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Pyrrole Antibacterial Agents. 1. Compounds Related to Pyoluteorin

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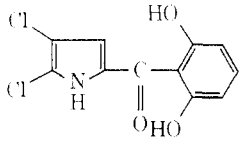
The naturally occurring halogenated pyrroles **1–5** have all yielded to synthesis.[1-9] All of these materials possess antibacterial properties of potential interest in human chemotherapy. We have prepared variations of pyoluteorin structure **1** and have examined them for *in vitro* and *in vivo* activity against a variety of pathogens and for antimalarial activity in mice. In addition, selected members of the series were examined for anthelmintic and antischistosomal activities.



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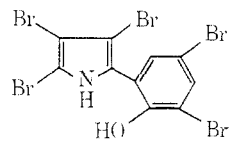

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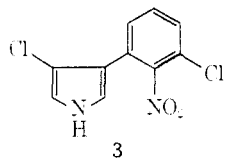

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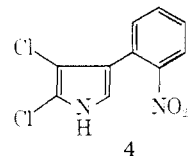

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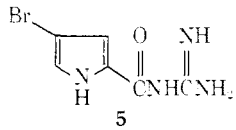

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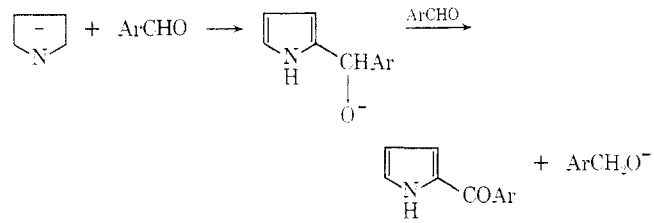
Chemistry. With the exception of **1** (see Experimental Section), three general methods were employed for the synthesis of 2-aroylpyrroles: acylation of pyrrole Grignard reagent[10] (method A), acylation with 4,5-dihalopyrrol-2-ylcarbonyl chloride (method B), and base-catalyzed condensation of pyrrole with arylaldehydes (method C).[11] The reagents for method B were conveniently prepared in high yield by halogenation of the trichloroacetylation product of pyrrole,[12] followed by hydrolysis and conversion of the resulting acid to the corresponding acyl chloride by means of $SOCl_2$.

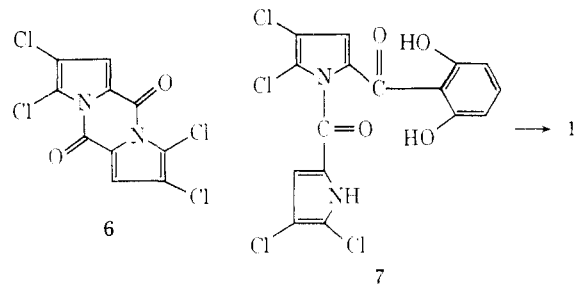
Method C has been described using equimolar quantities of $NaNH_2$, pyrrole, and arylaldehyde in refluxing C_6H_6 for 16 hr. The author reported that more than 1 equiv of aldehyde did not improve the yields (27–54%) despite the stoichiometry in the proposed mechanism (Scheme I). We have found that the product 2-aroylpyrroles undergo proton exchange with the pyrrolylsodium† and thus consume part of the limiting reagent. Using excess aldehyde with pyrrole and NaH in a molar ratio of 1:2 and with a 10% solution of DMF in C_6H_6 as solvent, yields of 70–74% were obtained in 1–3 hr. Halogenation of the 2-aroylpyrroles was carried out using the element in HOAc.[14] Cleavage of methyl ethers was accomplished using $AlCl_3$ or $AlBr_3$. Pyoluteorin itself was prepared from the pyrocoll **6** and 1-lithio-2,6-di(tetrahydropyranyloxy)-benzene,[15] followed first by acid hydrolysis (giving **7**) and then base hydrolysis (Scheme II). The compounds prepared by the above procedures are listed in Table I.

†For a discussion of acidity of substituted pyrroles, see ref 13.

Scheme I



Scheme II



6 **7** **1**

Biological Screening. All compounds with an *in vitro* MIC of 15.6 μg/ml or less against *Staphylococcus aureus* are shown in Table II along with their activity against three other organisms.

Although some of these compounds (**1**, **14**, **18**, **27**, **31**) showed a high order of *in vitro* activity against *Staph. aureus* at 200 mg/kg sc, none was effective in preventing mortality in mice infected with this organism or with *Klebsiella pneumoniae*. All compounds, when given at 200 mg/kg po, were ineffective in reducing parasite counts in mice infected with *Plasmodium berghei* (NK65 or NYU-2 strains). Selected agents at a dose of 100–200 mg/kg po did not reduce worm populations in mice infected with *Schistosoma mansoni* (**9**, **12**, **15–17**, **22**, **30**, **31**) nor produce clearances in mice infested with pinworms, roundworms, or tapeworms (**11–14**, **16**, **20**, **26**, **28**, **29**, **32**). Bailey and Rees[1] have reported that pyoluteorin has *in vitro* activity comparable to or better than cryptosporiopsin or nystatin against the Dutch elm disease fungus *Ceratocystis ulmi*. Agar growth studies‡ with this organism revealed that the isomers of pyoluteorin **26** and **30** were respectively 5 and 14 times as potent as **1** in inhibiting the growth of the fungus. Furthermore, the nonhydroxylated analog **18** was 20 times as effective as **1** (all drugs at 10 ppm).

Experimental Section§

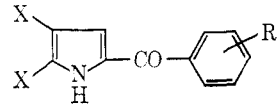
Aryl 2-Pyrrolyl Ketones. General syntheses for compounds in Table I are as follows.

Method A. The procedure of Pesson, *et al.*,[10] was followed exactly.

‡We are grateful to Mr. O. F. Greenwell and Mr. J. R. Willard of the Niagara Chemical Division of FMC Corp., Middleport, N. Y., for providing us with the *in vitro* data.

§All melting points were obtained on a Mel-Temp apparatus and are uncorrected. Where glpc analyses were used, determinations were performed on a Hewlett-Packard research chromatograph, Model 5751B, equipped with glass columns packed with 3% OV 17 on 100–120 mesh Gas Chrom Q. Microanalytical determinations were carried out by Instranal Laboratories, Inc., Rensselaer, N. Y., and Galbraith Laboratories, Inc., Knoxville, Tenn.

Table I. 2-Aroyl-4,5-dihalopyrroles



Compd	X	R	Method	% yield[a]	Mp, °C	Analyses[b]
1	Cl	2,6-diOH			181–182	
8	Cl	H	C	74	189.5–191.5	Cl, N
9	Br	H	C		170–172	C, H, N
10	Cl	4-Cl	C	70	233–235	C, H, N
11	Br	4-Cl	C		246–248	C, H, N
12	Cl	2-Cl	A	48	180–183	C, H, N, Cl
13	Br	2-Cl	A		193–195	C, H, N
14	Cl	3-Cl	A	40	208–209	C, H, N, Cl
15	Br	3-Cl	A		203–205	C, H, N, Br
16	Cl	4-F	A	30	224–226	C, H, N, Cl
17	Br	4-F	A		215–216	C, H, N, Br
18	Cl	4-CF_3	A	56	180–181	C, H, N, Cl
19	Br	4-CF_3	A		196–198	C, H, N, Br
20	Cl	4-CH_3	A	50	182–184	C, H, N, Cl
21	Br	3-Br	A	54	210–211	C, H, N, Br
22	Br	2,4,6-triCH_3	B	63	164–166	C, H, N
23	Cl	4-OCH_3	C	70	186–188	C, H, N
24	Br	4-OCH_3	C		202–203	C, H, N
25	Br	3-OCH_3	C	73	131–132	C, H, N
26	Cl	2,5-diOCH_3	B	58	148–150	C, H, N
27	Cl	2,5-diOH	B		238–239	C, H, N
28	Br	2,5-diOCH_3	B	64	166–168	C, H, N
29	Br	2,5-diOH	B		202–203 dec	C, H, N
30	Cl	2,4-diOCH_3	B	45	147–149	C, H, N
31	Cl	2,4-diOH	B		233–235	C, H, N
32	Cl	3,4-diOCH_3	B	33	167–169	C, H, N

[a] Of 2-aroylpyrrole by method cited. [b] Analysis of indicated elements agreed within ±0.4% with calculated values.

Table II. *In Vitro* Antibacterial Activity of 2-Aroyl-4,5-dihalopyrroles

Compd	MIC,[a] μg/ml *Staph. aureus*	*P. aerug*[b]	*E. coli*[c]	*P. vulg*[d]
1	3.1	125	6.2	125
13	15.6	>125	125	>125
14	7.8	62.5	>62.5	>62.5
16	15.6	125	>125	>125
17	15.6	125	>125	>125
18	3.1	>125	>125	>125
22	15.6	>125	>125	>125
27	0.98	125	125	62.5
29	15.6	125	125	62.5
31	3.9	>125	31.3	>125

[a] Minimum inhibitory concentration; procedure of W. A. Goss and E. B. Cimijotti, *Appl. Microbiol.*, **16,** 1414 (1968). [b] *Pseudomonas aeruginosa.* [c] *Escherichia coli.* [d] *Proteus vulgaris.*

Method B. 4,5-Dibromopyrrol-2-yl 2,5-Dimethoxyphenyl Ketone (28). 4,5-Dibromopyrrole-2-carbonyl chloride was prepared from pyrrol-2-yl trichloromethyl ketone[12] by halogenation in HOAc, hydrolysis of the trichloroacetyl function, and treatment of the resulting acid with $SOCl_2$ in C_6H_6. A solution of 28.7 g (0.1 mol) of the acid chloride and 13.8 g (0.1 mol) of *p*-dimethoxybenzene in 100 ml of C_6H_6 was stirred at 10° while 26 g (0.1 g-atom) of $SnCl_4$ was added in 10 min. The mixture was stirred 18 hr at ambient temperature and was then quenched with cold H_2O. Et_2O was added and the solution was washed successively with 2 *N* HCl and saturated $NaHCO_3$ and then dried (Na_2SO_4) and concentrated to 100 ml. On cooling, the solution deposited 22.5 g of solid, mp 166–168°. Concentration of the filtrate and crystallization of the residue from EtOH gave a second crop of 2.4 g: mp 166–167°; total yield 64%.=

=This procedure failed with the trimethyl ethers of phloroglucinol and pyrogallol.

Method C. *p*-Methoxyphenyl Pyrrol-2-yl Ketone. A 21.1-g (0.5 g-atom) sample of NaH in oil was washed free of oil by decantation and was suspended in a mixture of 90 ml of C_6H_6 and 10 ml of DMF. A solution of 16.75 g (0.25 mol) of freshly distilled pyrrole in 100 ml of the same solvent was added over 40 min with stirring and external warming to 45–50°. This was followed by the addition, over 70 min, of 75 g (0.55 mol) of *p*-anisaldehyde, during which time the temperature slowly rose to 65°. After an additional 30 min, the solution was cooled and cautiously diluted with H_2O. The organic layer was separated, dried, and concentrated and low boilers were distilled off at 100° and 0.1 Torr. The residue was crystallized from *i*-PrOAc–hexane to give 34.9 g (70% of theory) of off-white solid, mp 107–109° (reported[10] mp 112°), homogeneous by glpc.

4,5-Dibromopyrrol-2-yl *m*-Methoxyphenyl Ketone. A solution of 16.7 g (0.083 mol) of *m*-methoxyphenyl pyrrol-2-yl ketone in 100 ml of HOAc and 10 ml of CCl_4 was stirred and cooled to a slush. A solution of 26.6 g (0.166 g-atom) of Br_2 in 50 ml of HOAc was added dropwise with continued cooling. The product which precipitated from the reaction mixture was crystallized from *i*-PrOH to give 18.6 g (62.5% yield) of light sensitive needles, mp 131–132°.

4,5-Dichloropyrrol-2-yl 4-Resorcinyl Ketone (31). A solution of 19 g (0.064 mol) of **30** in 500 ml of C_6H_6 was added dropwise to a stirred mixture of 100 g (0.75 mol) of anhydrous $AlCl_3$ in 500 ml of C_6H_6. The mixture was refluxed for 17 hr, cooled, and poured into 1 l. of 3 *N* HCl. The product was extracted with Et_2O. The organic solution was dried (Na_2SO_4), charcoaled, and concentrated to 200 ml. The yellow crystallization product (13.5 g, mp 233–236°, 78% yield) was recrystallized from EtOH–H_2O to give 6.5 g (37% yield), mp 233–235°.

In the demethylation of **28**, the use of $AlBr_3$ in CH_2Cl_2 at ambient temperature for 5 days produced **29** in 73% yield.

4,5-Dichloropyrrol-2-yl 2-Resorcinyl Ketone (Pyoluteorin, 1). A 15-g (0.083 mol) sample of 4,5-dichloropyrrole-2-carboxylic acid [mp 164–166° dec. *Anal.* ($C_5H_3Cl_2NO_2$) C, H, N] was converted to the acid chloride with $SOCl_2$. This was dissolved in 60 ml of C_6H_6 and to the solution was slowly added a solution of 9 g (0.09 mol) of Et_3N in 30 ml of C_6H_6. The mixture was stirred for 0.5 hr and 50 ml of H_2O was added. The product was filtered, washed with Et_2O, and dried at 60° *in vacuo* to give 12.8 g (95%

yield) of the pyrocoll 6, mp 326–331°. *Anal.* ($C_{10}H_2Cl_4N_2O_2$) C, H, N. To a stirred solution of 0.01 mol of 1-lithio-2,6-di(tetrahydropyranyloxy)benzene[15] in 35 ml of Et_2O was added 3.0 g (9.3 mmol) of 6. The mixture was stirred 1 hr at ambient temperature and refluxed 1 hr. The cooled mixture was stirred 1 hr with 20 ml of Me_2CO and 80 ml of 3 *N* HCl and filtered to give 0.8 g (27%) of recovered 6. An Et_2O extract of the filtrate was extracted with 1% Na_2CO_3 (3 × 50 ml) and then with 10% K_2CO_3 (3 × 5 ml). The K_2CO_3 solutions were acidified and extracted with Et_2O from which 1 g of crude 7 could be recovered by evaporation (37% yield based on recovered material). The acylated pyrrole could be purified by crystallization from Me_2CO–hexane to give yellow crystals, mp 214–215° dec. *Anal.* ($C_{16}H_{18}Cl_4N_2O_4$) C, H; N: calcd, 6.46; found, 5.96. Hydrolysis was accomplished by heating 100 mg of crude 7 and 5 ml of 10% NaOH on a steam bath for 30 min. The cooled solution was acidified with concentrated HCl and extracted with Et_2O. The extracts were washed with 1% $NaHCO_3$, dried (Na_2SO_4), and evaporated. Crystallization of the residue from Me_2CO–hexane gave 50 mg (30% yield), mp 171–172° dec (reported[16] mp 174–175°). *Anal.* ($C_{11}H_7O_3NCl_2$) C, H, N, Cl.

Acknowledgment. We are grateful to Drs. W. A. Goss, J. R. O'Connor, and A. Yarinsky for providing the biological data cited.

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Pyrrole Antibacterial Agents. 2.[1] 4,5-Dihalopyrrole-2-carboxylic Acid Derivatives

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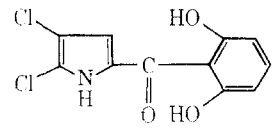
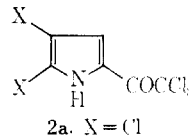
We have previously described[1] our efforts to modify the structure of the naturally occurring antibiotic pyoluteorin, 1, by varying the halogen and aroyl portions of the molecule. The novelty of the 4,5-dihalopyrrole entity led us to the development of the synthesis of the highly versatile intermediates **2a–c**. Using these compounds as starting materials, we have prepared a variety of 4,5-dihalopyrrole-2-carboxylic acid derivatives (Table I) and have screened them *in vitro* and *in vivo* against a variety of pathogens.

Chemistry. Trichloroacetylation of pyrrole[2] gave an excellent yield of 3 which was readily halogenated to **2a–c**.

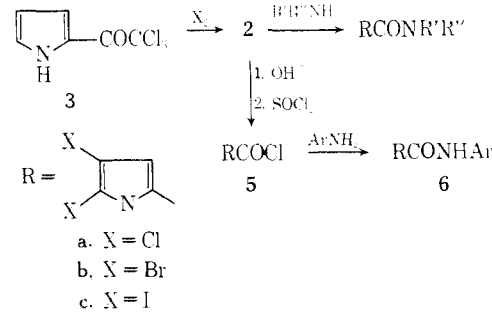


1



2a. X = Cl
b. X = Br
c. X = I

Treatment of the latter compounds with NH_3 or aliphatic amines gave amides **4**. Anilides **6** were prepared by acylating the amines in pyridine solution with the acid chlorides **5** derived from **2a–c** by base hydrolysis and treatment with $SOCl_2$.



a. X = Cl
b. X = Br
c. X = I

Similarly, pyrrole can be sequentially dichloroacetylated or trifluoroacetylated and halogenated, but these derivatives offer no synthetic advantage. The halogenated dichloroacetyl compounds can be N-alkylated with K_2CO_3 and MeI. The compounds prepared are found in Table I.

Biological Screening. The compounds were assayed for antimicrobial activity by the method of Goss and Cimijotti.[3] All compounds with an *in vitro* MIC of 15.6 μg/ml or less against *Staphylococcus aureus* are shown in Table II along with their activity against three other organisms. All of these were examined for their ability to prevent mortality in mice infected with *Staph. aureus* or with *Klebsiella pneumoniae*. Despite the fact that several of the test compounds had *in vitro* MIC values of <1 μg/ml, none was active *in vivo* against the two organisms at a screening dose of 200 mg/kg sc. None of the compounds in Table I showed significant *in vivo* antimalarial, anthelmintic, or antischistosomal activity.

Experimental Section†

The following procedures are typical for preparation of the compounds in Table I.

4,5-Dichloropyrrol-2-yl Trichloromethyl Ketone (2a). A solution of 15.6 g (0.22 mol) of Cl_2 in 450 ml of glacial HOAc was added slowly to a stirred solution of 22.3 g (0.105 mol) of pyrrol-2-yl trichloromethyl ketone[2] in 50 ml of HOAc. The temperature rose slightly during the addition. After 2 hr, the solution was concentrated under reduced pressure, excess 10% K_2CO_3 was added, and the mixture was extracted with Et_2O. The extracts were dried (Na_2SO_4) and decolorized (Darco), and the solvent was removed under reduced pressure. Crystallization of the residue from C_6H_6 gave 20.2 g (81% yield) of light tan powder, mp 129–131°.

4,5-Diiodopyrrol-2-yl Trichloromethyl Ketone (2c). A solution of 21.3 g (0.10 mol) of pyrrol-2-yl trichloromethyl ketone[2] in 200 ml of HOAc was stirred and heated on a steam bath while 100 ml (0.21 mol) of 2.075 *N* $NaCl_2I$[4] in H_2O was added over 45 min. The solution was heated an additional 1.5 hr and was then concentrated using a rotary evaporator. Saturated $NaHCO_3$ was added to neutralize the remaining acid, and the product was extracted with Et_2O. The product was crystallized from Et_2O–hexane (charcoal) to give 25.7 g (55% yield) of light yellow needles, mp 176–177°.

†All melting points were obtained on a Mel-Temp apparatus and are uncorrected. Microanalytical determinations were carried out by Instranal Laboratories, Inc., Rensselaer, N.Y., and Galbraith Laboratories, Inc., Knoxville, Tenn.