Reaction of 4,5-Diamino-3-methyl-1-phenylpyrazole with 3-Dimethylaminopropiophenones. Synthesis of New 4-Aryl-6-methyl-8-phenyl-2,3-dihydropyrazolo[3,4-*b*]diazepines and 4-Aryl-8-methyl-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepines

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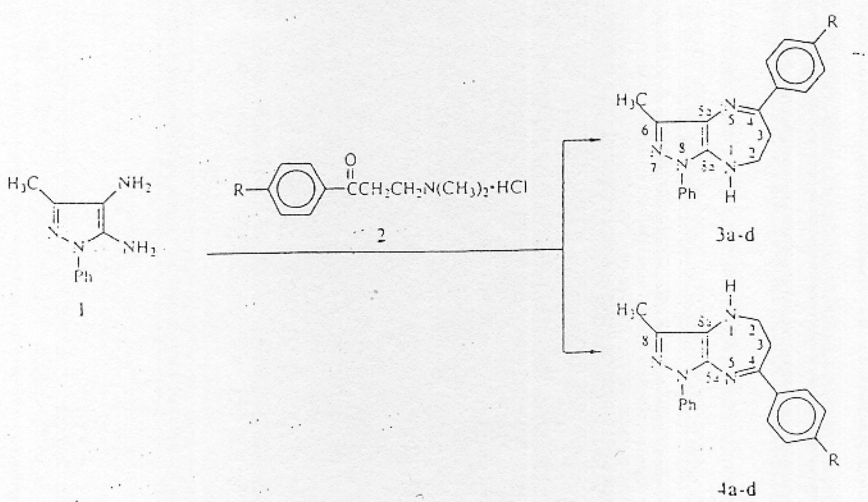
New 4-Aryl-6-methyl-8-phenyl-2,3-dihydropyrazolo[3,4-*b*]diazepines and 4-aryl-8-methyl-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepines were obtained from the reaction of 4,5-diamino-3-methyl-1-phenylpyrazole 1 with one equivalent of the 3-dimethylaminopropiophenones 2 in absolute ethanol. The structures of 4-aryl-6-methyl-8-phenyl-2,3-dihydropyrazolo[3,4-*b*]diazepines 3 and 4-aryl-8-methyl-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepines 4 were determined by detailed nmr measurements.

Benzodiazepines are an important class of psychotherapeutic compounds. In recent years, some examples of heterocyclic rings fused to the seven-member diazepine ring system have appeared in literature [1,2]. In particular, good CNS activity was reported for various pyrazolodiazepines [3]. Some of these compounds are known to have activities as psycotropics [4-7].

We have reported that the reaction of α,β-unsaturated ketones and its precursors as β-dimethylaminopropiophenones with 1,2-diamines [8-18] is a very convenient and versatile method for the synthesis of fused diazepine system. In this work we studied the reaction of 4,5-diamino-3-methyl-1-phenylpyrazole **1** with 1-aryl-2-propenones generated *in situ* from β-dimethylaminopropiophenones **2** (Scheme 1).

Reaction of 4,5-Diamino-3-methyl-1-phenylpyrazole **1** with β-dimethylaminopropiophenones **2** in ethanol afforded compounds **3a-d** and **4a-d**. Because diamine **1** has non-equivalent amino groups at the *ortho* position, the regioisomeric cyclization products **3** and **4** were expected. In all cases, the formation of products **3** and **4** was observed. The compounds **3a-d** and **4a-d** were separated by column chromatography.

Scheme 1



	3a	3b	3c	3d	4a	4b	4c	4d
R	H	Cl	Br	NO_2	H	Cl	Br	NO_2
mp. °C	240	220	221	214	95	154	177	209
Yield, %	35	33	37	35	30	32	30	33

Structural assignment of 3 and 4 was made on spectroscopic grounds. The infrared spectra of **3a-d** and **4a-d** showed typical absorption between 3174 and 3404 cm^{-1} (N-H) and 1554-1594 cm^{-1} (C=N and C=C). The uv/visible spectrum of **3a-d** and **4a-d** in ethanol contains three or four bands; most characteristic is an absorption maximum in the range of 243-288 nm and a second one shifted towards longer wavelengths (345 ≤ λ_{max} ≤ 419 and 386 ≤ λ_{max} ≤ 454 nm for 3 and 4 respectively). The ^{1}H-nmr spectra of compounds **3a-d** showed the geminal protons joined to C-2 and C-3 at δ 3.38-3.53 (multiplet) and δ 3.13-3.29 (multiplet) ppm, respectively. The proton of the N-H group appears as a triplet at δ 4.44-4.71 ppm indicating the vicinal position of the protons on C-2. In addition, two doublets are observed in the spectra of **3b-d** (multiplet for **3a**) related to aromatic protons (δ 7.28-8.25 ppm) with *ortho*-constant J = 7.7±0.3 Hz. The compounds **4a-d** present ^{1}H-nmr spectra similar to spectra of compounds 3 geminal protons joined to C-2 and C-3 at δ 3.45-3.53 (multiplet) and δ 3.21-3.30 (multiplet) ppm, respectively. The proton of N-H group appears as a triplet at δ 3.45-3.63 ppm and two doublets are observed in the spectra of 4b-d (multiplet for 4a) related to aromatic protons (δ 7.28-8.25 ppm) with ortho-constant J = 7.3±0.3 Hz. The ^{1}H-nmr spectral data for all the products are summarized in Table 1. The ^{13}C-nmr spectra of 3a and 4a showed 15 signals. DEPT experiments indicated that one signal corresponds to CH_3, two to CH_2, six to CH and six to Cq. The ^{13}C-nmr data of **3a-d** and **4a-d** are summarized in Table 2 respectively. Assignment of the ^{1}H and ^{13}C resonances of compounds 3 and 4 was deduced from the concerted application of both direct and long range heteronuclear chemical shift correlation experiments. One-bond proton-carbon chemical shift correlations were established using the HMQC [19] sequence and $(CH)_n$ groups were unambiguously characterized from the analysis of long-range correlation responses over to two and three bonds (^2J or ^3J couplings) using the HMBC [20] thecnique. This procedure was exemplified for compounds **3a** and **4a**, for which all the connectivities, observed in the HMBC diagram are given in Table 3. For the unequivocal structural assignment of obtained compounds, the starting point was the C-5a and C-8a resonances for isomers 3 and 4. The C-8a shows correlated peaks to CH_2-2; C-5a and C-8a show correlated peaks to methyl group at position 6 for 3 and position 8 for 4 respectively. The signal of C-5a appear at δ 115.6-115.9 and 134.0-137.1 ppm for 3 and 4, respectively. On the other hand, C-8a show signal at 138.9-139.4 for 3 and 123.1-123.9 ppm for 4. These can be explained in the terms of the *push-pull* effect of the amino and C=N groups linked to the C=C double bond in structure 3 and 4. Also, the assignation of structures for

Table 1

^{1}H NMR Chemical Shift (δ) for Compounds 3a-d and 4a-d (Chloroform-d, 300 MHz)

Compound	CH_3	Pyrazolodiazepine 1-NH	2-CH_2	3-CH_2	Phenyl H_o	H_m	H_p	Aryl H_o	H_m	H_p
3a	2.38	4.44	3.39	3.17	7.47	7.40	7.25	7.83	7.33	7.30
3b	2.36	4.46	3.38	3.13	7.46	7.40	7.26	7.77	7.28	–
3c	2.35	4.46	3.39	3.13	7.46	7.40	7.26	7.70	7.43	–
3d	2.46	4.71	3.53	3.29	7.55	7.51	7.37	8.25	8.05	–
4a	2.25	3.45	3.45	3.24	7.77	7.42	7.25	7.86	7.37	7.40
4b	2.26	3.46	3.46	3.21	7.73	7.42	7.26	7.80	7.33	–
4c	2.27	3.47	3.47	3.23	7.75	7.44	7.28	7.74	7.51	–
4d	2.29	3.63	3.53	3.30	7.74	7.49	7.31	8.22	8.00	–

Table 2

^{13}C NMR Chemical Shift (δ) for Compounds 3a-d and 4a-d (Chloroform-d, 300 MHz)

	CH_3	Pyrazolodiazepine C-2	C-3	C-4	C-5a	C-6	C-8	C-8a	Phenyl C_i	C_o	C_m	C_p	Aryl C_i	C_o	C_m	C_p
3a	11.5	41.6	35.6	156.8	115.9	149.7	–	138.9	138.8	123.8	129.6	127.2	141.0	126.5	128.3	128.7
3b	11.5	41.5	35.4	155.2	115.7	149.7	–	139.0	138.7	123.8	129.6	127.3	139.4	127.7	128.5	134.7
3c	11.5	41.5	35.3	155.2	115.6	149.7	–	139.0	138.7	123.8	131.4	123.0	139.8	128.0	129.6	127.3
3d	11.4	41.2	35.4	153.0	115.8	150.0	–	139.4	138.4	123.6	123.8	127.5	146.6	126.9	127.3	147.5
4a	11.5	43.0	36.7	161.1	134.3	–	137.5	123.1	140.2	124.1	128.4	125.6	139.9	127.1	128.5	129.7
4b	11.5	42.9	36.6	159.4	134.0	–	137.4	123.3	140.1	124.1	128.4	125.7	138.4	128.4	128.6	135.8
4c	11.5	42.8	36.6	159.5	134.0	–	137.4	123.4	140.1	124.1	128.6	125.8	138.8	128.4	131.6	124.3
4d	11.4	42.6	36.9	157.3	137.1	–	139.9	123.9	145.5	123.7	124.2	126.0	143.0	127.6	128.5	147.3

Table 3

Long-range Proton-carbon Couplings Found in the HMBC Spectra of compounds 3a and 4a Protons Showing HMBC Correlation (^3J couplings)

Carbon	3a	4a
2	–	–
3	H-1	H-1
4	H-2; H_o	H-2, H_o
5a	CH_3; H-1	H-1
6	–	–
8	–	H-1
8a	H-2	CH_3; H-2

compounds 3 and 4 were done by results from selective low-power ^{13}C, ^1H decoupling experiments. In fact, C-5a in 3 and 4 appears as doublets in the coupled ^{13}C nmr spectra. Radiation onto the proton signal of 1-NH turns the C-5a signal into a singlet.

EXPERIMENTAL

All melting points are uncorrected. Column chromatographic purifications were performed on Merck silica gel (60-200 mesh). The ir spectra were recorded on a ATI-Mattson spectrophotometer in potassium bromide pellets. The uv-vis spectra were recorded on a Shimadzu UV-160 A spectrophotometer on an ethanol solution. The ^1H and ^{13}C nmr spectra were run on a Bruker AVANCE DRX 300 spectrometer in deuteriochloroform. The mass spectra were recorded on a Fisons-Platform interface APCI in methanol. The elemental analyses were determinated on a LECO CHNS-900 analyzer.

4-Aryl-6-methyl-8-phenyl-2,3-dihydropyrazolo[3,4-*b*]diazepines 3 and 4-Aryl-8-methyl-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepines 4.

General Procedure.

A solution of 1-phenyl-3-(dimethylamino)-1-propanone hydrochloride (0.68 g, 3.2 mmoles), 4,5-diamino-3-methylpyrazole (0.51 g, 3.2 mmoles) was refluxed in 15 ml of absolute ethanol for 1-7 hours (reaction control by tlc). The reaction mixture was evaporated and resulting precipitate was filtered, washed with ethanol, dryed and purified by silica gel chromatography with a mixture ethyl acetate/n-hexane (40:60) as the eluent. The first chromatographic fraction corresponds to compound 3 and the second one to compound 4. The yields and melting points of compounds 3 and 4 are summarized in Scheme 1.

6-Methyl-4,8-diphenyl-2,3-dihydropyrazolo[3,4-*b*]diazepine 3a.

The mass spectrum shows $(M+H)^+$ = 303 (100).

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53. Found: C, 75.39; H, 6.14; N, 18.42.

4-(*p*-Chlorophenyl)-6-methyl-8-phenyl-2,3-dihydropyrazolo[3,4-*b*]diazepine 3b.

The mass spectrum shows $(M+H)^+$ = 339/337 (80/100).

Anal. Calcd. for $C_{19}H_{17}N_4Cl$: C, 67.75; H, 5.09; N, 16.63. Found: C, 67.70; H, 5.17; N, 16.56.

4-(*p*-Bromophenyl)-6-methyl-8-phenyl-2,3-dihydropyrazolo[3,4-*b*]diazepine 3c.

The mass spectrum shows $(M+H)^+$ = 383/381 (100/73).

Anal. Calcd. for $C_{19}H_{17}N_4Br$: C, 59.85; H, 4.49; N, 14.69. Found: C, 59.74; H, 4.44; N, 14.76.

6-Methyl-4-(*p*-nitrophenyl)-8-phenyl-2,3-dihydropyrazolo-[3,4-*b*]diazepine 3d.

The mass spectrum shows $(M+H)^+$ = 348 (70).

Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.63; H, 4.65; N, 20.23.

8-Methyl-4,6-diphenyl-2,3-dihydropyrazolo[4,3-*b*]diazepine 4a.

The mass spectrum shows $(M+H)^+$ = 303 (100).

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53. Found: C, 75.52; H, 6.07; N, 18.36.

4-(*p*-Chlorophenyl)-8-methyl-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepine 4b.

The mass spectrum shows $(M+H)^+$ = 339/337 (77/100).

Anal. Calcd. for $C_{19}H_{17}N_4Cl$: C, 67.75; H, 5.09; N, 16.63. Found: C, 67.81; H, 5.03; N, 16.66.

4-(*p*-Bromophenyl)-8-methyl-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepine 4c.

The mass spectrum shows $(M+H)^+$ = 382/381 (83/100).

Anal. Calcd. for $C_{19}H_{17}N_4Br$: C, 59.85; H, 4.49; N, 14.69. Found: C, 59.78; H, 4.54; N, 14.61.

8-Methyl-4-(*p*-nitrophenyl)-6-phenyl-2,3-dihydropyrazolo[4,3-*b*]diazepine 4d.

The mass spectrum shows $(M+H)^+$ = 348 (100).

Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.74; H, 4.84; N, 20.11.

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