Synthesis of 4-Aryl-4,7,8,9-tetrahydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-ones

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

J. Heterocyclic Chem., **35**, 575 (1998).

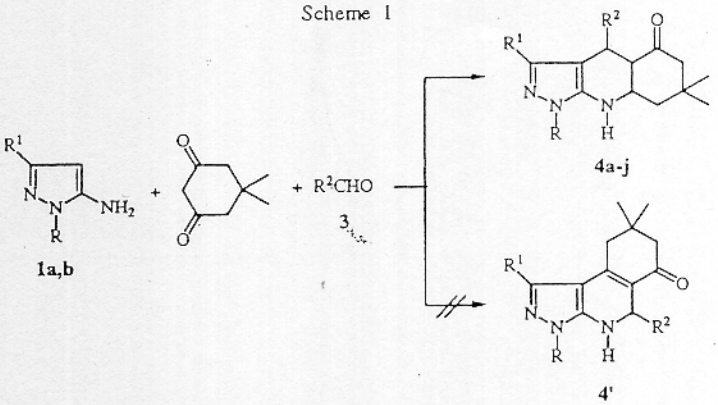
It has been reported [1,2] that fused heterocyclic quinolines exhibit a considerable activity as anxiolityc and as memory enhancers. Some pyrazolo[3,4-*b*]quinolines have show bactericidal activity [3], they have been used, also as antiviral agents and vasodilators [4] and have been evaluated for enzymatic 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-6*H*-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 equimolecular 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 regiospecifically 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 ^{1}H-nmr spectra, in particular the chemical shift for the H-4 proton and a singlet for the 9-NH proton [6]. The ^{1}H-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-CH_2.

Scheme 1



	R	R_1	R_2	mp. °C	Yield, %
4a	C_6H_5	CH_3	C_6H_5	218	66
4b	C_6H_5	CH_3	4-$CH_3C_6H_4$	266	60
4c	C_6H_5	CH_3	4-$CH_3OC_6H_4$	143	60
4d	C_6H_5	CH_3	4-ClC_6H_4	219	72
4e	C_6H_5	CH_3	4-BrC_6H_4	241	75
4f	H	4-ClC_6H_4	C_6H_5	338	70
4g	H	4-ClC_6H_4	4-ClC_6H_4	319	65
4h	H	4-ClC_6H_4	4-$CH_3OC_6H_4$	313	60
4i	H	4-ClC_6H_4	4-ClC_6H_4	302	78
4j	H	4-ClC_6H_4	4-ClC_6H_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 ^{1}H-nmr spectra of compounds **4f-j** (Table 2), besides the signals for the 6- and the 8-CH_2 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

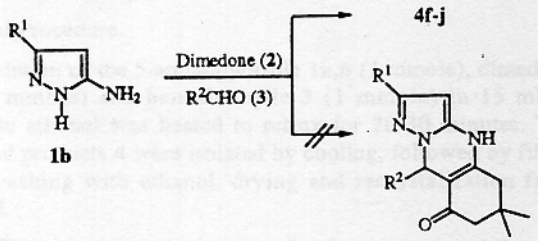
Table 1

^{1}H-NMR Data of **4a-e** (δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 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	2.51	9.39	7.36-7.53	7.07-7.23
4b	0.93	1.00	1.88	4.95	1.98	2.15	2.51	9.36	7.36-7.52	7.00-7.11
4c	0.92	0.99	1.88	4.93	1.98	2.15	2.50	9.35	7.35-7.52	6.76-7.12
4d	0.92	1.00	1.88	5.01	1.99	2.16	2.49	9.45	7.37-7.53	7.22-7.30
4e	0.92	1.00	1.87	4.99	1.99	2.16	2.50	9.45	7.37-7.55	7.16-7.43

CH_3 for **4b** 2.21 ppm and OCH_3 for **4c** 3.67 ppm.

Scheme 2



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 ^{13}C-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 ^{1}H,^{1}H COSY, and ^{1}H,^{13}C Shift correlation spectra.

Table 2

^{1}H-NMR Data of **4f-j** (δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 sulfoxide, 300 MHz)

	CH_3 s		1-NH s	4-H s	6-CH_2 dd		8-CH_2 dd		9-NH s	3-(*p*-ClC_6H_4) dd	4-Aryl dd
4f	0.85	1.01	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	1.00	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	1.00	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	1.00	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	1.00	12.69	5.35	1.97	2.16	2.38	2.50	10.01	7.44-7.57	7.07-7.30

CH_3 for **4g** 2.13 ppm and OCH_3 for **4h** 3.62 ppm.

Table 3

^{13}C-NMR Data of **4a-j** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 sulfoxide, 300 MHz)

Compound	C-3a	C-4	C-4a	C-5	C-6	C-7	C-8	*o,m*-CH	*p*-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 ^{1}H- 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-6*H*-pyrazolo[3,4-*b*]quinolin-5-ones **4a-e** and 4-Aryl-3-(4-chlorophenyl)-7,7-dimethyl-4,7,8,9-tetrahydro-1*H*,6*H*-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 recrystalization from ethanol.

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

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

Anal. Calcd. for $C_{25}H_{25}N_3O$: 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-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4b**.

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

Anal. Calcd. for $C_{26}H_{27}N_3O$: 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-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4c**.

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

Anal. Calcd. for $C_{26}H_{27}N_3O_2$: 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-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4d**.

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

Anal. Calcd. for $C_{25}H_{24}N_3OCl$: 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-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4e**.

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

Anal. Calcd. for $C_{25}H_{24}N_3OBr$: 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-1*H*,6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4f**.

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

Anal. Calcd. for $C_{24}H_{22}N_3OCl$: 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-1*H*,6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4g**.

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

Anal. Calcd. for $C_{25}H_{24}N_3OCl$: 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-1*H*,6*H*-pyrazolo[3,4-*b*]quinolin-5-one **4h**.

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

Anal. Calcd. for $C_{25}H_{24}N_3O_2Cl$: C, 69.26; K 5.58; N, 9.70. Found: C, 69.35; K 5.46; N, 9.81.

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

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

Anal. Calcd. for $C_{24}H_{21}N_3OCl_2$: 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-1*H*,6*H*-pyrazolo[3,4-*b*]quinolin-5 -one **4j**.

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

Anal. Calcd. for $C_{24}H_{21}N_3OClBr$: C, 59.87; H, 4.40; N, 8.73. Found: C, 59.95; H, 4.47; N, 8.64.

Acknowledgment.

The authors thank The Colombian Institute for Science and Research (COLCIENCIAS, Project 1106-05411-95) and Universidad del Valle for financial support and CEPEDEQ (Centro para el Desarrollo de la Química), Universidad de Chile for use of instruments.

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