with the product obtained from method A by comparison of uv and ir spectra.

2-Carboxy-3-hydroxy-3H-pyrido[3,2,1-*kl*]phenothiazinium Bisulfate (X).—A solution of 2.4 g (7.4 mmoles) of VI in 50 ml of concentrated H_2SO_4 was heated on water bath for 20 hr. The mixture was poured onto ice water and a yellow precipitate was formed. A crude yield of 2.9 g (99.8%) of brown solid was obobtained and recrystallized from *t*-BuOH and distilled H_2O. The first crop was recrystallized from a mixture of *t*-BuOH and deionized distilled H_2O to which a few drops of concentrated H_2SO_4 had been added. Brown crystals were obtained, mp 300°. *Anal.* ($C_{16}H_{11}NO_7S_2$) C, H, N, S.

Acknowledgment.—The authors thank S. C. Jong for assistance in the microbiological testing.

The Bacteriostatic Effectiveness of 1-Acyl-3-(3,4-dichlorophenyl)ureas

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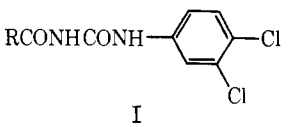
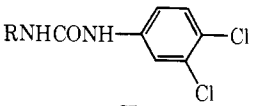
In continuation of our search for antibacterial compounds, a number of 1-acyl-3-(3,4-dichlorophenyl)ureas (I) were prepared. 1-Acylureas have been reported,[1]



I

but not as bacteriostats. A recent communication[2] from this laboratory described the synthesis and bacteriostatic properties of a similar series of compounds, the 1-alkyl-3-(3,4-dichlorophenyl)ureas (II). The activity was found to increase with chain length, reaching a maximum with the *n*-octyl derivative, then decreasing as the chain was lengthened further. A series of N-acylureas were prepared to determine whether these also are antibacterial and, if so, the chain length of R at which optimum activity occurs.



II

Synthesis of the desired materials involved treating 3,4-dichlorophenyl isocyanate with aliphatic amides, halogenated benzamides, and nicotinamide under anhydrous conditions. Relevant data, including minimum inhibitory concentrations (MIC's) in soap for *Staphylococcus aureus* ATCC 6538 are shown in Table I.

In the aliphatic series maximum activity (1–5 μg/ml) was observed when R was Pr, Bu, or 9-decenyl. In the series derived from benzamides, MIC's of 0.1–0.5 μg/ml were observed when R was 2,4-dichlorophenyl, and 1–5 μg/ml when R was 3,4-dichlorophenyl. Interestingly, in the carbanilide series, a structurally related group of compounds, maximum activity is observed with the 3,4-dichloro isomer and not the 2,4 derivative.[3]

Experimental Section

Since one of the reactants is 3,4-dichlorophenyl isocyanate, which readily forms 3,3′,4,4′-tetrachlorocarbanilide in the presence of water, the reaction must be carried out under extremely anhydrous conditions. The first few members of the series were prepared by first heating the amide in C_6H_6 for 2 hr and azeotroping moisture through a Dean–Stark trap, then adding 1 equiv of 3,4-dichlorophenyl isocyanate in dry *o*-dichlorobenzene. The mixture was heated to 130–140° and C_6H_6 was collected. Finally, the reaction was continued under reflux for 10 hr. At the end of this period, most of the solvent was distilled off and the residue was cooled and triturated with C_6H_6, causing a crude product to precipitate. The solid was filtered off and air dried. In most cases it was found to be a mixture of 3,3′,4,4′-tetrachlorocarbanilide and the desired material. Separation was achieved by boiling the mixture in C_6H_6, filtering while hot, and cooling the filtrate, whereupon the acylurea precipitated.

The method of choice, which avoids formation of tetrachlorocarbanilide, was to run the reaction in dry PhMe for 24 hr according to the procedure of Wiley.[1] Yields were generally in excess of 70% and ranged from 38 to 97%. The following preparation is representative.

TABLE I
1-ACYL-3-(3,4-DICHLOROPHENYL)UREAS
3,4-$Cl_2C_6H_3NHCONHCOR$

No.	R	Mp, °C[a]	Yield, %	MIC, μg/ml[b]	Formula[c]	Recrystn solvent
1	C_2H_5	173	78	20	$C_{10}H_{10}Cl_2N_2O$	EtOH
2	*n*-C_3H_7	155–156	38	1–5	$C_{11}H_{12}Cl_2N_2O_2$	PhH
3	*n*-C_4H_9	159	97	1–5	$C_{12}H_{14}Cl_2N_2O_2$	PhH
4	*n*-C_5H_{11}	130–131	86	20	$C_{13}H_{16}Cl_2N_2O_2$	PhH
5	*n*-C_7H_{15}	128–129	82	20	$C_{15}H_{20}Cl_2N_2O_2$	EtOH
6	*n*-C_8H_{17}	114–115	78	20	$C_{16}H_{22}Cl_2N_2O_2$	EtOH
7	*n*-$C_{11}H_{23}$	105–106	70	20	$C_{19}H_{28}Cl_2N_2O_2$	EtOH
8	9-Decenyl	100	69	5	$C_{18}H_{24}Cl_2N_2O_2$	EtOH
9	*n*-$C_{13}H_{27}$	99–100	52	20	$C_{18}H_{32}Cl_2N_2O_2$	EtOH
10	3-Pyridyl	272–273	94	20	$C_{13}H_9Cl_2N_3O_2$	*d*
11	*o*-ClC_6H_4	208	70	20	$C_{14}H_9Cl_3N_2O_2$	Me_2CO
12	*p*-ClC_6H_4	273	87	20	$C_{14}H_9Cl_3N_2O_2$	*d*
13	2,4-$Cl_2C_6H_3$	222	65	0.1–0.5	$C_{14}H_8Cl_4N_2O_2$	Me_2CO
14	3,4-$Cl_2C_6H_3$	235–236	96	1–5	$C_{14}H_8Cl_4N_2O_2$	Me_2CO

[a] All melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. [b] Minimum inhibitory concentration against *S. aureus* ATCC 6538. [c] All compounds were analyzed for C and H, and the results were within 0.4% of the theoretical values except for **13** where the C variance was 0.5%. [d] Triturated with Me_2CO.

(1) P. F. Wiley, *J. Am. Chem. Soc.*, **71**, 1310 (1949).

(2) T. A. Schenach, J. Brown, Jr., A. J. Wysocki, and F. Yackovich, *J. Med. Chem.*, **9**, 426 (1966).

(3) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).

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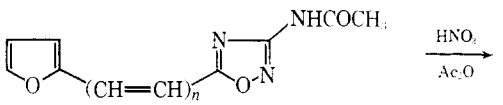
A novel synthesis of 5-substituted 3-amino-1,2,4-oxadiazoles has been developed in our laboratories.[1] Since the 5-nitrofuryl-2 group is present in a number of compounds showing antimicrobial activity, we decided to prepare a number of substituted 3-amino-1,2,4-oxadiazoles containing the 5-nitrofuryl-2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



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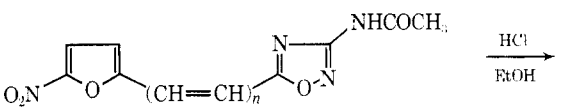

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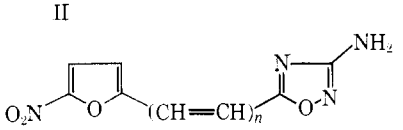
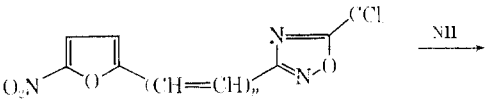


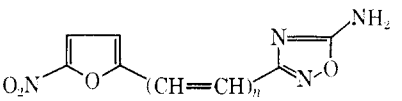
IIIa, $n = 0$
b, $n = 1$

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

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



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.* ($C_6H_5N_3O_2$) 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.* ($C_8H_7N_3O_3$) 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

(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).