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Reaction of 5-amino-3-methyl-1-phenylpyrazole (**1a**) and 5-amino-3-(4-chlorophenyl)-1H-pyrazole (**1b**) with dimedone (**2**) and *p*-substituted benzaldehydes **3** in ethanol, afforded in all cases tricyclic linear 4-aryl-7,7-dimethyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-*b*]quinolin-5-ones (**4a-j**) in good yields. The linear structures and hence the regioselectivity of the reaction were established by nmr measurements.

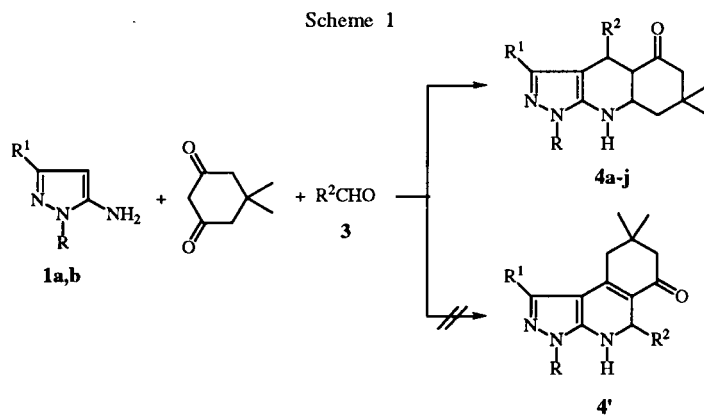
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It has been reported [1,2] that fused heterocyclic quinolines exhibit a considerable activity as anxiolytic and as memory enhancers. Some pyrazolo[3,4-*b*]quinolines have shown bactericidal activity [3], they have been used, also as antiviral agents and vasodilators [4] and have been evaluated for enzymatic inhibitory activity [5].

In a previous report [6], we reported a preparation of fused quinolines. In this paper we sought to develop this efficient and versatile synthesis of novel 4-aryl-7,7-dimethyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-*b*]quinolin-5-ones from 5-aminopyrazoles **1a,b** in which the quinoline ring is constructed from dimedone (**2**) and an appropriately substituted benzaldehyde **3**.

The preparation of tetrahydropyrazolo [3,4-*b*]quinolin-5-ones **4a-j** has been carried out by refluxing equimolar amounts of 5-aminopyrazole **1a,b** in absolute ethanol with dimedone (**2**) and the appropriate benzaldehyde derivative **3** during 20-30 minutes. The one step cyclocondensation reaction can afford linear and/or angular products **4/4'** (Scheme 1).

The cyclocondensation of amines **1a,b** with **2** and **3** gave regioselectively the linear isomers, tetrahydropyrazolo[3,4-*b*]quinolin-5-ones **4a-j**. The support for the linear structures for **4a-j** was provided by the ¹H-nmr spectra, in particular the chemical shift for the H-4 proton and a singlet for the 9-NH proton [6]. The ¹H-nmr spectra of compounds **4a-e** measured in dimethyl-*d*₆ sulfoxide (Table 1) contain two relatively sharp singlets at 4.93-5.01 ppm and 9.35-9.45 ppm for 4-H and 9-NH respectively, with integrals in a ratio of 1:1. The fact that 4-H and 9-NH are not coupled is evidence for the linear structure **4** and allows us to discard the angular structure **4'**. The signals at δ 1.98-1.99 ppm and 2.15-2.16 ppm resonated as a doublet of doublets with ²J = 16 ± 0.5 Hz, and were assigned to the methylene protons of C-6. The signal at δ 2.49-2.51 ppm appears as a singlet and corresponds to 8-CH₂.



	R	R ₁	R ₂	mp, °C	Yield, %
4a	C ₆ H ₅	CH ₃	C ₆ H ₅	218	66
4b	C ₆ H ₅	CH ₃	4-CH ₃ C ₆ H ₄	266	60
4c	C ₆ H ₅	CH ₃	4-CH ₃ OC ₆ H ₄	143	60
4d	C ₆ H ₅	CH ₃	4-ClC ₆ H ₄	219	72
4e	C ₆ H ₅	CH ₃	4-BrC ₆ H ₄	241	75
4f	H	4-ClC ₆ H ₄	C ₆ H ₅	338	70
4g	H	4-ClC ₆ H ₄	4-ClC ₆ H ₄	319	65
4h	H	4-ClC ₆ H ₄	4-CH ₃ OC ₆ H ₄	313	60
4i	H	4-ClC ₆ H ₄	4-ClC ₆ H ₄	302	78
4j	H	4-ClC ₆ H ₄	4-ClC ₆ H ₄	309	82

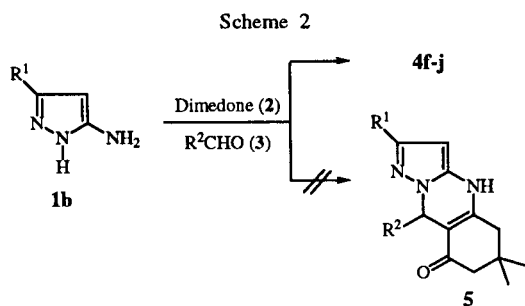
There are two possibilities for ring closure if the N1-position is unsubstituted like in **1b**, either to the N1 or to the C4-atom (Scheme 2). Both cyclizations have been reported in the reaction of 5-aminopyrazoles with 1,3-dicarbonyl [7] and α,β-unsaturated carbonyl compounds [8-10], but we observed only cyclization to the C4-atom.

Thus, in the ¹H-nmr spectra of compounds **4f-j** (Table 2), besides the signals for the 6- and the 8-CH₂ as doublet of doublets with ²J = 16.1 ± 0.2 and 17.5 ± 0.2 Hz, there appeared two relatively sharp singlets at 5.30-5.37 and 9.90-10.01 ppm

Table 1

¹H-NMR Data of **4a-e** (δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d₆ sulfoxide, 300 MHz)

	CH ₃ s	3-CH ₃ s	4-H s	6-CH ₂ dd	8-CH ₂ s (dd)	9-NH s	1-Phenyl m	4-Aryl dd
4a	0.93	1.01	1.88	4.99	1.99	2.16	7.36-7.53	7.07-7.23
4b	0.93	1.00	1.88	4.95	1.98	2.15	7.36-7.52	7.00-7.11
4c	0.92	0.99	1.88	4.93	1.98	2.15	7.35-7.52	6.76-7.12
4d	0.92	1.00	1.88	5.01	1.99	2.16	7.37-7.53	7.22-7.30
4e	0.92	1.00	1.87	4.99	1.99	2.16	7.37-7.55	7.16-7.43

CH₃ for **4b** 2.21 ppm and OCH₃ for **4c** 3.67 ppm.

for 4-H and 9-NH respectively and additional NH-signals at δ 12.62-12.69 ppm corresponding to the 1-NH protons. The pyrazole ring =CH-signal above 6 ppm disappeared [10,11]. On the basis of these results, the isomeric structure **5** for the reaction products **4f-j** can be discarded.

In the ¹³C-nmr spectra the number of signals belonging to quaternary, tertiary secondary and primary carbon atoms for new compounds **4a-j** could be determined (Table 3). The assignment of the signals was supported by ¹H, ¹H COSY, and ¹H, ¹³C Shift correlation spectra.

Table 2

¹H-NMR Data of **4f-j** (δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d₆ sulfoxide, 300 MHz)

	CH ₃ s	1-NH s	4-H s	6-CH ₂ dd	8-CH ₂ dd	9-NH s	3-(<i>p</i> -ClC ₆ H ₄) dd	4-Aryl dd		
4f	0.85	12.64	5.35	1.96	2.16	2.39	2.50	9.94	7.44-7.57	6.95-7.14
4g	0.85	12.62	5.31	1.96	2.16	2.37	2.49	9.91	7.45-7.59	6.87-7.03
4h	0.85	12.62	5.30	1.96	2.15	2.37	2.48	9.90	7.45-7.59	6.65-7.05
4i	0.85	12.69	5.37	1.99	2.16	2.38	2.50	10.01	7.45-7.57	7.11-7.17
4j	0.85	12.69	5.35	1.97	2.16	2.38	2.50	10.01	7.44-7.57	7.07-7.30

CH₃ for **4g** 2.13 ppm and OCH₃ for **4h** 3.62 ppm.

Table 3

¹³C-NMR Data of **4a-j** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d₆ sulfoxide, 300 MHz)

Compound	C-3a	C-4	C-4a	C-5	C-6	C-7	C-8	<i>o,m</i> -CH	<i>p</i> -CH	Cq	CH ₃
4a	104.4	35.9	109.7	194.1	50.6	32.1	40.8	123.3, 127.7, 128.0, 129.5	125.7, 126.9	136.4, 138.4, 146.1, 147.8, 151.5	12.1, 26.9, 29.0
4b	104.5	35.4	109.9	194.1	50.6	32.1	40.8	123.2, 127.6, 128.6, 129.5	126.9	134.5, 136.3, 138.4, 144.9, 146.1, 151.3	12.1, 20.7, 26.9, 29.1
4c	104.6	35.0	110.0	194.2	50.7	32.1	40.9	113.3, 123.2, 128.7, 129.5	126.9	136.4, 138.9, 146.1, 148.4, 151.2, 157.3	12.1, 26.9, 29.1, 55.1
4d	103.8	35.5	109.3	194.1	50.5	32.1	40.8	123.3, 127.9, 129.5, 129.6	127.0	130.2, 136.4, 138.3, 146.1, 146.7, 151.7	12.1, 26.9, 28.9
4e	103.7	35.5	109.2	194.1	50.5	32.1	40.8	123.3, 129.5, 130.0, 130.8	127.0	118.7, 136.4, 138.3, 146.1, 147.1, 151.7	12.1, 26.9, 28.9
4f	103.9	35.3	107.8	192.9	50.5	32.1	41.0	127.6, 127.7, 127.8, 128.9	125.6	128.4, 132.6, 136.4, 147.5, 148.3, 152.3	26.7, 29.1
4g	104.0	34.9	108.1	192.9	50.6	32.1	41.0	127.5, 127.8, 128.4, 128.9	---	128.5, 132.6, 136.4, 136.3, 144.7, 148.2, 152.1	20.7, 26.7, 29.1
4h	104.1	34.5	108.2	193.0	50.6	32.1	41.0	113.2, 127.8, 128.6, 129.0	---	129.0, 132.5, 136.2, 139.8, 148.4, 152.0, 157.1	26.7, 29.1, 54.9
4i	103.4	35.0	107.4	193.0	50.5	32.1	41.0	127.8, 127.8, 129.0, 129.5	---	13 0.1, 13 2.0, 136.6, 138.6, 142.0, 148.2, 152.5	26.7, 29.1
4j	103.2	35.1	107.4	193.0	50.5	32.1	41.0	127.8, 129.0, 129.9, 131.2	---	118.6, 13 2.7, 136.6, 138.5, 146.8, 148.1, 152.4	26.7, 29.1

EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are uncorrected. The ir spectra were obtained in potassium bromide pellets with a Perkin-Elmer 599B spectrometer. The ^1H - and ^{13}C nmr spectra were run on a Bruker AVANCE DRX 300 spectrometer in Dimethyl- d_6 sulfoxide. The mass spectra were recorded on a Fisons-Platform interface APCI in methanol. The elemental analysis have been obtained using a LECO CHNS-900 equipment.

Synthesis of 4-Aryl-3,7,7-trimethyl-1-phenyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b]quinolin-5-ones **4a-e** and 4-Aryl-3-(4-chlorophenyl)-7,7-dimethyl-4,7,8,9-tetrahydro-1H,6H-pyrazolo[3,4-b]quinolin-5-ones **4f-j**.

General Procedure.

A solution of the 5-aminopyrazole **1a,b** (1 mmole), dimedone (**2**) (1 mmole) and benzaldehyde **3** (1 mmole) in 15 ml of absolute ethanol was heated to reflux for 20-30 minutes. The cyclized products **4** were isolated by cooling, followed by filtration, washing with ethanol, drying and recrystallization from ethanol.

3,7,7-Trimethyl-1,4-diphenyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b]quinolin-5-one **4a**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 384$ (100).

Anal. Calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.45; H, 6.53; N, 10.90.

3,7,7-Trimethyl-4-(4-methylphenyl)-1-phenyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b]quinolin-5-one **4b**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 398$ (100).

Anal. Calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}$: C, 78.55; H, 6.85; N, 10.58. Found: C, 78.45; H, 6.93; N, 10.50.

4-(4-Methoxyphenyl)-3,7,7-trimethyl-1-phenyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b]quinolin-5-one **4c**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 414$ (45).

Anal. Calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_2$: C, 75.51; H, 6.59; N, 10.17. Found: C, 75.45; H, 6.53; N, 10.09.

4-(4-Chlorophenyl)-3,7,7-trimethyl-1-phenyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b]quinolin-5-one **4d**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 420/418$ (35/100).

Anal. Calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{OCl}$: C, 71.91; H, 5.80; N, 10.07. Found: C, 71.85; H, 5.73; N, 10.20.

4-(4-Bromophenyl)-3,7,7-trimethyl-1-phenyl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4-b]quinolin-5-one **4e**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 464/462$ (65/75).

Anal. Calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{OBr}$: C, 65.06; H, 5.25; N, 9.11. Found: C, 65.15; H, 5.13; N, 9.22.

3-(4-Chlorophenyl)-7,7-dimethyl-4-phenyl-4,7,8,9-tetrahydro-1H,6H-pyrazolo[3,4-b]quinolin-5-one **4f**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 406/404$ (72/100).

Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{OCl}$: C, 71.44; H, 5.50; N, 10.42. Found: C, 71.45; H, 5.43; N, 10.51.

3-(4-Chlorophenyl)-7,7-dimethyl-4-(4-methylphenyl)-4,7,8,9-tetrahydro-1H,6H-pyrazolo[3,4-b]quinolin-5-one **4g**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 420/418$ (52/100).

Anal. Calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{OCl}$: C, 71.91; H, 5.80; N, 10.07. Found: C, 71.85; H, 5.86; N, 10.14.

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-7,7-dimethyl-4,7,8,9-tetrahydro-1H,6H-pyrazolo[3,4-b]quinolin-5-one **4h**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 436/434$ (26/100).

Anal. Calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_2\text{Cl}$: C, 69.26; H, 5.58; N, 9.70. Found: C, 69.35; H, 5.46; N, 9.81.

3,4-Di-(4-chlorophenyl)-7,7-dimethyl-4,7,8,9-tetrahydro-1H,6H-pyrazolo[3,4-b]quinolin-5-one **4i**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 442/440/438$ (14/45/100).

Anal. Calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{OCl}_2$: C, 65.89; H, 4.84; N, 9.61. Found: C, 65.85; H, 4.78; N, 9.53.

4-(4-Bromophenyl)-3-(4-chlorophenyl)-7,7-dimethyl-4,7,8,9-tetrahydro-1H,6H-pyrazolo[3,4-b]quinolin-5-one **4j**.

This compound was obtained by the general procedure as white crystals. The mass spectrum shows $(\text{M}+\text{H})^+ = 486/484/482$ (37/100/85).

Anal. Calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{OClBr}$: C, 59.87; H, 4.40; N, 8.73. Found: C, 59.95; H, 4.47; N, 8.64.

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