiphenyl sulfone molecule left only one nucleophilic amino group to be formylated. In this way a product was obtained which was found to be 98% pure 4-amino-4′-formamidodiphenyl sulfone monohydrochloride as shown by its elemental analysis and acid–base titration. Its purity could not be enhanced by crystallization for fear of deformylation.

Compound **9** was prepared by refluxing 4,4′-dihydrazinodiphenyl sulfone with formic acid while **22** was the acetylation product of **15**.

Experimental Section

Symmetrically Substituted Diaminodiphenyl Sulfones from 4,4′-Difluorodiphenyl Sulfone (1–8).—In general 4,4′-difluorodiphenyl sulfone was heated with an excess (3 *M* or more) of the amine in DMSO at a temperature varying from 100 to 140° for a period of 3–10 hr. In some cases (1–**3**, **5**, **9**) a 2–3 *M* proportion of Et_3N was used as an acceptor for the liberated HF. After the heating period, the mixture was cooled to room temperature and diluted with H_2O whereby the product generally separated as a precipitate which could be removed by filtration or extracted with a solvent when it happened to be gummy, such as in **7**.

4,4′-Di(1,2-dihydro-1-keto-2-phthalazinyl)diphenyl Sulfone (10).—A mixture of 2-carboxybenzaldehyde (1.8 g, 0.012 mol), 4,4′-dihydrazinodiphenyl sulfone dihydrochloride (2.1 g, 0.006 mol), 250 ml of EtOH, and 150 ml of H_2O was refluxed for 15 min when a precipitate was formed. EtOH was allowed to boil off and the mixture was filtered to give 2.6 g of the product.

4-Fluoro-4′-substituted Aminodiphenyl Sulfones (11–14).—In preparing these compounds one molar proportion of 4,4′-difluorodiphenyl sulfone and the amine were heated together in DMSO in the presence of Et_3N. The reaction mixture was cooled to room temperature and diluted with H_2O whereby the product usually separated as a solid or as a gummy material, which was crystallized from an appropriate solvent. The hydrochlorides of

(1) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **32**, 2319 (1966).

(2) E. Fromm and J. Whittmann, *Chem. Ber.*, **41**, 2269 (1908).

(3) H. Heymann and L. F. Fieser, *J. Amer. Chem. Soc.*, **67**, 1979 (1945).

(4) H. Heymann and C. Heidelberger, *ibid.*, **67**, 1986 (1945).

(5) W. H. Hartung, "Medicinal Chemistry," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1967, p 353.