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Ethyl 3-pyrrolicarboxylates and their corresponding acids are brominated with copper(II) bromide. The reaction afforded at 0°, with high-yield nuclear monobromination.

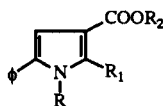
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## Introduction.

Recently, we have described the bromination of some 3-acetylpyrroles with copper(II) bromide [1]. As a result of such a study, it was found that the only products obtained, with very high yields, were the 4-bromo-3-acetylpyrroles.

The outstanding biological activity of many halopyrroles [2], particularly of some halogenated pyrrol-3-carboxylic acids [3], prompted us to continue our study in this area. In the present work the experiments with copper(II) bromide have been extended to some ethyl 3-pyrrolicarboxylates and to their corresponding acids (Table 1).

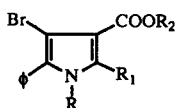
Table 1



Compound	Molecular Formula (M <sup>+</sup> )	Analyses Calcd./Found %			R	R <sub>1</sub>	R <sub>2</sub>	Solvent [a]	Yield %	Mp (°C)	IR ν (cm <sup>-1</sup> )
		C	H	N							
I	C <sub>12</sub> H <sub>11</sub> NO <sub>2</sub> (201)	71.62 71.80	5.51 5.55	6.96 7.02	H	CH <sub>3</sub>	H	A	>95	190-191	3340 (NH) 2600 (COOH) 1680 (CO)
II	C <sub>13</sub> H <sub>13</sub> NO <sub>2</sub> (215)	72.54 72.75	6.09 6.15	6.51 6.48	CH <sub>3</sub>	CH <sub>3</sub>	H	B	>95	217-218	2620 (COOH) 1700 (CO)
III	C <sub>18</sub> H <sub>15</sub> NO <sub>2</sub> (277)	77.96 78.20	5.45 5.54	5.05 5.21	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	A	>95	231-232	2600 (COOH) 1670 (CO)
IV	C <sub>14</sub> H <sub>15</sub> NO <sub>2</sub> (229)	73.34 73.52	6.59 6.70	6.11 6.02	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	A	60	115-116	3300 (NH) 1600 (CO)
V	C <sub>15</sub> H <sub>17</sub> NO <sub>2</sub> (243)	74.05 74.08	7.04 6.96	5.76 5.87	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	A	60	88-89	1700 (CO)
VI	C <sub>20</sub> H <sub>19</sub> NO <sub>2</sub> (305)	78.66 78.50	6.27 6.20	4.59 4.71	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	A	65	93-94	1690 (CO)
VII	C <sub>17</sub> H <sub>13</sub> NO <sub>2</sub> (263)	77.55 77.80	4.98 5.06	5.32 5.25	H	C <sub>6</sub> H <sub>5</sub>	H	A	>95	207-208	3420-3460 (NH) 2600 (COOH) 1680-1655 (CO)
VIII	C <sub>18</sub> H <sub>15</sub> NO <sub>2</sub> (277)	77.96 77.90	5.45 5.38	5.05 5.20	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	B	>95	213-214	2620 (COOH) 1600 (CO)
IX	C <sub>23</sub> H <sub>17</sub> NO <sub>2</sub> (339)	81.39 81.25	5.05 5.08	4.13 4.21	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	C	>95	278-279	2600 (COOH) 1680 (CO)
X	C <sub>19</sub> H <sub>17</sub> NO <sub>2</sub> (291)	78.33 78.60	5.88 5.99	4.81 4.70	H	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	A	70	160-161	3300 (NH) 1670 (CO)
XI	C <sub>20</sub> H <sub>19</sub> NO <sub>2</sub> (305)	78.66 78.81	6.27 6.39	4.59 4.65	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>		70	oil	1700 (CO)
XII	C <sub>25</sub> H <sub>21</sub> NO <sub>2</sub> (367)	81.72 81.90	5.76 5.89	3.81 4.02	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C	60	130-131	1700 (CO)

[a] A = ethanol, B = acetonitrile, C = acetic acid.

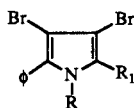
Table 2



Compound	Molecular Formula (M <sup>+</sup> )	Analyses			R	R <sub>1</sub>	R <sub>2</sub>	Solvent [a]	Yield %	Mp (°C)	IR ν (cm <sup>-1</sup> )
		Calcd./Found %									
		C	H	N							
XIII	C <sub>12</sub> H <sub>10</sub> BrNO <sub>2</sub> (279)	51.45	3.59	5.00	H	CH <sub>3</sub>	H	A	90	171-172	3360 (NH) 2560 (COOH) 1650 (CO)
		51.62	3.70	5.19							
XIV	C <sub>13</sub> H <sub>12</sub> BrNO <sub>2</sub> (293)	53.08	4.11	4.76	CH <sub>3</sub>	CH <sub>3</sub>	H	A	85	172-173	2600 (COOH) 1650 (CO)
		53.25	4.21	4.92							
XV	C <sub>18</sub> H <sub>14</sub> BrNO <sub>2</sub> (355)	60.69	3.96	3.92	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	C	85	214-215	2590 (COOH) 1670 (CO)
		60.52	3.88	4.13							
XVI	C <sub>14</sub> H <sub>14</sub> BrNO <sub>2</sub> (307)	54.56	4.58	4.54	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	A	90	155-156	3310 (NH) 1680 (CO)
		54.42	4.44	4.70							
XVII	C <sub>15</sub> H <sub>16</sub> BrNO <sub>2</sub> (321)	55.91	5.00	4.35	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	A	80	100-101	1700 (CO)
		56.12	5.17	4.20							
XVIII	C <sub>20</sub> H <sub>18</sub> BrNO <sub>2</sub> (383)	62.51	4.72	3.64	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	A	85	170-171	1710 (CO)
		62.70	4.80	3.51							
XIX	C <sub>17</sub> H <sub>12</sub> BrNO <sub>2</sub> (341)	59.66	3.53	4.09	H	C <sub>6</sub> H <sub>5</sub>	H	A	>95	213-214	3300 (NH) 2580 (COOH) 1650 (CO)
		59.81	3.64	3.95							
XX	C <sub>18</sub> H <sub>14</sub> BrNO <sub>2</sub> (355)	60.69	3.96	3.93	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	A	>95	243-244	2600 (COOH) 1660 (CO)
		60.72	3.84	4.02							
XXI	C <sub>23</sub> H <sub>16</sub> BrNO <sub>2</sub> (417)	66.04	3.85	3.35	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	C	>95	308-309	2580 (COOH) 1660 (CO)
		66.25	4.00	3.50							
XXII	C <sub>19</sub> H <sub>16</sub> BrNO <sub>2</sub> (369)	61.63	4.36	3.78	H	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	A	>95	129-130	3290 (NH) 1675 (CO)
		61.80	4.42	3.70							
XXIII	C <sub>20</sub> H <sub>18</sub> BrNO <sub>2</sub> (383)	62.51	4.72	3.64	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	A	>95	124-125	1700 (CO)
		62.40	4.66	3.60							
XXIV	C <sub>25</sub> H <sub>20</sub> BrNO <sub>2</sub> (445)	67.27	4.52	3.14	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C	>95	159	1700 (CO)
		67.40	4.60	3.28							

[a] A = ethanol, C = acetonitrile.

Table 3



Compound	Molecular Formula (M <sup>+</sup> )	Analyses			R	R <sub>1</sub>	Solvent [a]	Yield %	Mp (°C)	IR ν (cm <sup>-1</sup> )
		Calcd./Found %								
		C	H	N						
XXV	C <sub>11</sub> H <sub>9</sub> Br <sub>2</sub> N (313)	41.94	2.88	4.44	H	CH <sub>3</sub>	A	10	100-101	3420 (NH)
		41.72	2.80	4.70						
XXVI	C <sub>12</sub> H <sub>11</sub> Br <sub>2</sub> N (327)	43.80	3.37	4.26	CH <sub>3</sub>	CH <sub>3</sub>	A	15	80-81	
		44.02	3.50	4.12						
XXVII	C <sub>16</sub> H <sub>11</sub> Br <sub>2</sub> N (375)	50.96	2.94	3.71	H	C <sub>6</sub> H <sub>5</sub>	A	95	142-143	3420 (NH)
		50.84	2.88	3.94						
XXVIII	C <sub>17</sub> H <sub>13</sub> Br <sub>2</sub> N (389)	52.20	3.35	3.58	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	A	90	101-102	
		52.45	3.46	3.52						
XXIX	C <sub>22</sub> H <sub>15</sub> Br <sub>2</sub> N (451)	58.30	3.34	3.09	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	B	90	226-227	
		58.55	3.47	3.00						

[a] A = ethanol, B = acetonitrile.

Table 4  
<sup>1</sup>H-NMR (δ) Data of Compounds I-XII (deuteriochloroform as solvent) [a]

Compound	<sup>1</sup> H-NMR (δ) Data
I	2.60 (3H, s, CH <sub>3</sub> ), 6.83 (1H, d, J = 3 Hz, CH), 7.10-7.90 (5H, m, C <sub>6</sub> H <sub>5</sub> ), 11.60 (1H, s broad, NH)
II	2.60 (3H, s, CH <sub>3</sub> ), 3.50 (3H, s, N-CH <sub>3</sub> ), 6.60 (1H, s, CH), 7.40 (5H, s broad, C <sub>6</sub> H <sub>5</sub> )
III	2.27 (3H, s, CH <sub>3</sub> ), 6.70 (1H, s, CH), 6.90-7.60 (10H, m, 2 C <sub>6</sub> H <sub>5</sub> )
IV	1.40 (3H, t, J = 7.0 Hz, CH <sub>2</sub> CH <sub>3</sub> ), 2.60 (3H, s, CH <sub>3</sub> ), 4.27 (2H, q, J = 7.0 Hz, CH <sub>2</sub> ), 6.80 (1H, d, J = 2.5 Hz, CH), 7.10-7.60 (5H, m, C <sub>6</sub> H <sub>5</sub> ), 9.20 (1H, s broad, NH)
V	1.33 (3H, t, J = 7.0 Hz, CH <sub>2</sub> CH <sub>3</sub> ), 2.60 (3H, s, CH <sub>3</sub> ), 3.47 (3H, s, N-CH <sub>3</sub> ), 4.27 (2H, q, J = 7.0 Hz, CH <sub>2</sub> ), 6.60 (1H, s, CH), 7.46 (5H, s broad, C <sub>6</sub> H <sub>5</sub> )
VI	1.37 (3H, t, J = 7.0, CH <sub>2</sub> CH <sub>3</sub> ), 2.40 (3H, s, CH <sub>3</sub> ), 4.33 (2H, q, J = 7.0 Hz, CH <sub>2</sub> ), 6.80 (1H, s, CH), 6.90-7.50 (10H, m, 2 C <sub>6</sub> H <sub>5</sub> )
VII	6.97 (1H, d, J = 3.2 Hz, CH), 7.10-7.85 (10H, m, 2 C <sub>6</sub> H <sub>5</sub> ), 11.70 (1H, s, broad, NH)
VIII	3.30 (3H, s, CH <sub>3</sub> ), 6.75 (1H, s, CH), 7.40 (10H, s broad, 2 C <sub>6</sub> H <sub>5</sub> )
IX	6.83 (1H, s, CH), 7.10 (15H, s broad, 3 C <sub>6</sub> H <sub>5</sub> )
X	1.20 (3H, t, J = 7.0 Hz, CH <sub>3</sub> ), 4.07 (2H, q, J = 7.0 Hz, CH <sub>2</sub> ), 6.90 (1H, d, J = 3.2 Hz, CH), 7.03-7.60 (10H, m, 2 C <sub>6</sub> H <sub>5</sub> ), 9.20 (1H, s broad, NH)
XI	1.13 (3H, t, J = 7.0, CH <sub>2</sub> CH <sub>3</sub> ), 3.33 (3H, s, CH <sub>3</sub> ), 4.10 (2H, q, J = 7.0 Hz, CH <sub>2</sub> ), 6.70 (1H, s, CH), 7.35 (10H, s, broad, C <sub>6</sub> H <sub>5</sub> )
XII	1.20 (3H, t, J = 7.0 Hz, CH <sub>3</sub> ), 4.17 (2H, q, J = 7.0 Hz, CH <sub>2</sub> ), 7.00 (1H, s, CH), 6.80-7.50 (15H, m, 3 C <sub>6</sub> H <sub>5</sub> )

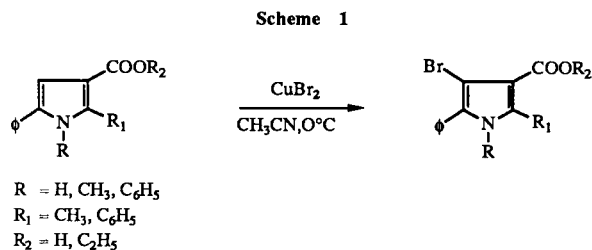
[a] Spectra recorded in deuteriodimethyl sulfoxide for I, III, VII and IX.

## Results.

We have found that the compounds studied at 0° were brominated, with high yields, exclusively at the cyclic carbon atom even with a large excess of copper(II) bromide (Table 2).

## EXPERIMENTAL

All melting points were determined on a Buchi-Tottoli micro melting point apparatus and are uncorrected. The IR spectra were recorded in nujol mull with a Perkin-Elmer Infrared 137 E spectrophotometer. The <sup>1</sup>H NMR spectra were recorded on EM-360 A Varian spectrometer in deuteriochloroform unless otherwise noted, using TMS as the internal standard. Mass spectra were recorded on a Jeol-JMS-01-SG-2 spectrometer operating with an ionizing electron beam at 75 eV. Elemental analysis for C, H, N were performed on a H.P. 185 B CHN Analyzer.



The experiments carried out at 60° have shown that the acids XIX, XX and XXI which have a phenyl group at the 5-carbon atom were decarboxylated providing in quantitative yields the 3,4-dibromo derivatives. When at the same position there is a methyl group, compounds XIII and XIV, bromination is only a minor reaction and complex mixtures were obtained (Table 3). The structure of the products of the reaction were confirmed by elemental analysis and spectroscopic data (IR, MS, NMR) (Table 4 and Table 5).

Table 5  
<sup>1</sup>H-NMR Data of Compounds XXV-XXIX δ (ppm),  
 (deuteriochloroform)

Compound	<sup>1</sup> H-NMR (δ) Data
XXV	2.25 (3H, s, CH <sub>3</sub> ), 7.00-7.60 (5H, m, C <sub>6</sub> H <sub>5</sub> ), 8.10 (1H, s broad, NH)
XXVI	2.27 (3H, s, CH <sub>3</sub> ), 3.38 (3H, s, N-CH <sub>3</sub> ), 7.20-7.50 (5H, m, C <sub>6</sub> H <sub>5</sub> )
XXVII	7.20-7.80 (m, C <sub>6</sub> H <sub>5</sub> ), 8.35 (1H, s broad, NH)
XXVIII	3.33 (3H, s, CH <sub>3</sub> ), 7.43 (10H, s broad, 2 C <sub>6</sub> H <sub>5</sub> )
XXIX	7.25 (s, broad, C <sub>6</sub> H <sub>5</sub> )

### General Procedure for the Halogenation with Copper(II) Bromide.

The pyrrolecarboxylic acid or ester (0.01 mole) was dissolved in 100 ml of acetonitrile. To this solution, after cooling at 0°, was added 0.03 mole of copper(II) bromide as a solid. The mixture was held at 0° under magnetic stirring. After 4 hours the reaction mixture was poured into about 500 ml of water and extracted three times with ether. The combined organic phases, dried over sodium sulphate, were evaporated to dryness under reduced pressure. The residue was recrystallized from the appropriate solvent.

### General Procedure for the Brominative Decarboxylation of the 4-Bromo-3-pyrrolecarboxylic Acids.

The monobrominated acid (0.01 mole) was dissolved in 100 ml of acetonitrile and 0.03 mole of copper(II) bromide was added as a solid. After standing for 24 hours under magnetic stirring at room temperature, the mixture was poured into about 500 ml of water and extracted three times with ether. The combined organic phases were washed with 50 ml of 10% aqueous sodium hydroxide, dried over sodium sulphate and evaporated to dryness under reduced pressure. The resulting 3,4-dibromopyrroles were recrystallized from the appropriate solvent.

### General Procedure for the Preparation of Ethyl 3-Pyrrolecarboxylates.

The appropriate dione (0.1 mole) was dissolved in acetic acid

and refluxed for 1 hour at 80° under a nitrogen atmosphere with 0.5 mole of the appropriate amine. After cooling to room temperature, the reaction mixture was poured into ice-water, neutralized with saturated aqueous sodium bicarbonate solution and extracted three times with ether. The combined organic phases were washed with water, dried over sodium sulphate and evaporated to dryness under reduced pressure. The residue was recrystallized from the appropriate solvent.

#### General Procedure for the Preparation of Pyrrole-3-carboxylic Acids.

A mixture of 0.01 mole of the ester, ethanol (25 ml) and 20% aqueous sodium hydroxide (25 ml) was stirred for 24 hours at 50°. The solution was brought to room temperature, poured into 500 ml of water and acidified using 10% aqueous sulfuric acid. The separated solid was filtered, washed and dried under vacuum. The acids obtained were used without any further

purification for the halogenation reaction.

#### Acknowledgements.

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#### REFERENCES AND NOTES

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