yield) of the pyrcoll 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.

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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.

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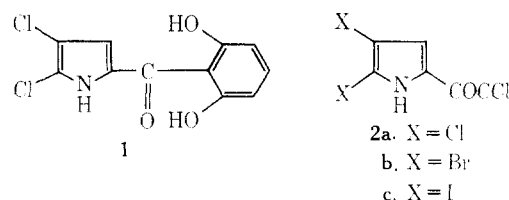
Treatment of the latter compounds with NH_3 or aliphatic amines gave amides 4. Anilides 6 were prepared by acylating the amines in pyridine solution with the acid chlorides 5 derived from 2a-c by base hydrolysis and treatment with $SOCl_2$.

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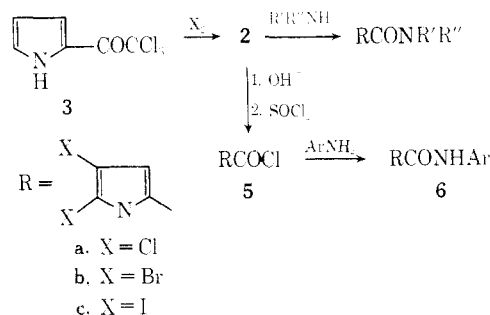
Similarly, pyrrole can be sequentially dichloroacetylated or trifluoroacetylated and halogenated, but these derivatives offer no synthetic advantage. The halogenated dichloroacetyl compounds can be N-alkylated with K_2CO_3 and MeI. The compounds prepared are found in Table I.

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°.

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

Compd	X	R	R'	Mp, °C	Formula	Analyses[a]
2a	Cl	H	CCl₃	129–131	C₆H₂Cl₃NO	C, H, N
2b	Br	H	CCl₃	136–138	C₆H₂Br₂Cl₃NO	C, H, N
2c	I	H	CCl₃	176–177	C₆H₂Cl₃I₂NO	C, H, N
3[b]	H	H	CCl₃	74.5–75	C₆H₄Cl₃NO	C, H, N
7[b]	H	H	CHCl₂	89–90	C₆H₅Cl₂NO	C, H, N
8	Br	H	CHCl₂	127–129	C₆H₃Br₂Cl₂NO	C, H, N
9	Br	CH₃	CHCl₂	127–130	C₇H₅Br₂Cl₂NO	C, H, N
10	Cl	H	CHCl₂	104–107	C₆H₃Cl₄NO	C, H, N
11	Cl	CH₃	CHCl₂	114–116	C₇H₅Cl₄NO	C, H, N
12	Br	H	CF₃	108–109	C₆H₂Br₂F₃NO	C, H, N
13	Cl	H	CF₃	86–87	C₆H₂Cl₂F₃NO	Cl, N
14	Br	H	NH₂	163–165	C₅H₄Br₂N₂O	C, H, N
15	Br	H	NH-n-C₄H₉	194–195	C₉H₁₂Br₂N₂O	Br, N
16	Br	H	N(CH₂)₅	174–176	C₁₀H₁₂Br₂N₂O	C, H, N
17	Br	H	N(C₂H₄)₂O	198–200	C₉H₁₀Br₂N₂O₂	Br, N
18	Br	H	3-BrC₆H₄NH	210–211	C₁₁H₇Br₃N₂O	N; Br[c]
19	Br	H	4-BrC₆H₄NH	243–245	C₁₁H₇Br₃N₂O	C, H, N
20	Br	H	4-ClC₆H₄NH	235–237	C₁₁H₇Br₂ClN₂O	C, H, N
21	Br	CH₃	4-ClC₆H₄NH	200–202	C₁₂H₉Br₂ClN₂O	C, H, N
22	Br	H	2,4-Br₂C₆H₃NH	272–275	C₁₁H₆Br₄N₂O	C, H, N
23	Br	H	3,5-Br₂C₆H₃NH	244–245	C₁₁H₆Br₄N₂O	C, H, N
24	Br	H	3,5-Cl₂C₆H₃NH	245–248	C₁₁H₆Br₂Cl₂N₂O	C, H, N
25	Br	H	3,5-(CF₃)₂C₆H₃NH	197–199	C₁₃H₆Br₂F₆N₂O	C, H, N
26	Br	H	4-H₂NSO₂C₆H₄NH	267–268	C₁₁H₉Br₂N₃O₃S	C, H, N
27	Br	H	2-NH(C₃H₂NS)[d]	265–266	C₈H₅Br₂N₃OS	C, H, N
28	Br	H	NHNH₂	213–214	C₅H₅Br₂N₃O	C, H, N
29	Br	H	NHN=CH(2-HOC₆H₄)	265–266	C₁₂H₉Br₂N₃O₂	C, H, N
30	Cl	H	OH	164–166	C₅H₃Cl₂NO₂	C, H, N
31	Cl	H	NH₂	159–160	C₅H₄Cl₂N₂O	C, H, N
32	Cl	H	NHCH₃	189–191	C₆H₆Cl₂N₂O	C, H, N
33	Cl	H	N(CH₃)₂	197–199	C₇H₈Cl₂N₂O	C, H, N
34	Cl	H	N(CH₂)₅	183–185	C₁₀H₁₂Cl₂N₂O	C, H, N
35	Cl	H	NHCH₂C₆H₅	183–185	C₁₂H₁₄Cl₂N₂O	C, H, N
36	Cl	H	C₆H₅NH	213–215	C₁₁H₈Cl₂N₂O	C, H, N
37	Cl	H	4-(CH₃O)C₆H₄NH	224–226	C₁₂H₁₀Cl₂N₂O₂	C, H, N
38	Cl	H	4-(CH₃)C₆H₄NH	227–229	C₁₂H₁₀Cl₂N₂O	C, H, N
39	Cl	H	4-FC₆H₄NH	227–228	C₁₁H₇Cl₂FN₂O	F, N
40	Cl	H	2-ClC₆H₄NH	231–233	C₁₁H₇Cl₃N₂O	C, H, N
41	Cl	H	3-ClC₆H₄NH	247–249	C₁₁H₇Cl₃N₂O	C, H, N
42	Cl	H	4-ClC₆H₄NH	256–258	C₁₁H₇Cl₃N₂O	C, H, N
43	Cl	H	2,3-Cl₂C₆H₃NH	259–261	C₁₁H₆Cl₄N₂O	C, H, N
44	Cl	H	2,4-Cl₂C₆H₃NH	262–264	C₁₁H₆Cl₄N₂O	C, H, N
45	Cl	H	2,5-Cl₂C₆H₃NH	245–247	C₁₁H₆Cl₄N₂O	C, H, N
46	Cl	H	2,6-Cl₂C₆H₃NH	212–214	C₁₁H₆Cl₄N₂O	C, H, N
47	Cl	H	3,4-Cl₂C₆H₃NH	261–263	C₁₁H₆Cl₄N₂O	C, H, N
48	Cl	H	3,5-Cl₂C₆H₃NH	234–235	C₁₁H₆Cl₄N₂O	C, H, N
49	Cl	H	2-[6-(CH₃)C₅H₃N]NH	235–236	C₁₁H₉Cl₂N₃O	C, H, N
50	I	H	ONa	Dec >200	C₅H₂I₂NNaO₂	C, H, N
51	I	H	NHCH₃	197–199	C₆H₆I₂N₂O	C, H, N
52	I	H	3,5-Cl₂C₆H₃NH	237–240	C₁₁H₆Cl₂I₂N₂O	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 K₂CO₃, and 125 ml of Me₂CO was stirred and refluxed for 1.5 hr. Most of the solvent was removed under reduced pressure, and the residue was partitioned between H₂O and Et₂O. The crude material obtained by removing the Et₂O 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 Et₂O–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 H₂O, 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 SOCl₂ was refluxed for 10 min and then concentrated. C₆H₆ was added, and the solution was concentrated again to remove excess SOCl₂. The crude acid chloride was dissolved in C₆H₆, and the solution was added dropwise to 7.5 g (0.067 mol) of p-fluoroaniline in 50 ml of C₅H₅N. The mixture was kept overnight, concentrated under reduced pressure, and treated with saturated NaHCO₃ and Et₂O. The organic layer was washed with 3 N HCl until the aqueous remained acidic, and the Et₂O solution was then dried (Na₂SO₄), decolorized (Darco), and concentrated.

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

	MIC,^{a} μg/ml			
Compd	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$_2$O to give 14.2 g (78% yield) of white powder, mp 227–228°.

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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-nor-progesterone 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 Δ^5(10)-3-keto system.[7] Since our 9β derivatives were formed under strongly acidic conditions from Δ^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.