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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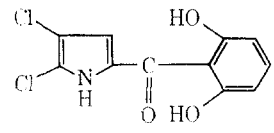
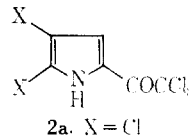
We have previously described[1] our efforts to modify the structure of the naturally occurring antibiotic pyoluteorin, **1**, by varying the halogen and aroyl portions of the molecule. The novelty of the 4,5-dihalopyrrole entity led us to the development of the synthesis of the highly versatile intermediates **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**.

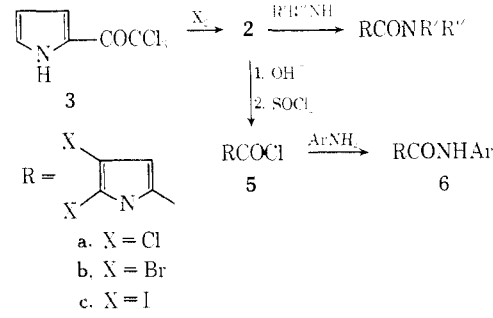


1



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†

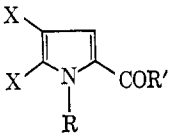
The following procedures are typical for preparation of the compounds in Table I.

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.

Table I. 4,5-Dihalopyrrole-2-carboxylic Acid Derivatives



Compd	X	R	R′	Mp, °C	Formula	Analyses[a]
2a	Cl	H	CCl_3	129–131	$C_6H_2Cl_5NO$	C, H, N
2b	Br	H	CCl_3	136–138	$C_6H_2Br_2Cl_3NO$	C, H, N
2c	I	H	CCl_3	176–177	$C_6H_2Cl_3I_2NO$	C, H, N
3[b]	H	H	CCl_3	74.5–75	$C_6H_4Cl_3NO$	C, H, N
7[b]	H	H	$CHCl_2$	89–90	$C_6H_3Cl_2NO$	C, H, N
8	Br	H	$CHCl_2$	127–129	$C_6H_3Br_2Cl_2NO$	C, H, N
9	Br	CH_3	$CHCl_2$	127–130	$C_7H_5Br_2Cl_2NO$	C, H, N
10	Cl	H	$CHCl_2$	104–107	$C_6H_3Cl_4NO$	C, H, N
11	Cl	CH_3	$CHCl_2$	114–116	$C_7H_5Cl_4NO$	C, H, N
12	Br	H	CF_3	108–109	$C_6H_2Br_2F_3NO$	C, H, N
13	Cl	H	CF_3	86–87	$C_6H_2Cl_2F_3NO$	Cl, N
14	Br	H	NH_2	163–165	$C_5H_4Br_2N_2O$	C, H, N
15	Br	H	NH-*n*-C_4H_9	194–195	$C_9H_{12}Br_2N_2O$	Br, N
16	Br	H	$N(CH_2)_5$	174–176	$C_{10}H_{12}Br_2N_2O$	C, H, N
17	Br	H	$N(C_2H_4)_2O$	198–200	$C_9H_{10}Br_2N_2O_2$	Br, N
18	Br	H	3-BrC_6H_4NH	210–211	$C_{11}H_7Br_3N_2O$	N; Br[c]
19	Br	H	4-BrC_6H_4NH	243–245	$C_{11}H_7Br_3N_2O$	C, H, N
20	Br	H	4-ClC_6H_4NH	235–237	$C_{11}H_7Br_2ClN_2O$	C, H, N
21	Br	CH_3	4-ClC_6H_4NH	200–202	$C_{12}H_9Br_2ClN_2O$	C, H, N
22	Br	H	2,4-$Br_2C_6H_3NH$	272–275	$C_{11}H_6Br_4N_2O$	C, H, N
23	Br	H	3,5-$Br_2C_6H_3NH$	244–245	$C_{11}H_6Br_4N_2O$	C, H, N
24	Br	H	3,5-$Cl_2C_6H_3NH$	245–248	$C_{11}H_6Br_2Cl_2N_2O$	C, H, N
25	Br	H	3,5-$(CF_3)_2C_6H_3NH$	197–199	$C_{13}H_6Br_2F_6N_2O$	C, H, N
26	Br	H	4-$H_2NSO_2C_6H_4NH$	267–268	$C_{11}H_9Br_2N_3O_3S$	C, H, N
27	Br	H	2-NH(C_3H_2NS)[d]	265–266	$C_8H_3Br_2N_3OS$	C, H, N
28	Br	H	$NHNH_2$	213–214	$C_5H_5Br_2N_3O$	C, H, N
29	Br	H	NHN=CH(2-HOC_6H_4)	265–266	$C_{12}H_9Br_2N_3O_2$	C, H, N
30	Cl	H	OH	164–166	$C_5H_3Cl_2NO_2$	C, H, N
31	Cl	H	NH_2	159–160	$C_5H_4Cl_2N_2O$	C, H, N
32	Cl	H	$NHCH_3$	189–191	$C_6H_6Cl_2N_2O$	C, H, N
33	Cl	H	$N(CH_3)_2$	197–199	$C_7H_8Cl_2N_2O$	C, H, N
34	Cl	H	$N(CH_2)_5$	183–185	$C_{10}H_{12}Cl_2N_2O$	C, H, N
35	Cl	H	$NHCH_2C_6H_5$	183–185	$C_{12}H_{14}Cl_2N_2O$	C, H, N
36	Cl	H	C_6H_5NH	213–215	$C_{11}H_8Cl_2N_2O$	C, H, N
37	Cl	H	4-$(CH_3O)C_6H_4NH$	224–226	$C_{12}H_{10}Cl_2N_2O_2$	C, H, N
38	Cl	H	4-$(CH_3)C_6H_4NH$	227–229	$C_{12}H_{10}Cl_2N_2O$	C, H, N
39	Cl	H	4-FC_6H_4NH	227–228	$C_{11}H_7Cl_2FN_2O$	F, N
40	Cl	H	2-ClC_6H_4NH	231–233	$C_{11}H_7Cl_3N_2O$	C, H, N
41	Cl	H	3-ClC_6H_4NH	247–249	$C_{11}H_7Cl_3N_2O$	C, H, N
42	Cl	H	4-ClC_6H_4NH	256–258	$C_{11}H_7Cl_3N_2O$	C, H, N
43	Cl	H	2,3-$Cl_2C_6H_3NH$	259–261	$C_{11}H_6Cl_4N_2O$	C, H, N
44	Cl	H	2,4-$Cl_2C_6H_3NH$	262–264	$C_{11}H_6Cl_4N_2O$	C, H, N
45	Cl	H	2,5-$Cl_2C_6H_3NH$	245–247	$C_{11}H_6Cl_4N_2O$	C, H, N
46	Cl	H	2,6-$Cl_2C_6H_3NH$	212–214	$C_{11}H_6Cl_4N_2O$	C, H, N
47	Cl	H	3,4-$Cl_2C_6H_3NH$	261–263	$C_{11}H_6Cl_4N_2O$	C, H, N
48	Cl	H	3,5-$Cl_2C_6H_3NH$	234–235	$C_{11}H_6Cl_4N_2O$	C, H, N
49	Cl	H	2-[6-$(CH_3)C_5H_3N$]NH	235–236	$C_{11}H_7Cl_3N_3O$	C, H, N
50	I	H	ONa	Dec >200	$C_5H_2I_2NNaO_2$	C, H, N
51	I	H	$NHCH_3$	197–199	$C_6H_6I_2N_2O$	C, H, N
52	I	H	3,5-$Cl_2C_6H_3NH$	237–240	$C_{11}H_6Cl_2I_2N_2O$	C, H, N

[a] Indicated analyses were within ±0.4% of theory except where noted. [b] G. Sanna, *Gazz. Chim. Ital.*, **63**, 479 (1933). [c] Br: calcd, 56.68; found, 56.19. [d] 2-Thiazolyl.

Dichloromethyl 4,5-Dichloro-1-methylpyrrol-2-yl Ketone (11). A mixture of 5.0 g (0.020 mol) of **10** (prepared in 44% yield from 7), 4.3 g (0.030 mol) of MeI, 9.1 g (0.066 mol) of K_2CO_3, and 125 ml of Me_2CO was stirred and refluxed for 1.5 hr. Most of the solvent was removed under reduced pressure, and the residue was partitioned between H_2O and Et_2O. The crude material obtained by removing the Et_2O was placed on a 5 × 50 cm dry alumina column and was eluted with 1:4 EtOAc–hexane. The segment containing the product was detected with uv light, and the product was eluted with MeOH. Crystallization from Et_2O–hexane gave 2.4 g (46% yield) of tan powder, mp 114–116°.

***N*-Butyl-4,5-dibromopyrrole-2-carboxamide (15).** *N*-Butylamine (10 g, 0.137 mol) was added rapidly to a solution of 23 g (0.062 mol) of **2b** in 25 ml of DMF, and the mixture was kept overnight. After the solution was diluted with 150 ml of H_2O, concentrated HCl was added to precipitate a solid. The product was crystallized from absolute EtOH to give 15.2 g (76% yield) of white powder, mp 194–195°.

4,5-Dichloro-4′-fluoropyrrole-2-carboxanilide (39). A mixture of 12 g (0.067 mol) of 4,5-dichloropyrrole-2-carboxylic acid (mp 167–168°, prepared in 88% yield by slurrying **2a** in a slight excess of 10% NaOH on the steam bath until no solid remained and then precipitating the product with concentrated HCl) and 20 ml of $SOCl_2$ was refluxed for 10 min and then concentrated. C_6H_6 was added, and the solution was concentrated again to remove excess $SOCl_2$. The crude acid chloride was dissolved in C_6H_6, and the solution was added dropwise to 7.5 g (0.067 mol) of *p*-fluoroaniline in 50 ml of C_5H_5N. The mixture was kept overnight, concentrated under reduced pressure, and treated with saturated $NaHCO_3$ and Et_2O. The organic layer was washed with 3 *N* HCl until the aqueous remained acidic, and the Et_2O solution was then dried (Na_2SO_4), decolorized (Darco), and concentrated.

Table II. *In Vitro* Antimicrobial Activity of 4,5-Dihalopyrrole-2-carboxylic Acid Derivatives

Compd	MIC,[a] μg/ml			
	Staph. aureus	*P. aerug*[b]	*E. coli*[c]	*P. vulg*[d]
8	7.8	250	15.6	125
10	3.9	250	31.2	62.5
12	1.95	500	31.2	250
13	3.9	>125	31.2	125
18	0.62	125	125	>125
19	0.31	62.5	7.8	250
20	0.12	>125	7.8	250
23	2.5	>125	>125	>125
24	5	>100	>100	>100
25	0.3	>100	>100	>100
36	7.8	>125	31.2	>250
38	15.6	>62.5	>125	>125
39	3.9	>125	7.8	>125
41	7.8	>62.5	>250	>125
42	0.97	>62.5	>250	>125
46	15.6	>125	125	>125
47	3.9	125	>125	>125
48	0.075	>62.5	>125	>125
52	0.8	>125	>250	>125

[a] Minimum inhibitory concentration. [b] *Pseudomonas aeruginosa*. [c] *Escherichia coli*. [d] *Proteus vulgaris*.

The crude material was crystallized from EtOH–H_2O to give 14.2 g (78% yield) of white powder, mp 227–228°.

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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14α,17α-Alkylidenedioxy Steroids. 2. 19-Nor-9α,10β- and 19-Nor-9β,10α-progesterone Analogs

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In our previous publication[1] we described the synthesis of a series of 14α,17α-alkylidenedioxyprogesterone derivatives. This report deals with the synthesis of some 19-nor analogs in the same series. The starting compound for this synthesis was 11α,14α,17α-trihydroxypregn-4-ene-3,20-dione (**1**).[1] This was converted in two steps into 14α,17α-dihydroxypregna-4,9(11)-diene-3,20-dione (**3**) which was dehydrogenated to 14α,17α-dihydroxypregna-1,4,9(11)-triene-3,20-dione (**4**) with *Corynebacterium simplex*.[2] The A ring of **4** was aromatized according to the method of K. Tsuda, *et al.*,[3] and then the 9 double bond was hydrogenated with Pd on C.[4] This resulted in a mixture of two compounds, 3,14α,17α-trihydroxy-19-norpregna-1,3,5(10)-trien-20-one (**6a**) and its 9β isomer **6b** which were easily separated by crystallization. Both steroids were converted to alkylidenedioxy compounds by condensation with various aldehydes.[1] At this stage the 9α and 9β configurations could be conclusively identified by comparing the nmr absorptions of the ethylidenedioxy groups.

In 9α compounds (*e.g.*, **7a**) the absorptions appear at higher field than in their 9β isomers (*e.g.*, **7b**) as a result of a downfield shift in the latter case, which is to be ascribed to a diamagnetic effect of the aromatic A ring in the (bent) 9β isomer.[5]

After protection of the 20-keto and the 3-hydroxyl groups by conversion to the corresponding ethylenedioxy and methoxy groups the products were subjected to a Birch reduction[6] and hydrolyzed to 14α,17α-alkylidenedioxy-19-norprogesterone derivatives. In two cases these products were converted to 3-enol ethers. The whole reaction sequence is outlined in Scheme I and described in detail for the ethylidenedioxy compound in the Experimental Section. The end products are listed in Table I with some pharmacological data.

We assigned the 9β,10α configuration to the 9β-19-norprogesterone derivatives on the following considerations. From Dreiding models it is obvious that Δ^4-3-keto steroids with a 9β,10β configuration are only possible with ring B in the boat form which is thermodynamically unfavorable. It is known that such steroids rearrange under acidic conditions to the 9β,10α configuration *via* a $\Delta^5(10)$-3-keto system.[7] Since our 9β derivatives were formed under strongly acidic conditions from $\Delta^5(10)$ steroids their configurations must be 9β,10α.

On one occasion there was a little complication in the reaction sequence. After Birch reduction of the benzylidenedioxy compound it appeared that the benzylidenedioxy group had been removed and the 14- and 17-hydroxyls had been formed again. We reintroduced the benzylidenedioxy group after acid removal of the protecting enol ether and ethylenedioxy groups. The latter reactions are also described in the Experimental Section.

Pharmacology. The compounds were tested as solutions or suspensions in maize oil (50 mg/ml for rats; 5 mg/ml for rabbits). The rats used in most of these experiments were the Wistar-derived Cpb strain from TNO (Zeist, Holland); in some experiments (indicated in Table I) the strain "Orga Cpb" from the same institute was used. The rabbits used were the "Bastard" strain bred by TNO.

The procedures used for testing the anticonceptive and progestational activities were essentially the same as reported earlier.[1] The results are summarized in Table I.

Just as the 19-methyl derivatives,[1] the 19-noralkylidenedioxyprogesterones show an optimum of activity in the region of the propylidenedioxy compounds (R = Et; **12a** and **12b**). The very long pregnancy delay produced by **16** (R = Ph) is striking since the 19-methyl analog[1] did not possess such activity. The activities of the 9α and 9β isomers of the 19-noralkylidenedioxyprogesterones do not differ much from each other (**11a,b**, **12a,b**, and **13a,b**). Both **12a** and **12b**, when given orally, are active in the pregnancy delay test in contrast to their 19-methyl analogs. Conversion of **12a** and **12b** into their 3-ethyl enol ethers **17a** and **17b**, respectively, failed to enhance oral activity of these compounds in the pregnancy delay test.

Experimental Section

General. Melting points were determined according to Tottoli on a Büchi melting point apparatus. The ultraviolet spectra were taken in methanol with a Zeiss PMQ II spectrophotometer. The infrared spectra were taken in chloroform with a Perkin-Elmer grating/prism spectrophotometer 221. Nmr spectra (in $CDCl_3$, using TMS as internal standard) were recorded on a Varian A-60 nmr spectrometer at the Centraal Laboratorium TNO (Delft). Elemental analyses were performed at the Microanalytical section of the Organic Laboratory of the Technical University, Delft. All reactions were followed by thin-layer chromatography.