Preparation of Monohalopyrroles (1)

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Monobromo-, monochloro- and monoiodopyrroles are obtained in excellent yields by using *N*-halosuccinimides in dimethylformamide as halogenating agents.

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In recent years, several halogenated pyrrole derivatives, isolated from natural sources have shown to possess various biological and pharmaceutical activities (pyrrolonitrin (2-4) and its derivatives (5,6), isopyrrolonitrin (7), pyoluteorin (8), bromonitrin (9,10), oroidin (11,12) *etc*).

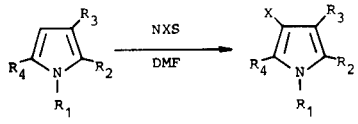
Despite the pharmacological importance of this class of compounds, their availability was limited by unsatisfactory synthetic methods which did not permit controlled halogenation of the pyrrole nucleus.

Several halogenating agents and different experimental conditions were employed in the halogenation of the pyrrole system, but monohalopyrroles were always isolated in low yields together with polyhalo derivatives and oxidized compounds (13-15).

We now report a new method that allowed us to prepare twenty-one monobromo, monochloro and monoiodopyrrole derivatives which have potential pharmaceutical activities and can be regarded as key intermediates in the synthesis of products of biological interest.

The reaction was carried out in dimethylformamide using *N*-bromo-, *N*-chloro- and *N*-iodosuccinimides as halogenating agents. The major advantages of this method are

Scheme



the excellent yields, the mild conditions of the reaction and the ease of isolation of the products. Moreover, the method allows the isolation of stable monohalopyrroles not bearing electron-withdrawing substituents which have been difficult to obtain by reported routes (14,15).

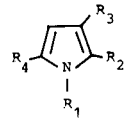
The screenings of some of the new compounds synthetized are in progress at the Diamond Shamrock Corporation.

While our studies were in progress Gilow and Burton (16) independently proposed the bromination and the chlorination of pyrrole, 1-methyl, 1-phenyl and 1-benzylpyrrole by using *N*-bromo- and *N*-chlorosuccinimides in THF and in DMF.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting points apparatus and are uncorrected. The ir spectra were determined in nujol mulls with a Perkin-Elmer 299 spectrophotometer. The nmr spectra were obtained with a Varian FT 80 spectrometer (TMS as internal reference) using deuteriochloroform as the solvent except in the case of compounds **7**, **16** and **21** which are recorded in DMSO-d_6. Mass spectra were run on a Jeol JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 KW accelerating voltage.

The pyrroles which were halogenated were prepared according to the procedure described in literature (see below).



R_1	R_2	R_3	R_4	Ref
H	C_6H_5	H	CH_3	20
H	C_6H_5	H	C_6H_5	20
H	C_6H_5	C_6H_5	C_6H_5	21
H	CH_3	$COOC_2H_5$	C_6H_5	22
H	C_6H_5	$COOC_2H_5$	C_6H_5	23
C_6H_5	C_6H_5	$COOC_2H_5$	C_6H_5	24
H	CH_3	$COCH_3$	2-NO_2-C_6H_4	25
CH_3	CH_3	$COCH_3$	2-NO_2-C_6H_4	26
C_6H_5	CH_3	$COCH_3$	2-NO_2-C_6H_4	26

General Procedure for the Preparation of Monohalopyrroles.

To a solution of the pyrrole (10 mmoles) in anhydrous DMF, 10 mmoles of *N*-halosuccinimide in 20 ml of anhydrous DMF was added dropwise with stirring. The reaction temperature was varied depending on the reactivity of the substrate and of the *N*-halosuccinimide and are listed in the Table 1. After no starting materials (see Table 1) were indicated by tlc, the solution was poured onto crushed ice and the solid was filtered, air dried and purified by recrystallization or by chromatography on a column of silica gel deactivated with water (15%).

Compounds **1** and **10** were eluted with light petroleum ether (bp 50-70°): ethyl acetate 100:2. Compounds **2** and **11** were eluted with light petroleum ether (bp 50-70°): ethyl acetate 100:1. Compound **17** was eluted with light petroleum ether (bp 50-70°): ethyl acetate 9:1.

Acknowledgement.

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Table 1

Compound No.	X	R_1	R_2	R_3	R_4	Yield % (a)	Reaction Time (hours)	Conditions Temp (°C)	Mp (°C)	Recrystallization Solvent (b)
1 (c)	Br	H	C_6H_5	H	CH_3	84	0.5	−18	87 (d)	A
2	Br	H	C_6H_5	H	C_6H_5	90	0.5	−10	69-70	A or B
3	Br	H	C_6H_5	C_6H_5	C_6H_5	92	0.5	−10	121 (e)	A or B
4	Br	H	CH_3	$COOC_2H_5$	C_6H_5	87	24	25	155 (f)	C
5	Br	H	C_6H_5	$COOC_2H_5$	C_6H_5	92	24	25	129	C
6	Br	C_6H_5	C_6H_5	$COOC_2H_5$	C_6H_5	65	24	25	158	C
7	Br	H	CH_3	$COCH_3$	2-NO_2-C_6H_4	94	24	25	218	C
8	Br	CH_3	CH_3	$COCH_3$	2-NO_2-C_6H_4	90	24	25	136	C
9	Br	C_6H_5	CH_3	$COCH_3$	2-NO_2-C_6H_4	80	24	25	122	B
10 (c)	Cl	H	C_6H_5	H	CH_3	70	0.5	−18	108	A
11	Cl	H	C_6H_5	H	C_6H_5	88	24	25	118	A or B
12	Cl	H	C_6H_5	C_6H_5	C_6H_5	90	24	25	142 (g)	B
13	Cl	H	CH_3	$COOC_2H_5$	C_6H_5	75	1	100	147	B
14	Cl	H	C_6H_5	$COOC_2H_5$	C_6H_5	88	1	100	129	C
15	Cl	C_6H_5	C_6H_5	$COOC_2H_5$	C_6H_5	91	1	100	134	C
16	Cl	H	CH_3	$COCH_3$	2-NO_2-C_6H_4	78	3	100	193	C
17	Cl	C_6H_5	CH_3	$COCH_3$	2-NO_2-C_6H_4	65	3	100	130	C
18	I	H	C_6H_5	C_6H_5	C_6H_5	71	6	−15	142	B
19	I	H	CH_3	$COOC_2H_5$	C_6H_5	87	24	25	156	C
20	I	H	C_6H_5	$COOC_2H_5$	C_6H_5	95	24	25	158	C
21	I	H	CH_3	$COCH_3$	2-NO_2-C_6H_4	90	24	25	215	C

(a) Yields reported are of recrystallized or chromatographed products. (b) A = light petroleum ether (bp 50-70°), B = cyclohexane, C = ethanol. (c) The product is quite stable if sheltered from the light and stored in the refrigerator. (d) Lit (17) mp 87°. (e) Lit (18) mp 122°. (f) Lit (17) mp 155°. (g) Lit (19) mp 140-141°.

Table 2

Analytical and Spectral Data of Monohalopyrroles

Compound No.	Molecular Formula (M^+)	Analyses Calcd./Found % C	H	N	IR ν (cm^{-1})	NMR δ (ppm)
1 (a)	$C_{11}H_{10}BrN$ (235)	55.95 55.71	4.27 4.43	5.93 5.78	3430 (NH)	2.25 (3H, s, CH_3), 6.48 (1H, d (b), CH), 7.13-7.60 (5H, m, C_6H_5), 8.16 (1H, br NH (c))
2	$C_{16}H_{12}BrN$ (297)	64.45 64.70	4.06 4.28	4.70 4.80	3410 (NH)	6.65 (1H, d (b), CH), 7.10-7.90 (10H, m, $2C_6H_5$), 8.45 (1H, br NH (c))
3 (d)	$C_{22}H_{16}BrN$ (373)	70.60 70.41	4.31 4.43	3.74 3.60	3400 (NH)	7.18-7.94 (15H, m, $3C_6H_5$), 8.78 (1H, br NH (c))
4 (e)	$C_{14}H_{14}BrNO_2$ (307)	54.56 54.71	4.58 4.39	4.55 4.41	3310 (NH), 1680 (CO)	1.35 (3H, t, CH_2CH_3), 2.50 (3H, s, CH_3), 4.30 (2H, q, CH_2CH_3), 7.30-7.85 (5H, m, C_6H_5), 8.95 (1H, br NH (c))
5	$C_{19}H_{16}BrNO_2$ (369)	61.63 61.80	4.36 4.48	3.78 3.65	3290 (NH), 1675 (CO)	1.17 (3H, t, CH_2CH_3), 4.20 (2H, q, CH_2CH_3), 7.25-7.90 (10H, m, $2C_6H_5$), 8.95 (1H, br NH (c))
6	$C_{25}H_{20}BrNO_2$ (445)	67.27 67.50	4.52 4.43	3.14 3.30	1705 (CO)	1.13 (3H, t, CH_2CH_3), 4.25 (2H, q, CH_2CH_3), 6.85-7.40 (15H, m, $3C_6H_5$)
7	$C_{13}H_{11}BrN_2O_3$ (322)	48.32 48.24	3.43 3.52	8.67 8.52	3250 (NH), 1635 (CO)	2.47 (6H, s, $2CH_3$), 7.65-8.17 (4H, m, C_6H_4), 12.04 (1H, br NH (c))
8	$C_{14}H_{13}BrN_2O_3$ (336)	49.87 50.04	3.89 3.71	8.31 8.23	1650 (CO)	2.41 (6H, s, $2CH_3$), 3.20 (3H, s, CH_3), 7.26-7.93 (4H, m, C_6H_4)
9	$C_{19}H_{15}BrN_2O_3$ (398)	57.16 57.31	3.79 3.92	7.02 6.85	1655 (CO)	2.36 (3H, s, CH_3), 2.64 (3H, s, CH_3), 7.05-7.94 (9H, m, C_6H_5 and C_6H_4)
10	$C_{11}H_{10}ClN$ (191)	68.93 68.74	5.26 5.38	7.31 7.20	3440 (NH)	2.22 (3H, s, CH_3), 6.42 (1H, d (b), CH), 7.05-7.65 (5H, m, C_6H_5), 8.15 (1H, br NH (c))

Table 2 continued

Compound No.	Molecular Formula (M^+)	Analyses Calcd./Found % C	H	N	IR ν (cm^{-1})	NMR δ (ppm)
11	$C_{16}H_{12}ClN$ (253)	75.74 75.89	4.77 4.88	5.52 5.59	3420 (NH)	6.58 (1H, d (b), CH), 7.10-7.90 (10H, m, $2C_6H_5$), 8.40 (1H, br, NH (c))
12 (f)	$C_{12}H_{16}ClN$ (329)	80.11 79.88	4.89 5.03	4.25 4.38	3410 (NH)	7.10-8.00 (15H, m, $3C_6H_5$), 8.30 (1H, br, NH (c))
13	$C_{14}H_{14}ClNO_2$ (263)	63.76 63.90	5.35 5.44	5.31 5.23	3300 (NH), 1670 (CO)	1.35 (3H, t, CH_2CH_3), 2.55 (3H, s, CH_3), 4.35 (3H, q, CH_2CH_3), 7.30-7.85 (5H, m, C_6H_5), 8.60 (1H, br, NH (c))
14	$C_{19}H_{16}ClNO_2$ (325)	70.04 70.22	4.95 5.08	4.30 4.46	3220 (NH), 1670 (CO)	1.10 (3H, t, CH_2CH_3), 4.15 (2H, q, CH_2CH_3), 7.30-7.85 (10H, m, $2C_6H_5$), 8.95 (1H, br, NH (c))
15	$C_{25}H_{20}ClNO_2$ (401)	74.71 74.93	5.02 4.91	3.49 3.58	1710 (CO)	1.13 (3H, t, CH_2CH_3), 4.23 (2H, q, CH_2CH_3), 6.68-7.40 (15H, m, $3C_6H_5$)
16	$C_{13}H_{11}ClN_2O_3$ (278)	56.02 56.21	3.98 4.01	10.05 10.18	3180 (NH), 1640 (CO)	2.45 (6H, s, $2CH_3$), 7.40-8.35 (4H, m, C_6H_4), 12.10 (1H, br, NH (c))
17	$C_{19}H_{15}ClN_2O_3$ (354)	64.32 64.23	4.26 4.34	7.90 8.02	1655 (CO)	2.40 (3H, s, CH_3), 2.65 (3H, s, CH_3), 7.00-8.13 (9H, m, C_6H_5 and C_6H_4)
18	$C_{22}H_{16}IN$ (421)	62.72 62.89	3.83 4.01	3.33 3.46	3410 (NH)	7.20-7.93 (15H, m, $3C_6H_5$), 8.53 (1H, br NH (c))
19	$C_{14}H_{14}INO_2$ (355)	47.34 47.51	3.97 4.09	3.94 3.80	330 (NH), 1670 (CO)	1.33 (3H, t, CH_2CH_3), 2.53 (3H, s, CH_3), 4.30 (2H, q, CH_2CH_3), 7.27-7.80 (5H, m, C_6H_5), 8.77 (1H, br, NH (c))
20	$C_{19}H_{16}INO_2$ (417)	54.69 54.54	3.87 3.98	3.36 3.28	3240 (NH), 1690 (CO)	1.16 (3H, t, CH_2CH_3), 4.20 (2H, q, CH_2CH_3), 7.26-7.93 (10H, m, $2C_6H_5$), 8.90 (1H, br, NH (c))
21	$C_{13}H_{11}IN_2O_3$ (370)	42.18 42.31	3.00 3.11	7.57 7.48	3280 (NH), 1630 (CO)	2.45 (3H, s, CH_3), 2.50 (3H, s, CH_3), 7.50-8.35 (4H, m, C_6H_4), 12.15 (1H, br, NH (c))

(a) Lit (17) ir: 3440 cm^{-1}; nmr (deuteriochloroform): δ 2.22 (3H), 6.40 (1H), 7.10-7.50 (5H), 8.10 (1H). (b) Singlet on exchange with deuterium oxide. (c) Exchangeable with deuterium oxide. (d) Lit (18) ir and nmr spectra were not reported. (e) Lit (17) ir: 3320 and 1700 cm^{-1}; nmr spectrum was not reported. (f) Lit (19) ir and nmr spectra were not reported.

REFERENCES AND NOTES

(1) An account of this work was presented at the Eighth International Congress of Heterocyclic Chemistry, Graz, August 1981, Abstract p 403.

(2) H. Imanaka, M. Ajisaka, K. Hattori, G. Tamura and K. Arima, Ferment. Technol. Today, Proc. Int. Ferment. Symp., 4th 1972, 619; *Chem. Abstr.*, **84**, 40573e (1976).

(3) T. Kamimura and M. Nishida, *Japan J. Antibiot.*, **29**, 1003 (1976).

(4) C. R. Howell and R. D. Stipanovic, *Phytopathology*, **69**, 480 (1979).

(5) K. Okuma, A. Ueda and A. Nakata, *Japan Kokai Tokkyo Koho*, **79**, 70,425 (Cl. A01N9/22) June 1979; *Chem. Abstr.*, **91**, 152742k (1979).

(6) S. Hashimoto, A. Nakada, A. Ueda and C. Ueki, Japan Kokai 76 88,630 (Cl. A01N9/22) August 1976; *Chem. Abstr.*, **85**, 187777d (1976).

(7) M. Hashimoto and K. Hattori, *Bull. Chem. Soc. Japan*, **39**, 410 (1966).

(8) A. J. Birch, P. Hodge, R. W. Rickards, R. Takeda and T. R. Watson, *J. Chem. Soc.*, 2641 (1964).

(9) M. Ajisaka, K. Kariyone, K. Jomon and H. Yazawa, Japan Kokai 72 14,916 (Cl. C12d,C07d,A61K) May 1972; *Chem. Abstr.*, **77**, 60049x (1972).

(10) S. Hanessian and J. S. Kaltenbronn, *J. Am. Chem. Soc.*, **88**, 4509 (1966).

(11) S. Forenza, L. Minale, R. Riccio and E. Fattorusso, *Chem. Commun.*, 1129 (1971).

(12) E. E. Garcia and L. E. Benjamin and R. I. Fryer, *ibid.*, 78 (1973).

(13) R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, London, 1977, pp 129-140.

(14) H. J. Anderson and S. Lee, *Can. J. Chem.*, **43**, 409 (1965).

(15) G. A. Cordell, *J. Org. Chem.*, **40**, 3161 (1975).

(16) H. M. Gilow and D. E. Burton, *J. Org. Chem.*, **46**, 2221 (1981).

(17) V. Sprio and S. Petruso, *Ann. Chim.*, **63**, 245 (1973).

(18) T. Aiello and S. Giambrone, *Boll. Sci. Fac. Chim. Ind. Bologna*, **11**, 93 (1953); *Chem. Abstr.*, **49**, 6226i (1955).

(19) A. H. Blatt, *J. Am. Chem. Soc.*, **58**, 590 (1936).

(20) J. M. Tedder and B. Webster, *J. Chem. Soc.*, 3273 (1960).

(21) F. Angelico and E. Calvello, *Gazz. Chim. Ital.*, **31**, 4 (1901).

(22) L. Lederer and C. Paal, *Ber.*, **18**, 2593 (1885).

(23) V. Sprio and I. Fabra, *Ann. Chim. Appl.*, **50**, 1635 (1960).

(24) S. Kapf and C. Paal, *Ber.*, **21**, 3061 (1888).

(25) E. Aiello, G. Dattolo, G. Cirrincione, S. Plescia and G. Daidone, *J. Heterocyclic Chem.*, **16**, 209 (1979).

(26) E. Aiello, G. Dattolo and G. Cirrincione, *J. Chem. Soc., Perkin Trans. I*, 1 (1981).