Eur J Med Chem (1995) 30, 509–513

Short communication

Synthesis and nematocidal activities of new analogs of pyrantel

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(Received 24 October 1994; accepted 8 February 1995)

Summary — A set of new analogs of pyrantel was synthesized in good yields by lithiation of 1,2-dimethyltetrahydropyrimidine with *n*-butyllithium in tetrahydrofuran and condensation with aromatic esters. Spectrometric studies showed the large influence of intramolecular bonding in the tautomeric equilibria between the possible structures. Anthelmintic screening showed *in vitro* efficiency against *Molinema dessetae*, but a weak activity against *Rhabditis pseudoelongata* and *Nippostrongylus brasiliensis*.

tetrahydropyrimidine / pyrantel / tautomeric equilibrium / nematocide

Introduction

A large number of tetrahydropyrimidines derivatives have been prepared and tested for anthelmintic activity. Pyrantel **1a** was first introduced as broad spectrum anthelmintic for veterinary or clinical uses, followed by morantel **1b** and oxantel **1c** (fig 1). McFarland *et al* studied structure–activity relationships in this field and noted the importance of the vinyl bridge [1–6]. More recently, Andreani *et al* [7] synthesized weakly active analogs of **1a** in which the tetrahydropyrimidine ring is replaced by an indolic heterocycle.

We have previously studied arylvinyl [8] and arylmercaptovinyl [9] compounds. The present work describes the synthesis and nematocidal activity of hydroxyvinyl derivatives. Two methods have been used previously for preparation of compounds **2–20**: i) reaction between acyl halides and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidines [10]; and ii) condensation of arylbromoketones with 2-mercapto-1-methyltetrahydropyrimidine, followed by desulfuration with triphenylphosphine [11]. In each case, the yields were very poor. This led us to study the reaction between aromatic esters and lithium derivatives of 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine, according to scheme 1.

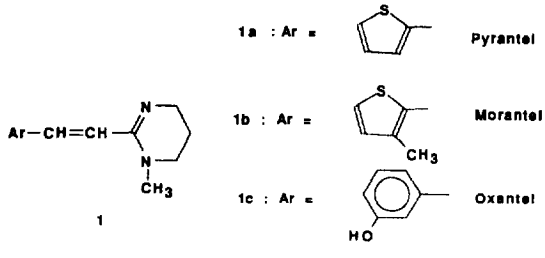
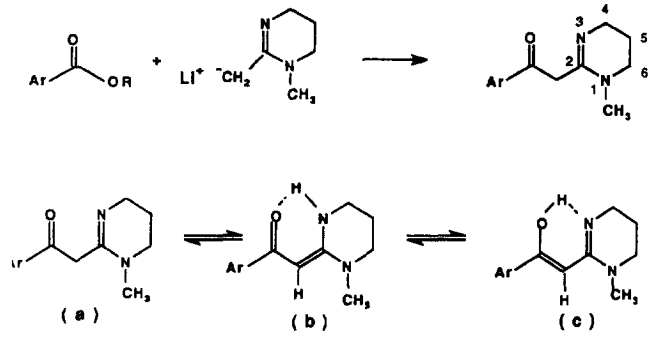


Fig 1. Structure of anthelmintic tetrahydropyrimidines.

Results and discussion

Structural determination

Physicochemical data and structures are reported in table I. Theoretically, **2–20** may exist as three tauto-



Scheme 1.

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Table I. Physicochemical data for derivatives **2–20**.

Compound	*Ar*	*Formula*	*Mp(°C)*	*Yield (%)*	*Analyses*
2	Phenyl	$C_{13}H_{16}N_2O$	114	75	C, H, N
3	4-Chlorophenyl	$C_{13}H_{15}ClN_2O$	146	70	C, H, Cl, N
4	3,4-Dichlorophenyl	$C_{13}H_{14}Cl_2N_2O$	139	80	C, H, Cl, N
5	4-Methoxyphenyl	$C_{14}H_{18}N_2O_2$	153	72	C, H, N
6	3-Methoxyphenyl	$C_{14}H_{18}N_2O_2$	96	60	C, H, N
7	2-Methoxyphenyl	$C_{14}H_{18}N_2O_2$	99	50	C, H, N
8	3,4-Dimethoxyphenyl	$C_{15}H_{20}N_2O_3$	142	70	C, H, N
9	3,4,5-Trimethoxyphenyl	$C_{16}H_{22}N_2O_4$	152	68	C, H, N
10	4-Hydroxyphenyl	$C_{13}H_{16}N_2O_2$	254	25	C, H, N
11	3-Hydroxyphenyl	$C_{13}H_{16}N_2O_2$	211	60	C, H, N
12	2-Hydroxyphenyl	$C_{13}H_{16}N_2O_2$	145	43	C, H, N
13	4-Hydroxy-3-methoxyphenyl	$C_{14}H_{18}N_2O_3$	219	32	C, H, N
14	3,4-Methylenedioxyphenyl	$C_{14}H_{16}N_2O_3$	151	90	C, H, N
15	1-Naphthyl	$C_{17}H_{18}N_2O$	134	53	C, H, N
16	2-Naphthyl	$C_{17}H_{18}N_2O$	159	80	C, H, N
17	2-Methoxy-1-naphthyl	$C_{18}H_{20}N_2O_2$	236	86	C, H, N
18	2-Furyl	$C_{11}H_{14}N_2O_2$	132	85	C, H, N
19	2-Thienyl	$C_{11}H_{14}N_2OS$	129	70	C, H, N, S
20	2-Benzofuryl	$C_{15}H_{16}N_2O_2$	135	88	C, H, N

meric forms: iminoketone **a**, enaminoketone **b** and iminoenol **c**. The structures were determined on the basis of IR and NMR data for the free bases and the corresponding salts.

For the free bases, the IR spectra in KBr pellets showed a broad band between 2900–2400 cm^{-1} and no band in the 1700–1600 cm^{-1} range (excluding the carbonyl group from **a**). In solution in CCl_4, no change was observed as dilution proceeded. This indicates intramolecular bonding, which is present in **b** or **c**.

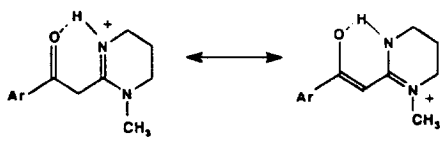

Fig 2. Possible structure for hydrochloride.

^1H NMR in $CDCl_3$ (table II) showed two signals for the free bases of **2–20**, one near 5 ppm (1H, C=CH, exchangeable, which is supplementary proof of tautomeric equilibrium between different structures) and one at 11 ppm (1H, OH or NH, exchangeable). Both of these peaks are in good agreement with the **b** or **c** structures being in tautomeric equilibrium. The CH_2 in position 6 appears as a triplet while that in position 4 is a multiplet (except in compound **15**, in which it is a triplet). This is in agreement with structure **b**. However, this does not exclude the presence of strong hydrogen bonding, as in **c**. By irradiation of the signal at 11 ppm, the CH_2 in positions 4 and 6 appear as two triplets. Moreover, all attempts to methylate with methyl halides or diazomethane failed.

^{13}C NMR (table III) showed a single ethylenic signal near 80 ppm and a signal near 180 ppm, in good agreement with **b**.

Table II. ^{1}H NMR of free bases **2–20** ($CDCl_3$ at 200 MHz).

Compound	*H_4 (m, 2H)*	*H_6 (t, 2H)*	*H_5 (m, 2H)*	*N-CH_3 (s, 3H)*	*NH (s, 1H)*	*=CH (s, 1H)*	*Ar*
2	3.37	3.29	2.00	2.97	11.63	5.17	7.35–7.78 (m, 5H)
3	3.31	3.26	1.92	2.92	11.53	5.07	7.23 and 7.63 (2dd, 4H, J_1 = 8 Hz, J_2 = 2 Hz)
4	3.32	3.28	1.95	2.95	11.50	5.05	7.40 (d, 1H, H_5, J = 8 Hz); 7.60 (dd, 1H, H_6, J = 8 Hz); 7.85 (d, 1H, H_2, J = 2 Hz)
5	3.38	3.27	2.00	2.98	11.61	5.15	6.88 and 7.77 (2d, 4H, J = 8 Hz); 3.82 (s, 3H, methoxy)
6	3.28	3.21	1.93	2.90	11.60	5.15	6.90 and 7.32 (2m, 3H); 7.50 (d, 1H, J = 3 Hz); 3.92 (s, 3H, methoxy)
7	3.32	3.28	2.00	2.90	11.52	5.02	6.86 (m, 2H); 7.24 and 7.50 (2d, 2H, J = 8 Hz); 3.85 (s, 3H, methoxy)
8	3.24	3.17	1.85	2.84	11.50	5.05	6.67 (d, 1H, H_5, J_1 = 8 Hz, J_2 = 2 Hz); 7.23 (dd, 1H, H_6, J_1 = 8 Hz, J_2 = 2 Hz); 7.48 (d, 1H, H_2, J = 2 Hz); 3.75 and 3.80 (2s, 6H, 2 methoxy)
9	3.40	3.35	2.02	3.00	11.61	5.11	7.06 (s, 2H); 3.86 (s, 6H, 2 methoxy); 3.90 (s, 3H, methoxy)
10	3.40	3.34	1.96	3.04	11.63	5.24	6.80 and 7.75 (2d, 4H, J = 8 Hz); 9.80 (s, 1H, OH)
11	3.42	3.38	2.00	3.06	11.63	5.25	6.87 (d, 1H, J = 2 Hz); 7.20 to 7.35 (m, 3H)
12	3.34	3.28	1.96	3.31	10.88	5.21	6.72–7.51 (m, 4H); 14.18 (s, 1H, OH)
13	3.44	3.37	2.00	3.05	12.15	5.25	7.32 (d, 1H, J = 8 Hz, H_5); 7.85 (dd, 1H, H_6, J_1 = 8 Hz, J_2 = 2 Hz); 7.95 (d, 1H, H_2); 9.80 (s, 1H, OH)
14	3.28	3.20	2.01	3.04	11.49	5.47	6.70 and 7.30 (2d, 2H, J = 8 Hz); 7.25 (s, 1H); 5.90 (s, 2H, methylenedioxy)
15	3.31 (t)	3.20	1.93	2.79	11.45	4.84	7.37–8.35 (m, 7H); 11.45 (s, 1H, OH)
16	3.39	3.33	2.00	3.01	11.71	5.33	7.46–7.88 (m, 7H); 8.30 (s, 1H); 8.30 (s, 1H)
17	3.20	3.12	1.86	2.70	11.40	4.70	7.20–7.95 (m, 6H); 3.85 (s, 3H, methoxy)
18	3.36	3.30	1.98	2.98	11.29	5.29	6.41(dd, 1H, H_4, J_{AM} = 3.5 Hz, J_{AX} = 2 Hz); 6.86 (dd, 1H, H_3, J_{AM} = 3.5 Hz, J_{MX} = 1 Hz); 7.37 (dd, 1H, H_5, J_{AX} = 2 Hz, J_{MX} = 1 Hz)
19	3.36	3.30	1.96	2.95	11.26	5.12	6.99 (dd, 1H, H_4, J_{AM} = 5 Hz, J_{MX} = 3.5 Hz); 7.28 (dd, 1H, H_3, J_{AM} = 5 Hz, J_{MX} = 1 Hz); 7.41 (dd, 1H, H_5, J_{AX} = 3.5 Hz, J_{MX} = 1 Hz)
20	3.38	3.33	2.01	3.04	11.49	5.47	7.17–7.63 (m, 5H)

Table III. ^{13}C NMR of free bases **2–20** ($CDCl_3$ at 50.72 MHz).

Compound	C_2	C_4	C_5	C_6	NCH_3	$CH=$	CO	*Ar*
2	160.22	48.05	21.25	37.53	38.14	75.78	182.91	$C_{1'}$ 142.54, $C_{3'}$ and $C_{5'}$ 127.88, $C_{2'}$ and $C_{6'}$ 126.38, $C_{4'}$ 129.15
3	161.47	48.64	21.99	38.42	38.50	78.26	181.42	$C_{1'}$149.90, $C_{3'}$ and $C_{5'}$ 129.12, $C_{2'}$ and $C_{6'}$ 128.97, $C_{4'}$ 136.18
4	160.16	48.10	21.09	37.57	38.27	75.91	179.54	$C_{1'}$ 142.46, $C_{2'}$ 129.88, $C_{3'}$ and $C_{4'}$ 132.86 and 131.99, $C_{5'}$ 128.45, $C_{6'}$ 125.74
5	160.40	48.66	21.45	38.04	38.79	75.29	182.73	$C_{1'}$ 142.00, $C_{3'}$ and $C_{5'}$ 128.90, $C_{2'}$ and $C_{6'}$ 114.27, $C_{4'}$ 155.35, methoxy 55.27
6	160.18	48.00	21.19	37.52	38.12	75.86	182.39	$C_{1'}$ 144.20, $C_{2'}$ 111.47, $C_{3'}$ 159.47, $C_{4'}$ 115.23, $C_{5'}$ 128.77, $C_{6'}$ 118.72, methoxy 55.27
7	160.00	48.84	22.09	38.43	38.99	80.95	184.25	$C_{1'}$ 134.30, $C_{2'}$ 157.33, $C_{3'}$ 112.15, $C_{4'}$ 129.99, $C_{5'}$ 121.16, $C_{6'}$ 130.15, methoxy 56.64
8	159.94	47.89	21.12	37.36	37.97	74.81	181.89	$C_{1'}$ 135.36, $C_{2'}$ 109.94, $C_{3'}$ 148.31, $C_{4'}$ 149.82, $C_{5'}$ 109.61, $C_{6'}$ 118.75, methoxy 56.73
9	160.26	48.18	21.33	37.62	38.26	75.48	182.47	$C_{1'}$ 139.27, $C_{2'}$ and $C_{6'}$ 103.05, $C_{3'}$ and $C_{5'}$ 152.79, $C_{4'}$ 138.45
10	159.62	47.31	20.86	36.93	37.19	73.49	180.41	$C_{1'}$ 127.69, $C_{2'}$ and $C_{6'}$ 127.69, $C_{3'}$ and $C_{5'}$ 114.34, $C_{4'}$ 155.95
11	156.61	46.85	20.29	36.49	37.20	74.19	180.08	$C_{1'}$ 143.36, $C_{2'}$ 116.38, $C_{3'}$ 156.61, $C_{4'}$ 115.47, $C_{5'}$ 112.59, $C_{6'}$ 128.18
12	160.00	48.25	21.00	37.73	38.48	74.94	184.02	$C_{1'}$ 121.74, $C_{2'}$ 161.64, $C_{3'}$ 131.71, $C_{4'}$ 117.72, $C_{5'}$ 117.92, $C_{6'}$ 126.42
13	159.68	47.29	20.84	36.91	37.65	73.56	180.26	$C_{1'}$ 133.68, $C_{2'}$ 110.35, $C_{3'}$ 147.73, $C_{4'}$ 146.83, $C_{5'}$ 114.48, $C_{6'}$ 119.18
14	159.20	47.88	21.09	37.38	37.99	74.86	181.56	$C_{1'}$ 136.98, $C_{2'}$ 107.34, $C_{3'}$ 148.27, $C_{4'}$ 147.12, $C_{5'}$ 106.83, $C_{6'}$ 147.22, methylene 100.94
15	159.92	48.04	21.28	37.65	38.19	80.50	189.00	$C_{1'}$ 142.78, $C_{2'}$ 127.98, $C_{3'}$ 124.28, $C_{4'}$ 128.22, $C_{4a'}$ 131.79, $C_{5'}$ 126.61, $C_{6'}$ 125.00, $C_{7'}$ 125.62, $C_{8'}$ 125.91, $C_{8a'}$ 130.66
16	160.02	47.86	21.04	37.51	38.01	77.74	182.40	$C_{1'}$ 128.65, $C_{2'}$ 139.62, $C_{3'}$ 124.16, $C_{4'}$ 125.64, $C_{4a'}$ 132.87, $C_{5'}$ 126.04, $C_{6'}$ 127.18, $C_{7'}$ 125.69, $C_{8'}$ 127.29, $C_{8a'}$ 133.76
17	159.34	47.66	20.91	37.37	38.89	81.74	183.50	$C_{1'}$ 123.72, $C_{2'}$ 152.16, $C_{3'}$ 113.70, $C_{4'}$ 128.69, $C_{4a'}$ 128.45, $C_{8a'}$ 128.60, $C_{5'}$, $C_{6'}$, $C_{7'}$ and $C_{8'}$ 123.18, 125.29, 125.34, 127.33, methoxy 56.76
18	160.24	47.97	21.18	37.56	38.18	74.93	182.46	$C_{2'}$ 155.75, $C_{3'}$ 109.71, $C_{4'}$ 111.41, $C_{5'}$ 142.32
19	160.00	48.11	21.30	37.61	38.21	75.21	183.66	$C_{2'}$ 149.00, $C_{3'}$ 127.17, $C_{4'}$ 127.27, $C_{5'}$ 124.90
20	160.39	48.95	21.81	38.47	38.56	74.88	181.81	$C_{2'}$ 157.92, $C_{3'}$ 112.27, $C_{3a'}$ 126.61, $C_{4'}$ 124.15, $C_{5'}$, $C_{6'}$ 122.83, $C_{7'}$ 112.27, $C_{7a'}$ 156.19

For the corresponding salts, the IR spectra (in KBr pellets), showed strong bands at 1650 cm^{-1} (carbonyl), whilst the ^1H NMR spectra showed a signal at 4.9 ppm (s, 2H, $COCH_2C{=}N$) and the ^{13}C NMR spectra (in $CDCl_3$) had a signal near 185 ppm (carbonyl). No significant change occurs for CH_2 in position 6 and $N\text{-}CH_3$ in position 1 on the tetrahydropyrimidine ring, while the CH_2 in position 4 appears as multiplet. This is in favor of an iminonoketone structure protonated on nitrogen in positions 1 or 3 (fig 2).

Parasitology

The results of *in vitro* experiments are reported in table IV. Except for **12** and **19**, all of the compounds were poorly active or inactive *in vitro* against *Nippostrongylus brasiliensis* and *Rhabditis pseudoelongata*, but were generally effective against *Molinema dessetae*. Thus, **2–20** have a narrower spectrum than the reference. Only **19**, which is closely related to pyrantel, presented a similar spectrum of activity against the three nematodes.

The two most active compounds *in vitro* against *M dessetae* (**12** and **19**) were screened *in vivo* against rats infected with the same parasite (IP), but were ineffective. The LD_{50} were greater than 400 mg/kg for both compounds.

Experimental protocols

Chemistry

1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine
The free base was prepared and purified according Kraouti [12]. Acetimido ethyl ether hydrochloride and *N*-methyl-1,3-propane diamine were heated at 125°C for 15 h without any solvent, followed by distillation under reduced pressure (bp: 62°C/2 mmHg).

General method for preparation of 2–20
n-BuLi (0.022 mol in 15 ml hexane) was added dropwise with stirring and under argon atmosphere to a solution of 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (0.020 mol) in dry tetrahydrofuran (20 ml) at –70°C over 15 min. The mixture was stirred for a further 2 h, and the appropriate ester (0.022 mol) in dry tetrahydrofuran (20 ml) added dropwise with stirring. When the addition was complete the mixture was allowed to warm to room temperature and kept for a further 3 h. Methanol (10 ml) was added, the mixture evaporated under reduced pressure, and the residue taken up into chloroform and purified on silica column (eluate: chloroform/methanol).

The corresponding hydrochlorides were obtained from free bases by dissolving them in diethyl oxide and passing dry hydrogen chloride gas through the solution.

Parasitology

The free bases of **2–20** were screened *in vitro* against a free nematode, *R pseudoelongata*, an infecting larvae of an intestinal parasite of rats, *N brasiliensis* and an infecting larvae of a filaria, *M dessetae*. These three tests were chosen because they tend to detect *in vitro* activities that are generally confirmed *in vivo*. Experimental procedures has been published previously [13–16].

Table IV. *In vitro* anthelmintic activity of derivatives **2–20** (EC_{50} in μM).

Compound	L3 *of N brasiliensis*		*R pseudo-elongata*	L3 *of M dessetae*	
	24 h	*96 h*	*2 h*	*24 h*	*168 h*
2	11.3	46	1.9	0.32	0.32
3	I	I	87	0.80	0.40
4	47	35	I	105	88
5	I	I	I	2.4	2.0
6	I	I	I	I	I
7	I	I	I	I	I
8	I	I	I	2.6	2.3
9	I	I	I	101	72
10	I	I	I	108	108
11	I	194	I	129	129
12	6.0	4.3	0.56	3.0	1.7
13	I	I	I	114	114
14	I	I	I	108	108
15	118	84	38	3.4	3.0
16	I	82	75	3.0	1.1
17	I	I	I	101	101
18	25.2	19.3	3.1	4.0	2.0
19	9.0	7.7	1.2	3.6	1.8
20	I	49	123	2.3	1.9
Pyrantel	3.5	4	1.2	0.6	0.52

I: inactive compound (EC_{50} > 200 μM).

References

1 McFarland JW, Conover LH, Howes HL *et al* (1969) *J Med Chem* 12, 1066–1079
2 McFarland JW, Howes HL (1969) *J Med Chem* 12, 179–186
3 McFarland JW, Howes HL (1970) *J Med Chem* 13, 109–113
4 McFarland JW, Howes HL (1970) *J Med Chem* 13, 1135–1143
5 Kasubick RV, McFarland JW, James W (1968) S African patent 6800516; *Chem Abstr* (1969), 70, 68406n
6 McFarland JW, Howes HL (1972) *J Med Chem* 15, 365–368
7 Andreani A, Rambaldi M, Locatelli A, Andreani F, Poglaya G, Degli Espoti M (1992) *Eur J Med Chem* 27, 729–734
8 Kraouti N, Caujolle R, Labidalle S *et al* (1993) *Eur J Med Chem* 28, 979–982
9 Kraouti N, Labidalle S, Caujolle R, Payard M, Bories C, Loiseau PM, Gayral P (1994) *Il Farmaco* 49, 371–373
10 Nair MD, Rajappa S, Desai JA (1982) *Indian J Chem* 21-B, 1–3
11 Nair MD, Desai JA (1982) *Indian J Chem* 21-B, 4–7
12 Kraouti N (1994) Doctoral thesis, University of Toulouse, France, N° 1078
13 Loiseau PM, Madaule Y, Wolf J, Bories C, Gayral P (1987) *Eur J Med Chem* 22, 439–443
14 Brienne MJ, Varech D, Leclercq M *et al* (1987) *J Med Chem* 30, 2232–2236
15 Brienne MJ, Jacques J, Gayral P (1981) *Eur J Med Chem* 16, 363–367
16 Bories C, Loiseau PR, Legrand J, Gayral P (1987) *Bull Soc Fr Parasitol* 5, 75–79