The Chlorination of Pyrroles. Part II[1]

G. R. BIRCHALL AND A. H. REES
Department of Chemistry, Trent University, Peterborough, Ontario

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We report the chlorination of pyrryl-2-glyoxylic acid and derivatives and hence a synthesis of *O,O'*-dimethylpyoluteorin and 5-dechloro-*O,O'*-dimethylpyoluteorin. The different behavior of these compounds on demethylation is described and explained.

La chloruration de l'acide pyrolleglyoxylique-2 et quelques-uns de ses dérivés est rapportée; ces réactions constituent une synthèse de l'*O,O'*-diméthylpyolutéorine et du dechloro-5 *O,O'*-diméthylpyolutéorine. Le comportement différent de ces composés vis-à-vis de la réaction de déméthylation est décrit et expliqué.

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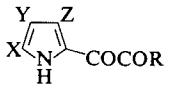
We found during the synthesis of pyoluteorin (2, 3) that the preparation (4) of pure 4,5-dichloropyrrole-2-carboxylate was troublesome. We therefore prepared pyrryl-2-glyoxylyl chloride (**1**, X = Y = Z = H; R = Cl) (5) and hence the acid (**1**, X = Y = Z = H; R = OH) and its isobutylamide **2**. We anticipated that chlorination at the 3-position would be blocked. This expectation was not fully met but we found that the products were more easily separated. We thus obtained the chloroamides **3**, **4**, and **5** and hence some of the corresponding ketoacids.



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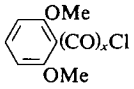

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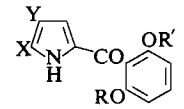
R = $NHCH_2CHMe$	
X = Y = Z = H	**2**
X = Y = Cl; Z = H	**3**
X = Z = Cl; Y = H	**4**
X = Z = H; Y = Cl	**5**

Before oxidation to the carboxylic acids, we used the salts of the ketoacids in reaction with **6** ($x = 1$) (2, 3). This went in poor yield when X = Y = Z = H. There was no improvement when we used 2,6-dimethoxyphenylglyoxylyl chloride (**6**, $x = 2$).

By reaction of **1** (X = Y = Cl; Z = H; R = Na) with **6** ($x = 1$) we obtained a pure sample of **8** (3) and hence of pyoluteorin.

Hydrolysis of **5** and oxidation gave 4-chloropyrrole-2-carboxylic acid. From this acid or the parent ketoacid we made 5-dechloro-*O,O'*-dimethylpyoluteorin **9** (6), identical with the compound obtained by partial hydrogenation of **8**. Demethylation with boron trichloride stopped at **10** in contrast to the complete demethylation of **8** under the same mild conditions. This resembled our earlier demethylation of **7** with this reagent which gave **11**. Complete demethylation to **12** (6) was done with aluminum bromide. The latter reagent converted **9** to 5-dechloropyoluteorin (**13**) (7).

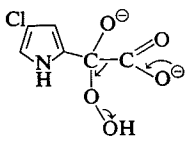


7 X = Y = H; R = R′ = Me
8 X = Y = Cl; R = R′ = Me
9 X = H; Y = Cl; R = R′ = Me
10 X = H; Y = Cl; R = Me; R′ = H
11 X = Y = R = H; R′ = Me
12 X = Y = R = R′ = H
13 X = R = R′ = H; Y = Cl

This difference is attributed to the acidity of the pyrrole NH whose anion can donate to the boron atom and promote a second mild demethylation in cases where there are sufficient electronegative groups in the heterocyclic ring or where the Lewis acid is sufficiently polar.

We prepared the ester **14** but neither it nor chloro-derivatives **15**, **16**, and **17** underwent thermal decarbonylation, probably because of NH to carbonyl bonding.

1 R = OCH_2CHMe_2	
X = Y = Z = H	**14**
X = Z = H; Y = Cl	**15**
X = Z = Cl; Y = H	**16**
X = Y = Cl; Z = H	**17**



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[1]For Part I, see ref. 1.

TABLE 1. The n.m.r. spectra ($CDCl_3$) of 2-pyrryl glyoxylic acid derivatives

Compound	1H	3H	4H	5H	CH_2CHMe_2	$—CHMe_2$	$—CHMe_2$	Amide H
2	−1.6m	2.81m	3.6m	2.48m	6.77t	8.1m	9.05d	2.3
3	−1.6m	2.55d			6.75t	8.1m	9.05d	2.5
4	−1.6d		3.81d		6.84t	8.2m	9.05d	2.5
		$J_{1,4}$ 1.8Hz						
5	−1.6m	2.92m		2.65m	6.78t	8.2m	9.05d	2.4
		After D_2O J 1.6Hz						
15	−0.5	2.8m		2.7m	5.83d	7.9m	8.94d	—

Finally we investigated the dichlorination in acetic acid of pyrryl-2-glyoxylic acid **1** (R = OH; X = Y = Z = H) to the 4,5-dichloro-derivative (plus minor amounts of 4-chloro-derivative). We attribute the absence of any other isomers to strong solvation of the ketoacid function, effectively blocking the 3-position. Taking advantage of the different NH acidities, we were able to selectively oxidize the monochloroketoacid to the easily separable monochloroacid with alkaline peroxide. We attribute the stability of the dichloroketoacid to the formation of an O,N-dianion, not attacked by HOO^- whereas in the monochloro-analogue there must be appreciable quantities of mono-anion present so that attack by HOO^- gives **18** which breaks down as indicated (8). This affords a convenient route to pure dichloroketoacid and hence by further oxidation to 4,5-dichloropyrrole-2-carboxylic acid.

Experimental

2-Pyrrylglyoxylic Acid and Isobutylamide

Pyrrole, 10.7 g in 50 ml dry ether was added dropwise with stirring to 16 ml oxalyl chloride in 200 ml ether at −70° over 3 h. The mixture was poured slowly into a vigorously stirred solution of 24 g sodium hydroxide in 240 ml ice-water and the aqueous layer was separated and acidified, giving ketoacid **1** (X = Y = Z = H; R = OH). This crude acid, in ether solution, was washed with water to remove oxalic acid and the solution dried ($MgSO_4$) and evaporated at 20° giving 15.4 g, 70% ketoacid, m.p. 112° crystallized from benzene (lit. m.p. 113° (9)).

When the ketoacid chloride, prepared as above, was poured into a stirred solution of 50 ml isobutylamine in 200 ml ether at −70° and the system allowed to warm up, the residue after filtration was crude amide. It was taken up in dichloromethane, filtered, dried ($MgSO_4$), and evaporated giving 28 g crystalline amide. This was chromatographed on 750 g neutral alumina. Elution with light petroleum/ether 4:1 gave 5 g di-isobutyloxamide, m.p. 168° (18%). Further elution, solvent ratio 20:7, gave *N*-isobutyl-2-pyrrylglyoxylamide, 20 g (70%), m.p. 90°, crystallized from aqueous ethanol; i.r. (Nujol) 3480 (NH), 1672, 1630 (CO bands) cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.8; H, 7.3; N, 14.4. Found: C, 61.65; H, 7.3; N, 14.5.

Chlorination of 2

Amide **2** (2% in acetic acid) was treated with 2.1 mol chlorine and left overnight at room temperature. Evaporation of the solvent and chromatography of the residue on silica, eluting with light petroleum/ether (increasing ratio), gave (*a*) 3,5-dichloro-derivative **4**, 6%, m.p. 118–119° crystallized from benzene/light petroleum; mass spectrum *m/e* 264 (20), 262 (40), 164 (64), 162 (100).

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O_2$: C, 45.6; H, 4.6; Cl, 26.9; N, 10.6. Found: C, 45.3; H, 4.2; Cl, 26.7; N, 10.6.

(*b*) 4,5-Dichloro-derivative **3**, 50%, m.p. 132°; mass spectrum *m/e* 264 (20), 262 (32), 57 (100).

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O_2$: C, 45.6; H, 4.6; Cl, 26.9; N, 10.6. Found: C, 45.7; H, 4.6; Cl, 27.2; N, 10.8.

(*c*) 4-Chloro-derivative **5**, 20%, m.p. 134°; mass spectrum *m/e* 230 (12), 228 (38), 130 (34), 128 (100), 57 (100).

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3$: Cl, 15.5. Found: Cl, 15.1.

A mixture of products (12%), was also obtained, containing the trichloroderivative, *m/e* 296 (M^+).

Chlorination (1.2 mol) under the same conditions, gave as above 5% **4**, 22% **3**, and 50% **5** after chromatography.

The orientations of the chlorinated amides (and esters) follow from their n.m.r. spectra, Table 1.

4,5-Dichloro-2-pyrrylglyoxylic Acid

Amide **3**, 1.8 g, and potassium hydroxide, 2.3 g in 10 ml ethanol and 50 ml water, were refluxed 2 h. After evaporation of the solvent, water was added and the alkaline solution extracted with ether and acidified giving 1.2 g (90%) of the acid m.p. 177°, yellow needles crystallized from benzene/light petroleum, i.r. (Nujol) 1710, 1643 (CO bands); mass spectrum *m/e* 209 (24), 207 (40), 164 (40), 162 (100).

Anal. Calcd. for $C_6H_3Cl_2NO_3$: N, 6.75. Found: N, 7.0.

4-Chloro-2-pyrrylglyoxylic Acid

Amide **5**, by the method above, gave the acid (90%), m.p. 160° crystallized from benzene/light petroleum; mass spectrum *m/e* 175 (16), 173 (48), 130 (34), 128 (100).

Anal. Calcd. for $C_5H_4ClNO_3$: Cl, 20.4. Found, Cl, 20.4.

2,6-Dimethoxybenzoyl Cyanide

Compound **6** ($x = 1$) (10), 20 g, was refluxed 20 h in 100 ml dry benzene with 10.3 g cuprous cyanide. After filtration, the organic layer was washed with sodium bicarbonate solution, then with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from benzene/light petroleum to give 11 g (60%) of ketonitrile, light yellow needles m.p. 69–70°, i.r. (Nujol) 2300 cm^{-1} (CN); mass spectrum *m/e* 191 (100%, M^+).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.8; H, 4.75; N, 7.3. Found: C, 62.9; H, 4.8; N, 7.4.

2,6-Dimethoxyphenylglyoxylamide

The above cyanide (9 g) was left for 5 days at 20° in 100 ml concentrated hydrochloric acid solution. Dilution with water gave the amide, 7.5 g (80%) m.p. 148–150°, crystallized from benzene/light petroleum, i.r. 3500, 3320, 1690, 1643 cm^{-1}; mass spectrum *m/e* 209 (4), 165 (100).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 56.8; H, 5.2; N, 6.3.

New Synthesis of 2,6-Dimethoxyphenylglyoxylic Acid

The above amide (7.5 g) was refluxed 1 h with 300 ml 5% potassium hydroxide solution. The cold solution was extracted with methylene chloride then acidified giving the acid, 5 g (66%), as an oil which slowly crystallized, m.p. 92–95° from benzene/petroleum ether (lit. m.p. 98° (11)); i.r. (Nujol) 1705, 1665 cm^{-1}; mass spectrum *m/e* 210 (14), 165 (100).

Monodechloro-O,O′-dimethylpyoluteorin (9)

Table 2 summarizes the syntheses of **9**. It formed colorless needles m.p. 150° from benzene/light petroleum, i.r. (Nujol) 3300, 1625, 1600 cm^{-1}; u.v. max (ethanol) 295 mμ.

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.6; H, 4.6; Cl, 13.4; N, 5.3. Found: C, 59.0; H, 4.6; Cl, 13.3; N, 5.1.

O,O′-Dimethylpyoluteorin (8)

The method of Table 2, after preparative t.l.c. and crystallization from benzene/light petroleum, gave 4% pure **8**, m.p. 193–196°; u.v. max (ethanol) 305 mμ; i.r. 1630, 1603 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}Cl_2NO_3$: C, 52.0; H, 3.7; Cl, 23.7; N, 4.7. Found: C, 52.4; H, 3.8; Cl, 23.4; N, 4.5.

Hydrogenation of O,O′-Dimethylpyoluteorin (8)

Compound **8**, 480 mg in 40 ml acetic acid containing 650 mg sodium acetate, was shaken in hydrogen with 1 g 5% palladium-on-charcoal. One molar equivalent was taken up in 1.5 h. After filtration and evaporation of the solvent, the residue was resolved by t.l.c. giving **8**, 180 mg and monodechloro-*O,O′*-dimethylpyoluteorin, **9**, 200 mg, identical with the material synthesized above.

5-Dechloro-O-monomethylpyoluteorin (10)

Compound **9** (80 mg) was demethylated with boron trichloride (3). The product, from the n.m.r. and mass spectrum was the monomethyl ether **10**, m.p. 148°, crystallized from benzene/light petroleum, 60 mg (80%), i.r. (Nujol) 3400, 3200, 1615, 1598 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: Cl, 14.1. Found: Cl, 13.9.

TABLE 2. Reactions of pyrrole acid salts with acid chlorides **6**

Pyrrole salt	Acid Chloride **6** x	Product	Yield (%)
2-COCOONa	1	**7**	5
2-COONa	2	**7**	5
4-Cl-2-COONa	1	9	5
4-Cl-2-COCOONa	1	**9**	2
4-Cl-2-COCOONa	2	**9**	1
4,5-di-Cl-2-COCOONa	1	**8**	4

Didechloro-O-monomethylpyoluteorin (11)

Didechloro-*O,O′*-dimethylpyoluteorin, 80 mg, was treated with boron trichloride as described (3). The product, after crystallization from benzene/light petroleum, had m.p. 129°, 60 mg (80%); i.r. (Nujol) 1613 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.1; N, 6.45. Found: C, 66.1; H, 4.8; N, 6.3.

The same product was obtained using aluminum chloride under mild conditions. Aluminum bromide effected removal of both methyl groups. So did boron tribromide (12).

5-Dechloropyoluteorin (13)

The dimethyl ether **9**, 135 mg, in 20 ml dry benzene, was treated with 400 mg anhydrous aluminum bromide, After stirring for 2 h at 20°, water was added and the organic layer separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was recrystallized from benzene giving 110 mg (90%) 5-dechloropyoluteorin, m.p. 197°; i.r. 3500–3400, 1633, 1598, 1560 cm^{-1}; u.v. max (ethanol) 330 mμ, log ε = 4.25; n.m.r. see Table 3.

Isobutyl Pyrryl-2-glyoxylate (1, X = Y = Z = H; R = i-Bu)

Pyrrole, 10.7 g was converted to the glyoxylyl chloride as above. The mixture, at −70° was poured slowly into a solution of sodium, 3.4 g, in excess isobutanol. The system was allowed to warm up with stirring and left for 24 h. Evaporation of the solvent left a residue which was absorbed onto 600 g silica and eluted with light petroleum/ether, 10:1, giving 25 g, 75% of ester **14**, i.r. 1740, 1655 cm^{-1}.

Chlorination of the Above Ester

The ester, 12.5 g, was treated with 1.2 mol chlorine in acetic acid. Work-up, as above, gave after column chromatography on silica, 7.5 g (50%) isobutyl 4-chloropyrryl-2-glyoxylate as colorless needles, m.p. 75°; mass spectrum *m/e* 231 (8), 229 (24), 130 (33), 128 (100).

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.7; H, 5.3; Cl, 15.4; N, 6.1. Found: C, 52.3; H, 5.3; Cl, 15.3; N, 6.3.

Hydrolysis with 40% potassium hydroxide solution gave pure 4-chloropyrryl-2-glyoxylic acid in quantitative yield.

TABLE 3. The n.m.r. spectra of pyoluteorins

Compound	Solvent	1H	3H	4H	5H	3′	4′	5′	Me	OH
9*	$CDCl_3$	0.0	3.54m	—	3.0 m	3.43d†	2.66m	3.43d	6.25	—
10	DMSO-d_6	−2.0	3.8 m		2.9 m	3.58d	2.9 m	3.58d	6.4	0.4
11*	$CDCl_3$	0.1	3.14m	3.75m	2.98m	3.4 d	2.7 m	3.14d	6.3	0.2
			After D_2O $J = 3.6$ Hz		$J = 2.4$ Hz					
					$J_{3,5} = 1.2$ Hz					
13*	DMSO-d_6	−2.0	3.8 m	—	2.97m	3.75d	3.12m	3.75d	—	0.63

*After D_2O, $J_{3,5} = 1.6$ Hz.
†The 3′,4′,5′ protons form an AB_2 system, $J_{A,B} = 7$–7.5 Hz (K. Bailey, personal communication; compare J. R. Dyer, ref. 13).

A mixture of isobutyl 3,5- and 4,5-dichloropyrryl-2-glyoxylates, 5.0 g (30%) was also obtained, shown by n.m.r. to be in the ratio of 1:3.

4-Chloropyrrole-2-carboxylic Acid

4-Chloropyrryl-2-glyoxylic acid, 3.2 g in 60 ml 2 *N* sodium hydroxide solution, was treated dropwise with 18 ml 3% hydrogen peroxide solution at 5°. The stirred solution was allowed to warm to room temperature over 20 h then acidified and extracted with ether. The ether solution was extracted with sodium bicarbonate solution and the latter acidified giving a precipitate of 2.2 g (83%) of 4-chloropyrrole-2-carboxylic acid; m.p. 195° not sharp; i.r. (Nujol) 1700 cm^{-1} (CO); mass spectrum *m/e* 147 (20), 145 (60), 129 (35), 127 (100).

Anal. Calcd. for $C_5H_4ClNO_2$: C, 41.3; H, 2.8; Cl, 24.4; N, 9.6. Found: C, 41.4; H, 2.8; Cl, 24.2; N, 9.5.

The mass spectra of pyrrole acids, ketoacids, and their derivatives show cleavage to the pyrrol cation, loss of carbon monoxide to a pyrryl ion and then loss of HCN to give a cyclopropenyl ion (1).

Chlorination of Pyrryl-2-glyoxylic Acid

The above acid, 1 g, in 5 ml acetic acid was treated dropwise with 2.2 mol chlorine in 25 ml acetic acid. The system was stirred 20 h at 20° and the solvent taken off under vacuum. The residue, crystallized from benzene/light petroleum gave a 0.7 g cocrystalline mixture of 4- and 4,5-dichloroketoacids, analyzed by n.m.r. in NaOD solution as being in the ratio 1:4. There was no signal above 3 τ, indicating a total lack of 4-H protons.

Oxidation of the Mixture of Chloroketoacids

The acid mixture above, 240 mg, was oxidized with excess alkaline peroxide as described previously. Preparative t.l.c. on silica, chloroform/methanol/acetic acid (50:5:1) then gave bands at R_f 0.4 and 0.1 due to the chloropyrrole-2-carboxylic acid, 20 mg and the dichloropyrroleketoacid, 150 mg, respectively, after recrystallization, identical with pure authentic specimens obtained earlier, above.

Oxidation of 4,5-Dichloropyrryl-2-glyoxylic Acid (1, X = Y = Cl; Z = H; R = OH)

The dichloroketoacid, 20 mg, in 4 ml 50% aqueous acetic acid was treated with 45 mg lead tetraacetate at 20°. After 1 h the solvent was removed and the residue was shaken with ether and dilute sulfuric acid. The ether extract was dried ($MgSO_4$) and evaporated and the residue purified by t.l.c. giving, after recrystallization from benzene/light petroleum, 8 mg 4,5-dichloropyrrole-2-carboxylic acid.

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