Nitrogen Bridgehead Compounds. Part 19 (1). Synthesis of Polymethylenepyrimidin-4-ones

József Kökösi, István Hermecz* (a), György Szász,
Zoltán Mészáros (a), Gábor Tóth (b) and Marianne Csákvári-Pongor (a)

Institute for Pharmaceutical Chemistry of the Semmelweiss Medical University,
H-1088 Budapest, Puskin u. 7, Hungary
(a) CHINOIN Pharmaceutical and Chemical Works,
H-1045 Budapest, Tó u. 1-5, Hungary
(b) Institute for General and Analytical Chemistry, Technical University,
H-1111 Budapest, Gellért tér 4, Hungary
Received November 12, 1981

Reaction of five-, six-, seven-, and eight-membered cyclic amidines (**1** n = 0-3) with diethyl ethoxymethylenemalonate (**2**) yields isomeric 2,3-polymethylene-4(3*H*)- and 1,2-polymethytlene-4(1*H*)-pyrimidinones (**3** and **4**) respectively, n = 0-3). With 2-aminopyrroline the isomer ratio was dependent upon the reaction conditions. The structure of the isomers **3** and **4** was studied by uv, ir and ^{1}H-nmr spectroscopy. Both isomers contain an active methylene group which can be deuterated. Deuteration was investigated with ^{1}H-nmr spectroscopy.

J. Heterocyclic Chem., **19**, 909 (1982).

Our research work on biologically active nitrogen bridgehead heterocycles (2) has now been extended to the n = 0,2,3 homologues of the **3**, (n = 1) tetrahydropyrido-[1,2-*a*]pyrimidines.

The **3** (n = 0,1,2) polymethylenepyrimidin-4-ones have earlier been synthetized by Agata *et al.* (3), who reacted the corresponding lactim ethers with diethyl ethoxymethylenemalonate (**2**) in the presence of ammonium acetate, in a yield of 7-50%.

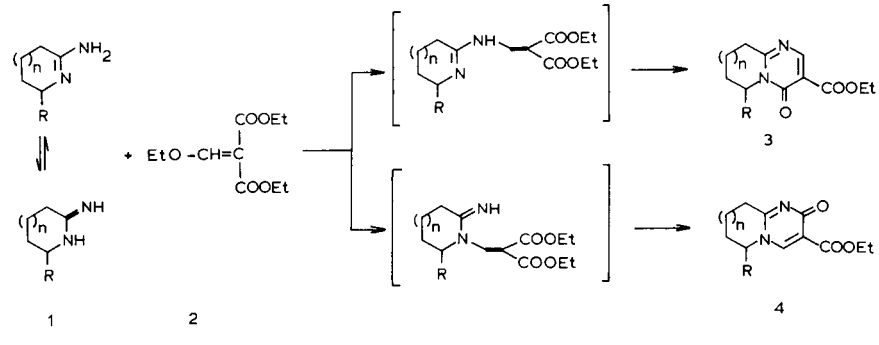
After French authors (4) we used the readily accessible cyclic amidines as starting materials. The cyclization of amidines with 1,3-bifunctional partners is a widely applied method for the preparation of various pyrimidine derivatives (5).

Since the amidines (**1**) contain two different nitrogen atoms, they can be expected to form with ethoxymethylenemalonate (**2**) isomeric **3** and **4** pyrimidinones, depending on whether the *exo*- or *endo*-positioned nitrogen is involved into the first step of the reaction (Scheme 1).

Results and Discussion.

The cyclization of the amidines (**1a-f**) and diethyl ethoxymethylenemalonate (**2**) was carried out in ethanolic solution at a temperature of -10°. The reactions yielded both of the expected isomeric pyrimidinones, **3** and **4**. The isomers were easily distinguished by tlc (see Experimental). The ratio of the two products depended on the size of ring (n), on the substituent (R) and in the five membered ring series (n = 0) also upon the reaction conditions.

Table I shows the yields achieved when the ethanolic solution of the amidine (**1**) was added dropwise to the



Scheme 1.

Table 1

Products from the Reaction of Amidines **1** with Diethyl Ethoxymethylenemalonate (**2**)

Products	n	R	Formula Molecular Weight	**3** 4(3*H*)-Pyrimidone Yield %	Mp °C	Analysis Calcd./Found C%	H%	N%	**4** 4(1*H*)-Pyrimidone Yield %	Mp °C	Analysis Calcd./Found C%	H%	N%	Total Yield % **3** + **4**
a	0	H	$C_{10}H_{12}N_2O_3$ 208.218	69.7	59-60 (a)	57.69 57.74	5.81 5.63	13.45 13.28	16	193	57.69 57.34	5.81 5.61	13.45 13.16	85.7
b	0	Me	$C_{11}H_{14}N_2O_3$ 222.245	65	oil (b)	59.45 59.61	6.35 6.42	12.60 12.43	32	130	59.45 59.17	6.35 6.08	12.60 12.83	97
c	1	H	$C_{11}H_{14}N_2O_3$ 222.245	72	133-135 (c)	59.45 59.18	6.35 6.31	12.60 12.52	25	197	59.45 59.21	6.35 6.38	12.60 12.51	97
d	1	Me	$C_{12}H_{16}N_2O_3$ 236.272	84	59-61	61.00 61.07	6..82 6.78	11.86 11.94	-	-				84
e	2	H	$C_{12}H_{16}N_2O_3$ 236.272	80.5	82-84 (d)	61.00 60.44	6.82 6.86	11.86 11.81	8.9	156	61.00 60.82	6.82 6.91	11.86 11.79	89.4
f	2	Me	$C_{13}H_{18}N_2O_3$ 250.299	56	oil (e)	62.38 62.55	7.25 7.40	11.19 11.07						56
g	3	H	$C_{13}H_{18}N_2O_3$ 250.299	80	oil (f)	62.38 62.51	7.25 7.42	11.19 11.00	4.8	166	62.38 62.18	7.25 7.22	11.19 11.24	84.8

(a) Oil (Lit 3). (b) HCl salt mp 162°. (c) (Lit 12) mp 132°. (d) (Lit 3) mp 80-82°. (e) HCl salt mp 168-172°. (f) Oil (Lit 3) HCl salt mp 105°.

ethanolic solution of the malonate (**2**). These conditions favoured the formation of **3**. The yield of **3** increased with increasing ring size (n).

The methyl substituent *ortho* to the ring nitrogen effected the ratio of the products differently: in the n = 0 series it caused a higher yield on **4**, probably by enhancing the nucleophilic power of the ring nitrogen in the first step of the reaction. From the amidines where n = 1,2 (**1d,f**) however, only compounds **3** were formed, in good yield, and compounds **4** were not even detected by tlc. The regiospecifity of these reactions can be interpreted in terms of the steric hindrance effect of the methyl group on the large rings, which overcompensates its inductive effect.

In reactions where the malonate was added to the amidines (**1** R = H) the reaction mixtures were intensively red coloured. The ratio of the products **3** and **4** did not differ from that in Table I, except for the reaction of **1a** where **3a** was obtained as the minor product in 23% yield, whereas **4a** was obtained in 72% yield.

When reacting 2-aminopyrroline with *beta*-oxo esters using base catalysis (sodium ethoxide) Le Berre and Renault (6) shifted the ratio of pyrimidones **3** and **4** in favour of **3**. In our case base catalysis could not be used because the addition of sodium ethoxide caused deep red coloration of the reaction mixture and the formation of a multitude of products as shown by tlc. We have established earlier (7) that pyrimidone **3d** readily transforms to a 1,8-naphthyridine derivative **5** on base catalysis.

3d **5**

Characterisation of **3** and **4** Pyrimidones.

The isomeric pyrimidones **3** and **4** were separated, on the basis of their different solubilities. Both types of compounds are readily soluble in water, but isomers **3** are more soluble in organic solvents then **4**. Pyrimidones **4** have higher melting points than their isomers **3** (*cf.* Table 1).

The isomers **3** and **4** are easily distinguished by spectroscopy. Homologues within one series show only slight differences. Allen *et al* (8) have earlier found that in the continuously and cross conjugated systems of types **3** and **4**, respectively, the ratio of the extinction coefficients measured at the two longest wavelength uv maxima is about 1 with type **3** whereas it is about ⅓ with type **4**. In our case the above ratio was in the range of 1.2-1.9 with pyrimidones **3**, while 0.4-0.6 with their isomers **4** (*cf.* Table 2).

In the ir spectra (taken as potassium bromide pellets) the vibrational band of the ring carbonyl appears by 35-55 wavenumbers lower in pyrimidones **4** than in **3**.

In the ^{1}H-nmr spectra the vinyl protons of **3** and **4** show

Table 2

UV and IR Data

Compound	n	R	UV λ max (nm) ϵ_a	ϵ_b	ϵ_a/ϵ_b	IR Potassium Bromide (cm^{-1}) ν 3-CO	ν C(4)O
3a	0	H	293 (15640)	266 (12790)	1.22	1745	1710
3b	0	Me	295 (12540)	229 (8880)	1.41	1740	1710
3c	1	H	302 (7680)	229 (5440)	1.41	1734	1700
3d	2	Me	301 (9100)	230 (6380)	1.56	1736	1670
3e	2	H	304 (7220)	227 (5330)	1.35	1745	1670
3f	2	Me	304 (6840)	228 (4170)	1.64	1742	1655
3g	3	H	304 (5040)	228 (3540)	1.82	1743	1710
4a	0	H	288 (5060)	238 (10230)	0.49	1734	1655
4b	0	Me	296 (6660)	226 (11655)	0.57	1710	1655
4c	1	H	286 (4848)	241 (11818)	0.41	1734	1648
4e	2	H	285 (5200)	243 (11870)	0.43	1730	1635
4g	3	H	293 (5040)	235 (10510)	0.48	1744	1660

Table 3

^{1}H-NMR Data

Compound	n	R	=CH	6-CH or 6-CH_2	7 and (7 + n)-CH_2	(n + 8)-CH_2	-O-CH_2-	OCH_2CH_3	R = Me
3a	0	H	8.58 s (1)	4.19 q (2) (a)	2.30 q (2)	3.22 t (2)	4.34 q (2)	1.34 t (3)	
4a	0	H	8.19 s (1)	4.23 t (2) (a)	2.36 q (2)	3.02 t (2)	4.26 q (2)	1.31 t (3)	
3b	0	Me	8.54 s (1)	4.84 m (1) (a)	H_{ax} 1.8-2.1 m (a) H_{eq} 2.25-2.7 m (1)	2.9-3.5 m (2)	4.33 q (2)	1.26 t (3)	1.48 d (3) (b)
4b	0	Me	8.15 s (1)	4.50 m (1) (a)	H_{ax} 1.85-2.1 m (1) H_{eq} 2.35-2.75 m (1)	3.01 t (2)	4.30 q (2)	1.33 t (3)	1.54 d (3) (c)
3c	1	H	8.54 s (1)	3.98 q (2) (a)	1.8-2.1 m (4)	2.98 m (2)	4.35 q (2)	1.35 t (3)	
4c	1	H	7.95 s (1)	4.02 q (2) (a)	1.85-2.15 m (4)	2.83 m (2)	4.28 q (2)	1.32 t (3)	
3d	1	Me	8.46 s (1)	5.06 m (1)	2.05 m (4)	3.12 m (2)	4.40 q (2)	1.43 t (2)	1.43 d (3) (d)
3e	2	H	8.48 s (1)	4.33 m (2) (a)	1.6-2.0 m (6)	3.02 m (2)	4.32 q (2)	1.37 t (3)	
4e	2	H	8.11 s (1)	4.10 m (2) (a)	1.7-2.0 m (6)	2.88 m (2)	4.27 q (2)	1.31 t (3)	
3f	2	Me	8.50 s (1)	5.84 m (1)	1.68-2.37 m (6)	3.28 m (1)	4.37 q (2)	1.37 t (3)	1.50 d (3) (e)
3g	3	H	8.57 s (1)	4.30 m (2) (a)	1.30-2.05 m (8)	3.02 m (2)	4.35 q (2)	1.38 t (3)	
4g	3	H	8.12 s (1)	4.11 m (2) (a)	1.5-2.15 m (8)	2.90 m (2)	4.28 q (2)	1.32 t (3)	

(a) Flexible saturated ring. (b) $J_{6e7e} \approx 0.5$ Hz, $J_{6e7a} \approx 8.0$ Hz. (c) After decoupling the methyl group the signal of 6-H becomes a triplet with J = 6.5 Hz. (d) $J_{6e7e} \approx J_{6e7a} \approx 3$ Hz. (e) $J_{6e7e} \approx J_{6e7a} \approx 5.7$ Hz.

characteristic differences: in deuteriochloroform δ = 8.5 ±0.1 ppm for compounds **3** and 8.1 ±0.2 ppm for compounds **4** (Table 3).

With the pyrido[1,2-*a*]pyrimidines **(3c,d)** we have demonstrated that their methylene group in position 9 is reactive and can be brought easily into electrophilic substitution reactions (1b,10,11). In order to estimate the electrophilic reactivity of the corresponding methylene groups of our bicycles **3** and **4** (n = 0-3) the deuteriation rate of the methylene group was determined in deuterium oxide by ^{1}H-nmr following the decrease of the intensity of the multiplet appearing in the range of 2.8-3.3 ppm. In the base form only the pyrido[1,2-*a*]pyrimidines show a slow deuteriation. After 48 hours **(4c)** exchanged in 50%, whereas derivatives **(3c,d)** exchanged only in 25%.

The hydrochloride salts of the bicycles all underwent deuteriation. Results are summarized in Table 4. Derivatives of type **4** contain a more active methylene group than their isomers **3**. As regards the influence of the ring size, the pyridopyrimidones where n = 1 **(3c,d** and **4c)** are the most reactive compounds, followed by the five membered (n = 0), eight membered (n = 3) and finally the seven-membered (n = 2) homologues. It can thus be expected that the bicyclic derivatives with a seven or eight membered ring are less reactive in electrophilic reactions than their six- and five-membered homologues. The study

Table 4

Hydrogen → Deuterium Exchange of the Active Methylene Group of Hydrochlorides of **3** and **4** in Deuterium Oxide

Compound	n	R	Time of Measurement After Dissolution (hours)	Exchange (%)
4c	1	H	immediately	100
3d	1	Me	0.25	100
3c	1	H	0.5	85
4b	0	Me	1.0	65
4a	0	H	1.0	50
3b	0	Me	1.0	30
3a	0	H	1.0	25
4e	2	H	22.0	70
3g	3	H	22.0	30
3e	2	H	22.0	15

of these aspects will be reported in a later communication.

EXPERIMENTAL

The uv spectra were recorded in 96% ethanol on a Unicam SP 800 instrument, ir spectra were taken as potassium bromide pellets on a Zeiss UR-20 spectrometer, and ^{1}H-nmr pmr spectra in deuteriochloroform with tetramethylsilane as internal standard on a JEOL MX-100 instrument. Melting points are uncorrected and measured in capillary tubes.

Addition of the Amidines (**1**) to Diethyl Ethoxymethylenemalonate.

a) A solution of sodium ethoxide prepared by dissolving sodium (0.1 g-atom) in ethanol (100 ml) was added dropwise to an ethanolic solution (100 ml) of the amidine hydrochloride (0.1 mole) under stirring and external cooling. After 1 hour of stirring the precipitated sodium chloride was filtered off and the solution of the amidine was added dropwise, over a period of 2 hours to a solution of diethyl ethoxymethylenemalonate (0.1 mole) in ethanol (100 ml) at -10°. After stirring for one more hour at 0°, the mixture was kept at 0° overnight. After evaporating the remaining yellow oil was dissolved in benzene (100 ml) and the solution extracted with 5% sodium hydrogen carbonate solution (2 × 20 ml). The aqueous phase was extracted with benzene (2 × 20 ml) and the combined benzene extracts dried over sodium sulphate. Evaporation gave the pyrimidone **4** which was recrystallized from acetone.

The aqueous phase was then extracted with chloroform (4 × 20 ml). The combined extracts were dried over sodium sulphate and evaporated. The residue crystallized soon. After recrystallization from acetone-diethylether the isomer **3** was obtained. For the characterization of the products see Table 1.

b) In the case of 2-aminopyrroline (**1a**) the pyrimidone **4a** precipitated from the alcoholic reaction mixture. It was filtered off and the filtrate was evaporated. To the residue, benzene (100 ml) was added and heated to reflux. On cooling an additional amount of **4a** precipitated, which was filtered off and washed with benzene. A total amount of 3.3 g (16%) pyrimidone **4a** was thus obtained, which was recrystallized from ethanol.

The benzene filtrate was extracted with water (2 × 10 ml). The combined aqueous extracts were made alkaline with sodium hydrogen carbonate and extracted with benzene (3 × 20 ml). The combined extracts were dried over sodium sulphate and evaporated to give 14.5 g (69.7%) of pyrimidone **3a**, which was recrystallized from diethylether.

Addition of Diethyl Ethoxymethylenemalonate (**2**) to a Solution of 2-Aminopyrroline (**1a**).

To a 2-aminopyrroline (0.1 mole) in ethanol (100 ml) a solution of malonate **2** (0.1 mole) in ethanol (20 ml) was added dropwise with intensive stirring at 0-5° in 30 minutes. After additional stirring at 5° for 2 hours the mixture was kept in the refrigerator overnight. The precipitated **4a** was filtered off, the filtrate evaporated, the residue mixed with benzene (100 ml) and heated to boiling. After cooling an additional amount of pyrimidone **4a** was filtered off and the combined product recrystallized from ethanol.

The benzene solution was extracted with water (2 × 10 ml) and the aqueous phase extracted with benzene (3 × 20 ml). The combined benzene extracts were dried over sodium sulphate and evaporated. The residue, a yellow oil, was dissolved in acetone-diethylether and dry hydrochloric acid gas was passed into the solution to yield 5.6 g (23%) of **3a**, hydrochloride, mp 184°.

REFERENCES AND NOTES

(1) Part 18. I. Hermecz, T. Breining, Z. Mészáros, A. Horváth, L. Vasvári-Debreczy, F. Dessy, Chr. DeVos and L. Rodriguez, *J. Med. Chem.*, in press.

(2a) Z. Mészáros, *Kém, Közl.*, **50**, 173 (1978); (b) I. Hermecz, T. Breining, Z. Mészáros, G. Tóth and I. Bitter, *Heterocycles*, **14**, 1953 (1980) and papers cited therein.

(3) I. Agata, S. Noguchi and K. Tanaka, Japan Kokai 73 34,897; *Chem. Abstr.*, **79**, 42537 (1974).

(4) A. LeBerre and C. Renault, *Bull. Soc. Chim. France*, 3133 (1969).

(5) D. J. Brown, "The Pyrimidines", Supplement I, Wiley-Interscience, New York, NY, 1970, p 20.

(6) A. LeBerre and C. Renault, *Bull. Soc. Chim. France*, 3139 (1969).

(7) I. Hermecz and Z. Mészáros, *Heterocycles*, **12**, 1407 (1979).

(8) C. F. H. Allen, J. Van Allen and C. V. Wilson, *J. Am. Chem. Soc.*, **66**, 1933 (1944).

(9) G. Náray-Szabó, I. Hermecz and Z. Mészáros, *J. Chem. Soc., Perkin Trans. I*, 753 (1974).

(10) I. Hermecz, I. Bitter, Á. Horváth, G. Tóth and Z. Mészáros, *Tetrahedron Letters*, 2557 (1979).

(11) I. Bitter, I. Hermecz, G. Tóth, P. Dvortsák, Z. Bende and Z. Mészáros, *ibid.*, 5039 (1979).

(12) Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth and I. Hermecz, *Arzneim.-Forsch.*, **22**, 815 (1972).