Synthesis of 1-Substituted 5-Aryl-3-styryl-2-pyrazolines and 3-Aryl-5-styryl-2-pyrazolines by the Reaction of Dibenzylideneacetones and *E,E*-Cinnamylideneacetophenones with Hydrazines

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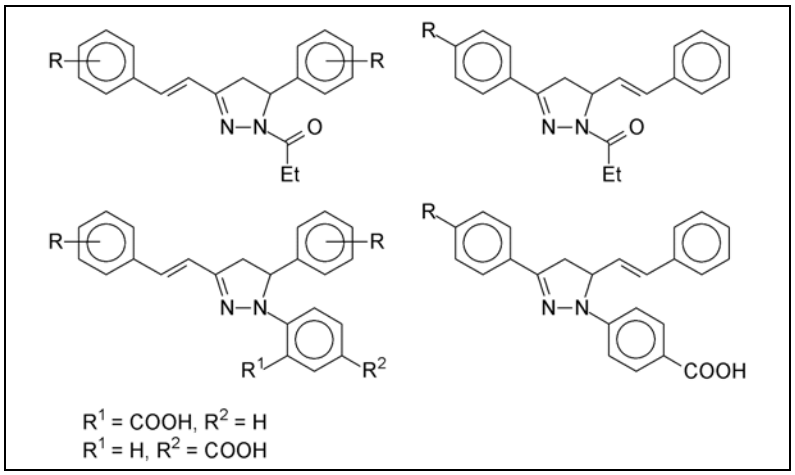

Dedicated to Professor Dr. Pál Sohár on the occasion of his 70th birthday

The reaction of dibenzylideneacetones or *E,E*-cinnamylidene- acetophenones and hydrazine hydrate provided 1-propionyl derivatives of 5-aryl-3-styryl-2-pyrazolines and 3-aryl-5-styryl-2-pyrazolines. These unsaturated ketones afforded 1-(2-carboxyphenyl) or 1-(4-carboxyphenyl) 5-aryl-3-styryl-2-pyrazolines and 1-(4-carboxyphenyl) derivatives of 3-aryl-5-styryl-2-pyrazolines on treatment with (2-carboxyphenyl)-hydrazine or (4-carboxyphenyl)hydrazine in hot acetic acid. Structures of all new 2-pyrazolines have been elucidated by microanalyses and a combined utilization of various spectroscopic methods.

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Introduction.

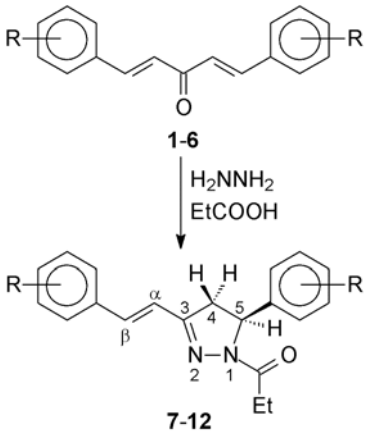
Pyrazolines are important nitrogen-containing five-membered heterocyclic compounds and various methods have been worked out for their synthesis [1-3]. Numerous pyrazolines have been found to possess bioactivities, *viz.* central nervous system [4], anti-microbial and antimycotic [5,6], immunosuppressive [7], *etc.* activities. Among the different pyrazoline isomers, 2-pyrazolines became the most frequently studied pyrazoline type compounds. As a result, a large number of 2-pyrazoline derivatives have been prepared, using different methods for their synthesis. A simple and convenient procedure is based on the reaction of α,β-unsaturated aldehydes and ketones with hydrazines [8-36]. Most of these pyrazoline derivatives are 1-substituted 3,5-diaryl-2-pyrazolines. Styryl-2-pyrazolines are less known compounds although there are three carbon atoms in the pyrazoline ring to which a styryl group may be attached. Their most frequent representatives are the 3-styryl-2-pyrazolines synthesized by the reaction of dibenzyl-ideneacetones with hydrazines [6,37-41]. 3-Styryl-2-pyrazolines have also been obtained as by-products by the reaction of 2-styrylchromones with hydrazine in hot methanolic solution [42]. 4-Styryl-2-pyrazolines have hitherto been synthesized only by us [43] by the reaction of *E,E*-cinnamylideneacetophenones with diazomethane. 5-styryl-2-pyrazolines have been prepared by the reaction of *E,E*-cinnamylideneaceto-phenones with hydrazines in various solvents [6,29, 40,44]. As a single example, Huisgen *et al.* [45] synthesized 1,3-diphenyl-5-styryl-2-pyrazoline by the cycloaddition of *trans*-phenyl-1,3-butadiene with (α-chlorobenzylidene)phenylhydrazine in the presence of triethylamine. Since styryl-2-pyrazolines showed anti-microbial and antimycotic activities [6], their new representatives can be useful substances in the drug research. As a continuation of our previous studies on the synthesis of styryl-2-pyrazolines [29,43], herein we report on the synthesis of new 1-substituted 3-styryl- and 5-styryl-2-pyrazolines.

Results and Discussion.

Acetic acid proved to be a convenient solvent for the synthesis of a wide variety of 2-pyrazolines by the reaction of α,β-unsaturated ketones and hydrazines [10,29-36,38,44]. If these starting materials were allowed to react with hydrazine in this solvent, 1-acetyl-2-pyrazoline was obtained in each case [29-36]. Previously, we have found that propionic acid is an equally convenient solvent for this purpose [34-36] and 1-propionyl-2-pyrazolines are obtained if the reactant is hydrazine. Since one of the aims of our present study was to synthesize 1-propionyl-2-pyrazolines bearing a styryl group, the utility of this solvent was investigated.

Dibenzylideneacetones **1-6** were allowed to react with hydrazine hydrate in hot propionic acid and 5-aryl-3-styryl-2-pyrazolines **7-12** were obtained in good yields (72-84%) as single isolable products (Scheme 1). Substituents of the aromatic rings was almost without influence both on the course of the reaction and on the yields of the isolated products.

Scheme 1

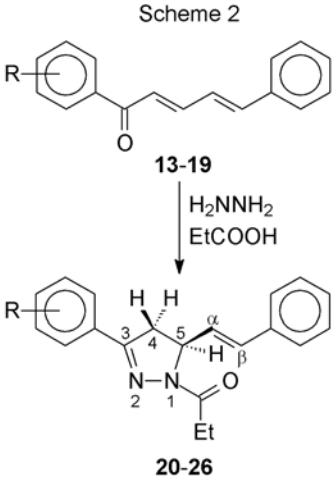


1, **7:** R = H
2, **8:** R = 4-Me
3, **9:** R = 4-MeO
4, **10:** R = 2-Cl
5, **11:** R = 4-Cl
6, **12:** R = 2,4-Cl_2

E,E-Cinnamylideneacetophenones **13-19** have also been reacted with hydrazine hydrate in hot propionic acid and 3-aryl-5-styryl-2-pyrazolines **20-26** were afforded in similarly good yields (69-92%) as sole products (Scheme 2). No by-products could be detected in the crude reaction mixtures by chromatography.

Our previous [34-36] and present experimental results unambiguously prove that propionic acid is a convenient solvent for the synthesis of 1-propionyl-2-pyrazolines. Formation of these 2-pyrazoline derivatives is almost independent of the type of groups attached to positions 1 and 3 of the propen-1-one.

Scheme 2

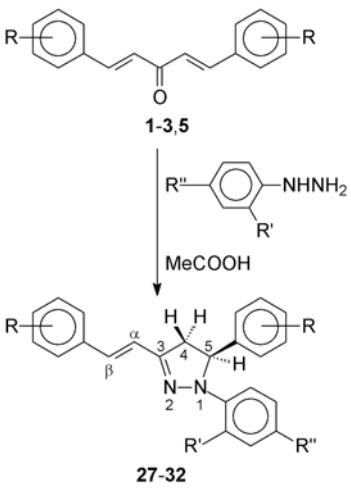


13, **20:** R = H
14, **21:** R = 4-Me
15, **22:** R = 4-MeO
16, **23:** R = 4-F
17, **24:** R = 4-Cl
18, **25:** R = 2-OH
19, **26:** R = 2-OH, 5-Cl

As mentioned, numerous 2-pyrazolines possess important bioactivities which stimulate the synthesis of their newer representatives bearing so-called pharmacophoric group. Such an opportunity is to insert a carboxy group into the molecule. For this reason, we have decided to introduce a carboxy group into styryl-2-pyrazolines by using (2-carboxyphenyl)hydrazine and (4-carboxyphenyl)hydrazine as reactants for this purpose.

Dibenzylideneacetones **1-3,5** were allowed to react with (2-carboxyphenyl)hydrazine or (4-carboxyphenyl)hydrazine in hot acetic acid and 1-(2-carboxyphenyl)-5-aryl-3-styryl-2-pyrazolines **27** and **28** or 1-(4-carboxyphenyl)-5-aryl-3-styryl-2-pyrazolines **29-32** were obtained as sole isolable products (Scheme 3). If (2-carboxyphenyl)-hydrazine was used as reactant, a multicomponent crude reaction mixture was obtained in each case. Compounds **27** and **28** were isolated in low yields (19% and 26%) by column chromatography. In the case of starting materials **2** and **3** we were unable to isolate the expected 2-pyrazolines even by careful chromatographic separations. These experiences may be the consequence of the formation of hydrogen bonding between the carboxy group and the nitrogen atoms of the hydrazine moiety at the *ortho*-position. A steric repulsion may also contribute to this effect. If the carboxy group and the hydrazine moiety were in the *para*-position, no adverse effect was observed and compounds **29-32** (Scheme 3) were obtained in good yields (71-89%). It means that the (4-carboxyphenyl)hydrazine reacts with α,β-unsaturated ketones like the phenylhydrazine [2,3].

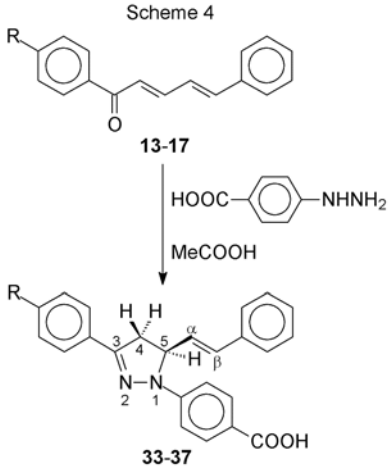
Scheme 3



1, **27:** R = R'' = H, R' = COOH
5, **28:** R = 4-Cl, R' = COOH, R'' = H
1, **29:** R = R' = H, R'' = COOH
2, **30:** R = 4-Me, R' = H, R'' = COOH
3, **31:** R = 4-MeO, R' = H, R'' = COOH
5, **32:** R = 4-Cl, R' = H, R'' = COOH

E,E-Cinnamylideneacetophenones **13-17** were also reacted with (2-carboxyphenyl)hydrazine or (4-carboxyphenyl)hydrazine in hot acetic acid and 1-(4-carboxyphenyl)-3-aryl-5-styryl-2-pyrazolines **33**-**37** were afforded in good yields (71-84%) (Scheme 4). However, if (2-carboxyphenyl)hydrazine was used as reactant, a multicomponent crude reaction mixture was obtained in each case from which the expected 2-pyrazoline could not be isolated. The same reasons may be true for these cases as mentioned for the similar reaction of the dibenzylideneacetones with (2-carboxyphenyl)hydrazine.

Scheme 4



13, **33:** R = H **16**, **36:** R = F
14, **34:** R = Me **17**, **37:** R = Cl
15, **35:** R = MeO

Structures of the synthesized styryl-2-pyrazolines **7-12** and **20-37** have been elucidated by microanalyses, ^{1}H and ^{13}C nmr and ir spectroscopies. In the ^{1}H nmr spectra of all new 2-pyrazolines, the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the 2-pyrazoline ring revealed an ABX spin system. The 2-pyrazoline skeleton is unambiguously proved by the chemical shifts, by the signal multiplicities and by the coupling constant values (*cf.* Experimental). Characteristic triplet and quartet signals of the ethyl part of the N-propionyl group of compounds **7-12** and **20-26** have also been detected. Protons of the styryl group could be assigned in most cases. If not, they were overlapped by the signals of the aromatic protons. In their ^{13}C nmr spectra, chemical shift data of carbon atoms C-3 (around 155 and 144 ppm), C-4 (40-42 ppm) and C-5 (55-62 ppm) corroborate the 2-pyrazoline structure deduced from the ^{1}H nmr spectroscopic measurements. ^{13}C nmr chemical shifts of the N-propionyl moiety have also been observed in the ^{13}C nmr spectra of compounds **7-12** and **20-26** (*cf.* Experimental). In the ir spectra of compounds **7-12** and **20-26**, the presence of an amide carbonyl band between 1650 and 1670 cm^{-1} refers to the presence of an N-propionyl group. While in the case of compounds **27-37** ir bands belonging to a carboxy group have also been observed. The C=N band of the new 2-pyrazolines was detected at around 1600 cm^{-1}. Therefore, informations originating from the ir spectra confirm the structures of all new compounds described in our present paper.

In conclusion, we have synthesized new 1-substituted 3-styryl-2-pyrazolines and 5-styryl-2-pyrazolines by the reaction of dibenzylideneacetones or *E,E*-cinnamylideneacetophenones with hydrazines in either hot acetic acid or propionic acid solutions. This simple procedure made possible the preparation of hitherto unknown 2-pyrazoline derivatives in high yields. 2-Pyrazolines synthesized in our present study may be beneficially used in drug research.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 spectrometer at 200/50 MHz in $CDCl_3$ or in DMSO-d_6 (internal standard TMS, δ = 0.0 ppm) at ambient temperature. Ir spectra were obtained by a Perkin-Elmer 16 PC apparatus in KBr discs. Elemental analyses were measured in-house with a Carlo Erba instrument, model 1106. The tlc was performed on Kieselgel 60 F_{254} (Merck) layer using toluene:ethyl acetate (4:1 v/v) or hexane:acetone (7:3 v/v) as eluents. Starting materials **1-6** and **13-19** were synthesized according to known procedures [38-40,43].

General Procedure for the Synthesis of 5-Aryl-3-styryl-2-pyrazolines **7-12** and 3-Aryl-5-styryl-2-pyrazolines **20-26**.

A mixture of dibenzylideneacetone **1-6** or *E,E*-cinnamylideneacetophenone **13-19** (5.0 mmoles), hydrazine hydrate (20.0 mmoles) and propionic acid (50 ml) was refluxed for 3 hours, then poured into water. The precipitate was separated by filtration, washed free of acid and crystallized from methanol to obtain 5-aryl-3-styryl-2-pyrazolines **7-12** (Scheme 1) and 3-aryl-5-styryl-2-pyrazolines **20**-**26** (Scheme 2).

5-Phenyl-1-propionyl-3-styryl-2-pyrazoline (**7**).

This compound was isolated as white needles in 82% yield, mp 117-118°; ^{1}H nmr ($CDCl_3$): δ 1.18 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.75 (q, 2H, J = 7.5 Hz, CH_2CH_3), 2.98 (dd, 1H, J = 4.5, 17.2 Hz, 4-H_{trans}), 3.54 (dd, 1H, J = 11.7, 17.2 Hz, 4-H_{cis}), 5.50 (dd, 1H, J = 4.5, 11.7 Hz, 5-H), 6.73 (d, 1H, J = 16.3 Hz, H_α), 7.12 (d, 1H, J = 16.3 Hz, H_β), 7.20-7.49 (m, 10 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.6, 27.3, 40.6, 59.8, 120.9, 125.6, 127.0, 127.6, 128.9, 129.1, 135.8, 137.1, 142.1, 154.8, 172.2; ir (KBr): cm^{-1} 1663, 1602, 1560, 1492, 1430, 1354, 1297, 1222, 1141, 1078, 1027, 964, 859, 750, 702.

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H 6.62; N, 9.20. Found: C, 78.81; H, 6.67; N, 9.28.

5-(4-Methylphenyl)-3-(4-methylstyryl)-1-propionyl-2-pyrazoline (**8**).

This substance was prepared as white needles in 72% yield, mp 94-95°; ^{1}H nmr ($CDCl_3$): δ 1.18 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.60 (s, 3H, Me), 2.66 (s, 3H, Me), 2.73 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.98 (dd, 1H, J = 4.7, 17.2 Hz, 4-H_{trans}), 3.54 (dd, 1H, J = 11.7, 17.2 Hz, 4-H_{cis}), 5.46 (dd, 1H, J = 4.7, 11.7 Hz, 5-H), 6.71 (d, 1H, J = 16.3 Hz, H_α), 7.07 (d, 1H, J = 16.3 Hz, H_β), 7.11-7.38 (m, 8 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.6, 19.8, 21.1, 27.3, 40.6, 59.5, 113.4, 114.4, 119.9, 122.5, 125.6, 127.0, 129.6, 129.7, 137.2, 139.3, 155.6, 174.1; ir (KBr): cm^{-1} 1667, 1603, 1560, 1512, 1437, 1354, 1296, 1226, 1138, 1027, 948, 858, 815.

Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.42. Found: C, 79.58; H, 7.22; N, 8.51.

5-(4-Methoxyphenyl)-3-(4-methoxystyryl)-1-propionyl-2-pyrazoline (**9**).

This compound was isolated as white plates in 84% yield, mp 122-123°; ^{1}H nmr ($CDCl_3$): δ 1.17 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.73 (q, 2H, J = 7.5 Hz, CH_2CH_3), 2.98 (dd, 1H, J = 4.5, 17.5 Hz, 4-H_{trans}), 3.53 (dd, 1H, J = 11.3, 17.5 Hz, 4-H_{cis}), 3.77 (s, 3H, MeO), 3.83 (s, 3H, MeO), 5.46 (dd, 1H, J = 4.5, 11.3 Hz, 5-H), 6.71 (d, 1H, J = 16.2 Hz, H_α), 6.98 (d, 1H, J = 16.2 Hz, H_β), 6.84-7.41 (m, 8 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.6, 27.3, 40.6, 55.1, 55.2, 59.2, 114.2, 114.4, 118.7, 126.4, 126.9, 128.5, 128.5, 134.4, 136.8, 154.9, 158.9, 160.3, 171.8; ir (KBr): cm^{-1} 1668, 1601, 1513, 1432, 1354, 1262, 1176, 1025, 962, 859, 827.

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.68. Found: C, 72.43; H, 6.71; N, 7.75.

5-(2-Chlorophenyl)-3-(2-chlorostyryl)-1-propionyl-2-pyrazoline (**10**).

This material was prepared as pale yellow needles in 81% yield, mp 162-163°; ^{1}H nmr ($CDCl_3$): δ 1.22 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.82 (q, 2H, CH_2CH_3), 2.94 (dd, 1H, J = 4.9, 17.3 Hz, 4-H_{trans}), 3.72 (dd, 1H, J = 12.0, 17.3, 4-H_{cis}), 5.89 (dd, 1H, J = 4.9, 12.0 Hz, 5-H), 6.99 (m, 8 arom. H + H_α and H_β); ^{13}C nmr ($CDCl_3$): δ 8.7, 27.3, 39.7, 57.7, 123.2, 126.0, 126.8, 127.2, 128.8, 129.9, 130.1, 131.9, 132.9, 133.8, 138.8, 154.9, 172.3; ir (KBr): cm^{-1} 1667, 1604, 1471, 1439, 1351, 1297, 1230, 1153, 1024, 955, 865, 758.

Anal. Calcd for $C_{20}H_{18}Cl_2N_2O$: C, 64.35; H, 4.86; N, 7.50. Found: C, 64.26; H, 4.91; N, 7.58.

5-(4-Chlorophenyl)-3-(4-chlorostyryl)-1-propionyl-2-pyrazoline (**11**).

This substance was obtained as pale yellow plates in 73% yield, mp 135-136°; ^{1}H nmr ($CDCl_3$): δ 1.21 (t, 3H, J. 7.4 Hz, CH_2CH_3), 2.76 (q, 2H, J = 7.4 Hz, CH_2CH_3), 2.97 (dd, 1H, J = 4.7, 17.4 Hz, 4-H_{trans}), 3.48 (dd, 1H, J = 11.9, 17.4 Hz, 4-H_{cis}), 5.46 (dd, 1H, J = 4.7, 11.9 Hz, 5-H), 6.70 (d, 1H, J = 16.4 Hz, H_α), 7.06 (d, 1H, J = 16.4 Hz, H_β), 7.12-7.43 (m, 8 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.8, 27.4, 40.6, 59.4, 121.3, 127.0, 128.1, 129.1, 133.4, 134.1, 134.8, 135.7, 140.4, 154.1, 172.1; ir (KBr): cm^{-1} 1662, 1589, 1489, 1439, 1353, 1301, 1262, 1227, 1148, 1088, 1011, 957, 862, 818.

Anal. Calcd for $C_{20}H_{18}Cl_2N_2O$: C, 64.35; H, 4.86; N, 7.50. Found: C, 64.43; H, 4.81; N, 7.44.

5-(2,4-Dichlorophenyl)-3-(2,4-dichlorostyryl)-1-propionyl-2-pyrazoline (**12**).

This material was isolated as yellow needles in 72% yield, mp 174-175°; ^{1}H nmr ($CDCl_3$): δ 1.20 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.80 (q, 2H, J = 7.6 Hz, CH_2CH_3), 2.89 (dd, 1H, J = 5.3, 17.5 Hz, 4-H_{trans}), 3.69 (dd, 1H, J = 12.0, 17.5 Hz, 4-H_{cis}), 5.81 (dd, 1H, J = 5.3, 12.0 Hz, 5-H), 6.97 (d, 1H, J = 8.3 Hz, H_α), 7.58 (d, 1H, J = 8.3 Hz, H_β), 7.04-7.42 (m, 6 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.7, 27.3, 39.6, 57.4, 123.5, 127.1, 127.6, 127.7, 127.8, 132.6, 134.1, 134.4, 135.3, 137.4, 154.6, 172.5; ir (KBr): cm^{-1} 1668, 1589, 1561, 1472, 1439, 1380, 1297, 1226, 1143, 1027, 958, 862, 814.

Anal. Calcd for $C_{20}H_{16}Cl_4N_2O$: C, 54.32; H, 3.65; N, 6.33. Found: C, 54.41; H, 3.61; N, 6.39.

3-Phenyl-1-propionyl-5-styryl-2-pyrazoline (**20**).

This compound was prepared as white plates in 89% yield, mp 134-135°; ^{1}H nmr ($CDCl_3$): δ 1.23 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.81 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.09 (dd, 1H, J = 4.8, 17.7 Hz, 4-H_{trans}), 3.53 (dd, 1H, J = 11.5, 17.7 Hz, 4-H_{cis}), 5.28 (m, 1H, 5-H), 6.20 (dd, 1H, J = 7.0, 15.8 Hz, H_α), 6.61 (d, 1H, J = 15.8 Hz, H_β), 6.71-7.01 (m, 10 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.8, 27.5, 38.9, 58.1, 126.6, 126.7, 127.4, 127.9, 128.6, 128.8, 130.3, 131.6, 131.8, 136.5, 154.0, 172.8; ir (KBr): cm^{-1} 1665, 1601, 1413, 1351, 1290, 1141, 1077, 960, 869, 767, 693.

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.98; H, 6.56; N, 9.14.

3-(4-Methylphenyl)-1-propionyl-5-styryl-2-pyrazoline (**21**).

This substance was isolated as white needles in 69% yield, mp 90-91°; ^{1}H nmr ($CDCl_3$): δ 1.23 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.39 (s, 3H, Me), 2.81 (q, 2H, J = 7.4 Hz, CH_2CH_3), 3.08 (dd, 1H, J = 4.5, 17.4 Hz, 4-H_{trans}), 3.50 (dd, 1H, J = 11.3, 17.4 Hz, 4-H_{cis}), 5.25 (m, 1H, 5-H), 6.20 (dd, 1H, J = 7.1, 15.9 Hz, H_α), 6.59 (d, 1H, J = 15.9 Hz, H_β), 7.20-7.64 (m, 9 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.8, 21.2, 27.4, 38.9, 57.9, 96.2, 97.9, 126.5, 126.7, 127.5, 127.8, 128.5, 128.9, 129.5, 131.5, 136.4, 140.6, 154.0,

172.7; ir (KBr): cm^{-1} 1655, 1599, 1436, 1345, 1293, 1243, 1141, 1036, 971, 868, 816, 750, 693.

Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.97; N, 8.79. Found: C, 79.30; H, 6.91; N, 8.86.

3-(4-Methoxyphenyl)-1-propionyl-5-styryl-2-pyrazoline (**22**).

This compound was prepared as white needles in 73% yield, mp 99-100°; ^{1}H nmr ($CDCl_3$): δ 1.21 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.80 (q, 2H, J = 7.4 Hz, CH_2CH_3), 3.05 (dd, 1H, J = 4.6, 17.4 Hz, 4-H_{trans}), 3.48 (dd, 1H, J = 11.4, 17.4 Hz, 4-H_{cis}), 3.83 (s, 3H, MeO), 5.23 (m, 1H, 5-H), 6.20 (dd, 1H, J = 7.1, 15.9 Hz, H_α), 6.61 (d, 1H, J = 15.9 Hz, H_β), 6.80-7.71 (m, 9 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.8, 27.4, 39.0, 55.2, 57.9, 114.2, 124.4, 126.7, 127.5, 127.8, 128.2, 128.5, 131.4, 136.5, 153.7, 161.5, 172.5; ir (KBr): cm^{-1} 1650, 1610, 1518, 1432, 1309, 1252, 1178, 1038, 977, 871, 838, 750, 695.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.37. Found: C, 75.51; H, 6.58; N, 8.43.

3-(4-Fluorophenyl)-1-propionyl-5-styryl-2-pyrazoline (**23**).

This compound was obtained as white plates in 73% yield, mp 107-108°; ^{1}H nmr ($CDCl_3$): δ 1.23 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.81 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.08 (dd, 1H, J = 4.7, 17.6 Hz, 4-H_{trans}), 3.50 (dd, 1H, J = 11.3, 17.6 Hz, 4-H_{cis}), 5.27 (m, 1H, 5-H), 6.20 (dd, 1H, J = 7.1, 15.9 Hz, H_α), 6.60 (d, 1H, J = 15.9 Hz, H_β), 7.07-7.78 (m, 9 arom. H); ^{13}C nmr ($CDCl_3$): δ 9.0, 27.6, 39.1, 52.2, 115.6, 116.0, 126.6, 127.1, 127.8, 128.3, 128.4, 131.5, 136.2, 152.7, 161.1, 166.3, 172.5; ir (KBr): cm^{-1} 1645, 1602, 1513, 1436, 1347, 1291, 1219, 1029, 880, 838, 755, 695.

Anal. Calcd for $C_{20}H_{19}FN_2O$: C, 74.52; H, 5.94; N, 8.69. Found: C, 74.59; H, 5.98; N, 8.61.

3-(4-Chlorophenyl)-1-propionyl-5-styryl-2-pyrazoline (**24**).

This material was obtained as pale yellow needles in 80% yield, mp 89-90°; ^{1}H nmr ($CDCl_3$): δ 1.22 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.79 (q, 2H, J = 7.4 Hz, CH_2CH_3), 3.05 (dd, 1H, J = 4.8, 17.6 Hz, 4-H_{trans}), 3.49 (dd, 1H, J = 11.6, 17.6 Hz, 4-H_{cis}), 5.27 (m, 1H, 5-H), 6.19 (dd, 1H, J = 6.9, 15.7 Hz, H_α), 6.60 (d, 1H, J = 15.7 Hz, H_β), 7.20-7.71 (m, 9 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.8, 27.4, 38.8, 58.2, 126.7, 127.2, 127.8, 127.9, 128.6, 129.0, 130.3, 131.7, 136.2, 136.3, 152.8, 172.7; ir (KBr): cm^{-1} 1651, 1592, 1493, 1433, 1345, 1289, 1246, 1090, 1027, 977, 874, 821, 756, 694.

Anal. Calcd for $C_{20}H_{19}ClN_2O$: C, 70.89; H, 5.65; N, 8.26. Found: C, 70.81; H, 5.61; N, 8.17.

3-(2-Hydroxyphenyl)-1-propionyl-5-styryl-2-pyrazoline (**25**).

This compound was prepared as pale yellow plates in 92% yield, mp 149-150°; ^{1}H nmr ($CDCl_3$): δ 1.17 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.63 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.12 (dd, 1H, J = 4.7, 17.6 Hz, 4-H_{trans}), 3.55 (dd, 1H, J = 11.4, 17.6 Hz, 4-H_{cis}), 5.14 (m, 1H, 5-H), 6.10 (dd, 1H, J = 7.3, 15.8 Hz, H_α), 6.56 (d, 1H, J = 15.8 Hz, H_β), 6.83-7.34 (m, 9 arom. H), 10.21 (s, 1H, OH); ^{13}C nmr ($CDCl_3$): δ 8.4, 27.5, 39.3, 56.7, 115.4, 117.1, 119.8, 126.5, 126.8, 128.1, 128.5, 128.6, 132.3, 132.4, 136.1, 156.5, 157.8, 171.7; ir (KBr): cm^{-1} 1667, 1610, 1493, 1436, 1311, 1263, 1150, 1031, 957, 877, 694.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.90; H, 6.22; N, 8.81.

3-(5-Chloro-2-hydroxyphenyl)-1-propionyl-5-styryl-2-pyrazoline (**26**).

This substance was obtained as yellow needles in 88% yield, mp 163-164°; ^{1}H nmr ($CDCl_3$): δ 1.21 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.71 (q, 2H, J = 7.4 Hz, CH_2CH_3), 3.19 (dd, 1H, J = 4.7, 17.6 Hz, 4-H_{trans}), 3.59 (dd, 1H, J = 11.4, 17.6 Hz, 4-H_{cis}), 5.24 (m, 1H, 5-H), 6.18 (dd, 1H, J = 7.1, 15.8 Hz, H_α), 6.63 (d, 1H, J = 15.8 Hz, H_β), 6.97-7.39 (m, 8 arom. H); ^{13}C nmr ($CDCl_3$): δ 8.4, 27.5, 39.1, 56.9, 116.5, 118.5, 124.5, 126.2, 126.7, 127.7, 128.2, 128.6, 131.9, 132.5, 135.9, 155.3, 156.3, 172.2; ir (KBr): cm^{-1} 1668, 1604, 1487, 1434, 1346, 1300, 1256, 1211, 1153, 1031, 956, 834, 755, 694.

Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.39; N, 7.89. Found: C, 67.79; H, 5.33; N, 7.96.

General Procedure for the Synthesis of 5-Aryl-3-styryl-2-pyrazolines **27-32** and 3-Aryl-5-styryl-2-pyrazolines **33-37**.

A mixture of dibenzylideneacetone **1-3,5** or *E,E*-cinnamylideneacetophenone **13-17** (10.0 mmoles), (2-carboxyphenyl)-hydrazine or (4-carboxyphenyl)hydrazine (30.0 mmoles) and acetic acid (120 ml) was refluxed for 8 hours, then poured onto crushed ice. The precipitate was separated by filtration, washed with water in crystallized from methanol to afford 5-aryl-3-styryl-2-pyrazolines **27-32** (Scheme 3) and 3-aryl-5-styryl-2-pyrazolines **33-37** (Scheme 4).

1-(2-Carboxyphenyl)-5-phenyl-3-styryl-2-pyrazoline (**27**).

This substance was obtained as white plates in 19% yield, mp 147-148°; ^{1}H nmr ($CDCl_3$): δ 3.02 (dd, 1H, J = 6.8, 16.8 Hz, 4-H_{trans}), 3.73 (dd, 1H, J = 12.3, 16.8 Hz, 4-H_{cis}), 5.27 (dd, 1H, J = 6.8, 12.3 Hz, 5-H), 6.53 (d, 1H, J = 16.2 Hz, H_α), 6.80-7.48 (m, 14 arom. H + H_β); ^{13}C nmr ($CDCl_3$): δ 42.2, 64.2, 104.9, 113.4, 120.3, 125.2, 125.8, 126.6, 127.5, 127.8, 128.0, 128.5, 128.7, 128.9, 129.2, 130.3, 130.9, 132.6, 137.1, 139.9, 144.3, 151.2; ir (KBr): cm^{-1} 1671, 1599, 1500, 1449, 1400, 1326, 1281, 1228, 1174, 1122, 1069, 951, 872, 746, 692.

Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.32; H, 5.41; N, 7.68.

1-(2-Carboxyphenyl)-5-(4-chlorophenyl)-3-(4-chlorostyryl)-2-pyrazoline (**28**).

This substance was obtained as yellow needles in 26% yield, mp 228-229°; ^{1}H nmr ($CDCl_3$): δ 2.98 (dd, 1H, J = 6.9, 17.2 Hz, 4-H_{trans}), 3.71 (dd, 1H, J = 12.4, 17.2 Hz, 4-H_{cis}), 5.26 (dd, 1H, J = 6.9, 12.4 Hz, 5-H), 6.48 (d, 1H, J = 16.4 Hz, H_α), 6.79-7.41 (m, 12 arom. H, + H_β); ^{13}C nmr ($CDCl_3$); δ 42.0, 63.6, 113.5, 119.7, 122.1, 127.2, 127.7, 129.0, 129.4, 131.3, 133.5, 135.1, 140.8, 143.8, 147.9, 152.4; ir (KBr): cm^{-1} 1672, 1597, 1547, 1498, 1394, 1316, 1227, 1088, 1014, 962, 872, 826, 753, 693.

Anal. Calcd for $C_{24}H_{18}Cl_2N_2O_2$: C, 65.91; H, 4.15; N, 6.40. Found: C, 65.98; H, 4.10; N, 6.48.

1-(4-Carboxyphenyl)-5-phenyl-3-styryl-2-pyrazoline (**29**).

This compound was prepared as white needles in 88% yield, mp 264-265°; ^{1}H nmr (DMSO-d_6): δ 3.09 (dd, 1H, J = 4.8, 17.4 Hz, 4-H_{trans}), 3.81 (dd, 1H, J = 11.5, 17.4 Hz, 4-H_{cis}), 5.52 (dd, 1H, J = 4.8, 11.5 Hz, 5-H), 6.89 (d, 1H, J = 16.3 Hz, H_α), 6.92-7.68 (m, 14 arom. H + H_β); ^{13}C nmr (DMSO-d_6): δ 41.8, 62.0, 111.9, 119.1, 120.7, 125.5, 126.8, 127.5, 128.3, 128.7, 129.0, 130.7, 134.7, 136.1, 141.7, 146.4, 151.1, 167.1; ir (KBr): cm^{-1}

1676, 1600, 1521, 1413, 1334, 1286, 1178, 1128, 1094, 947, 873, 838, 691.

Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.16; H, 5.52; N, 7.53.

1-(4-Carboxyphenyl)-5-(4-methylphenyl)-3-(4-methylstyryl)-2-pyrazoline (**30**).

This material was isolated as white plates in 89% yield, mp 262-263°; ^{1}H nmr (DMSO-d_6): δ 2.24 (s, 3H, Me), 2.30 (s, 3H, Me), 3.03 (dd, 1H, J = 4.9, 17.3 Hz, 4-H_{trans}), 3.78 (dd, 1H, J = 11.4, 17.3 Hz, 4-H_{cis}), 5.56 (dd, 1H, J = 4.9, 11.4 Hz, J = 5-H), 6.85 (d, 1H, J = 16.1 Hz, H_α), 6.98-7.71 (m, 12 arom. H + H_β), 12.30 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 20.5, 20.7, 41.8, 61.7, 111.8, 119.7, 125.4, 126.7, 129.3, 129.5, 130.7, 133.4, 134.7, 136.7, 137.9, 138.7, 146.4, 151.2, 167.0; ir (KBr): cm^{-1} 1660, 1599, 1521, 1411, 1340, 1267, 1175, 1131, 1094, 954, 875, 814, 772.

Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.06. Found: C, 78.69; H, 6.05; N, 7.14.

1-(4-Carboxyphenyl)-5-(4-methoxyphenyl)-3-(4-methoxystyryl)-2-pyrazoline (**31**).

This compound was obtained as pale yellow plates in 74% yield, mp 156-157°; ^{1}H nmr (DMSO-d_6): δ 3.04 (dd, 1H, J = 4.7, 17.6 Hz, 4-H_{trans}), 3.70 (s, 3H, MeO), 3.73 (dd, 1H, J = 11.2, 17.6 Hz, 4-H_{cis}), 3.77 (s, 3H, MeO), 5.56 (dd, 1H, J = 4.7, 11.2 Hz, 5-H), 6.72-7.78 (m, 12 arom. H + H_α + H_β), 12.10 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 40.7, 54.9, 55.1, 61.4, 111.8, 114.2, 114.3, 118.5, 119.6, 126.7, 128.3, 128.8, 130.7, 133.6, 134.5, 146.5, 151.4, 158.5, 159.5, 167.1, 171.9; ir (KBr): cm^{-1} 1677, 1597, 1510, 1409, 1288, 1253, 1174, 1129, 1093, 1032, 952, 837, 771.

Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.53. Found: C, 72.96; H, 5.69; N, 6.47.

1-(4-Carboxyphenyl)-5-(4-chlorophenyl)-3-(4-chlorostyryl)-2-pyrazoline (**32**).

This substance was prepared as yellow needles in 71% yield, mp 273-274°; ^{1}H nmr (DMSO-d_6): δ 3.09 (dd, 1H, J = 4.3, 17.3 Hz, 4-H_{trans}), 3.78 (dd, 1H, J = 11.9, 17.3 Hz, 4-H_{cis}), 5.69 (dd, 1H, J = 4.3, 11.9 Hz, 5-H), 6.90 (d, 1H, J = 16.4 Hz, H_α), 6.95-7.77 (m, 12 arom. H + H_β), 12.28 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 41.5, 61.3, 111.9, 120.2, 121.4, 127.5, 128.4, 128.9, 130.7, 132.0, 132.6, 133.4, 135.1, 141.1, 145.9, 150.9, 167.3; ir (KBr): cm^{-1} 1662, 1597, 1518, 1490, 1415, 1323, 1286, 1174, 1129, 1087, 954, 821, 770.

Anal. Calcd for $C_{24}H_{18}Cl_2N_2O_2$: C, 65.91; H, 4.15; N, 6.40. Found: C, 65.83; H, 4.20; N, 6.33.

1-(4-Carboxyphenyl)-3-phenyl-5-styryl-2-pyrazoline (**33**).

This substance was prepared as white needles in 84% yield, mp 207-208°; ^{1}H nmr (DMSO-d_6): δ 3.20 (dd, 1H, J = 4.9, 17.2 Hz, 4-H_{trans}), 3.73 (dd, 1H, J = 11.8, 17.2 Hz, 4-H_{cis}), 5.23 (m, 1H, 5-H), 6.39 (dd, 1H, J = 7.2, 15.9 Hz, H_α), 6.66 (d, 1H, J = 15.9 Hz, H_β), 7.21-7.86 (m, 14 arom. H), 12.22 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 40.6, 61.0, 112.1, 119.8, 125.9, 126.4, 127.8, 128.0, 128.5, 128.6, 129.1, 130.7, 131.2, 131.8, 135.8, 147.4, 150.3, 167.2; ir (KBr): cm^{-1} 1675, 1597, 1520, 1404, 1288, 1175, 1130, 1090, 965, 842, 691.

Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.31; H, 5.42; N, 7.68.

1-(4-Carboxyphenyl)-3-(4-methylphenyl)-5-styryl-2-pyrazoline (**34**).

This compound was obtained as white needles in 72% yield, mp 231-232°; ^{1}H nmr (DMSO-d_6): δ 2.24 (s, 3H, Me), 3.19 (dd, 1H, J = 5.1, 17.8 Hz, 4-H_{trans}), 3.74 (dd, 1H, J = 11.4, 17.8 Hz, 4-H_{cis}), 5.20 (m, 1H, 5-H), 6.26 (dd, 1H, J= 7.4, 16.1 Hz, H_α), 6.73 (d, 1H, J = 16.1 Hz, H_β), 7.69-7.83 (m, 13 arom. H), 12.28 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 20.8, 40.7, 60.9, 119.6, 124.8, 125.9, 126.4, 127.8, 128.1, 128.5, 129.1, 129.2, 130.7, 131.2, 135.8, 138.9, 147.5, 150.4, 167.2; ir (KBr): cm^{-1} 1669, 1599, 1523, 1400, 1326, 1288, 1174, 1129, 1098, 1043, 811, 769, 744, 689.

Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.58; H, 5.75; N, 7.24.

1-(4-Carboxyphenyl)-3-(4-methoxyphenyl)-5-styryl-2-pyrazoline (**35**).

This substance was prepared as white plates in 76% yield, mp 162-163°; ^{1}H nmr (DMSO-d_6): δ 3.26 (dd, 1H, J = 4.7, 17.1 Hz, 4-H_{trans}), 3.74 (dd, 1H, J = 11.7, 17.1 Hz, 4-H_{cis}), 3.81 (s, 3H, MeO), 5.22 (m, 1H, 5-H), 6.26 (dd, 1H, J = 7.2, 16.0 Hz, H_α), 6.71 (d, 1H, J = 16.0 Hz, H_β), 6.98-7.82 (m, 13 arom. H), 12.13 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 40.7, 55.2, 60.9, 111.9, 114.1, 119.4, 124.5, 126.4, 127.6, 127.8, 128.2, 128.5, 130.7, 131.1, 135.8, 147.6, 150.3, 160.2, 167.2; ir (KBr): 1668, 1597, 1511, 1398, 1289, 1174, 1130, 1088, 1041, 941, 873, 834, 692.

Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.45; H, 5.51; N, 7.11.

1-(4-Carboxyphenyl)-3-(4-fluorophenyl)-5-styryl-2-pyrazoline (**36**).

This material was isolated as pale yellow plates in 76%, mp 242-243°; ^{1}H nmr (DMSO-d_6): δ 3.20 (dd, 1H, J = 4.9, 17.3 Hz, 4-H_{trans}), 3.76 (dd, 1H, J = 11.4, 17.3 Hz, 4-H_{cis}), 5.26 (m, 1H, 5-H), 6.27 (dd, 1H, J = 7.5, 16.2 Hz, H_α), 6.74 (d, 1H, J = 16.2 Hz, H_β), 7.19-7.88 (m, 13 arom. H), 12.32 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 40.7, 61.2, 112.1, 115.4, 115.8, 119.8, 126.4, 127.8, 128.0, 128.2, 128.5, 130.7, 131.3, 135.8, 147.4, 149.5, 167.2; ir (KBr): cm^{-1} 1671, 1598, 1508, 1397, 1322, 1281, 1226, 1173, 1130, 1093, 964, 838, 692.

Anal. Calcd for $C_{24}H_{19}FN_2O_2$: C, 74.59; H, 4.96; N, 7.25. Found: C, 75.68; H, 4.91; N, 7.32.

1-(4-Carboxyphenyl)-3-(4-chlorophenyl)-5-styryl-2-pyrazoline (**37**).

This compound was prepared as yellow plates in 78% yield, mp 263-264°; ^{1}H nmr (DMSO-d_6): δ 3.28 (dd, 1H, J = 4.9, 17.0 Hz, 4-H_{trans}), 3.73 (dd, 1H, J = 11.2, 17.0 Hz, 4-H_{cis}), 5.21 (m, 1H, 5-H), 6.35 (dd, 1H, J = 7.1, 15.8 Hz, H_α), 6.74 (d, 1H, J = 15.8 Hz, H_β), 7.21-7.80 (m, 13 arom. H), 12.42 (s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 40.7, 61.2, 112.2, 120.1, 126.4, 127.6, 127.8, 127.9, 128.5, 128.7, 130.7, 131.3, 133.6, 135.8, 147.2, 149.3, 167.2; ir (KBr): cm^{-1} 1662, 1599, 1521, 1493, 1412, 1393, 1328, 1277, 1173, 1131, 1088, 957, 872, 748, 692.

Anal. Calcd for $C_{24}H_{19}ClN_2O_2$: C, 71.55; H, 4.75; N, 6.95. Found: C, 71.63; H, 4.69; N, 6.86.

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