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Received August 21, 2002**Dedicated to Professor Dr. László Tóke on the occasion of his 70th birthday.**

New 3-aryol-4-(3-chromonyl)-2-pyrazolines have been synthesized by the reaction of 3-(3-aryl-3-oxopropenyl)chromen-4-ones and diazomethane. Some of these 2-pyrazolines have also been N-acylated with a mixture of anhydrous pyridine and acetic anhydride or propionic anhydride. Structures of all new compounds have been elucidated by elemental analyses, mass spectrometry, ir and nmr spectroscopic measurements.

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For the synthesis of pyrazolines, an especially popular procedure is based on the cycloaddition of diazoalkanes to carbon-carbon double bonds. 1,3-Dipolar cycloaddition of diazomethane and α,β -unsaturated ketones has been studied by several research groups. Such a cycloaddition was first published by Azzarello as early as 1906 who prepared 3-acetyl-4-phenyl-2-pyrazoline by the reaction of benzalacetone with diazomethane in anhydrous ether [1]. Later on, 1,3-dipolar cycloaddition of a wide variety of chalcones and related α,β -unsaturated ketones with diazomethane was thoroughly investigated [2-13]. Experimental results proved that the only isolable products of these reactions are 2-pyrazolines where the methylene moiety of the diazomethane is connected to the β -carbon atom of the starting α,β -unsaturated ketones. Therefore, this 1,3-dipolar cycloaddition is completely regioselective and the initially formed 1-pyrazolines spontaneously rearrange into their thermodynamically more stable 2-pyrazoline isomers.

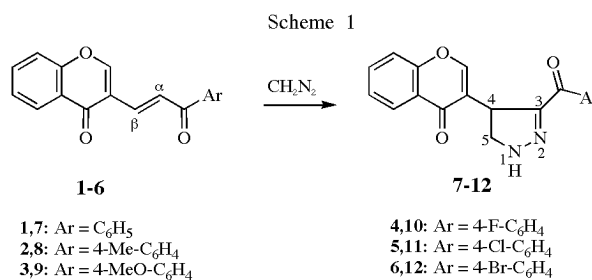
Previously we investigated the reaction of exocyclic α,β -unsaturated ketones with diazomethane in detail [14-19]. It has been concluded that this 1,3-dipolar cycloaddition of these α,β -enones is completely regioselective providing spiro-1-pyrazolines similarly to the above-mentioned α,β -unsaturated ketones. The reaction is also stereospecific, retaining the stereochemistry of the starting α,β -enones. Contrary to the above-mentioned cases, spiro-1-pyrazolines obtained from exocyclic α,β -unsaturated ketones are stable compounds which do not suffer spontaneous isomerization into the corresponding 2-pyrazolines. Our results are in harmony with those observed by others [20-22].

Pyrazolines were found to possess considerable biological and pharmacological activities. Their most important effects are antimicrobial [23], immunosuppressive [24], central nervous system [25], antiarrhythmic [26], anti-inflammatory [27], antihypertensive [28], etc. activities. For this reason, pyrazolines are useful substances in the drug

research which stimulates the efforts for the synthesis of their newer representatives. Reaction of α,β -enones with diazomethane affords a simple and convenient procedure to prepare a wide variety of pyrazolines for this purpose.

As far as the reaction of chalcones and related α,β -unsaturated ketones with diazomethane is concerned, there are conflicting data in the literature [12,13]. Our previous studies [7-10] unequivocally proved that the sole isolable product of this reaction is the appropriately substituted 2-pyrazoline. Nevertheless, the utilization of newer substrates may help to get additional information on the reaction of the α,β -enones with diazomethane. Therefore, in our present paper, the reaction of a series 3-(3-aryl-3-oxopropenyl)chromen-4-ones **1-6** with diazomethane is reported.

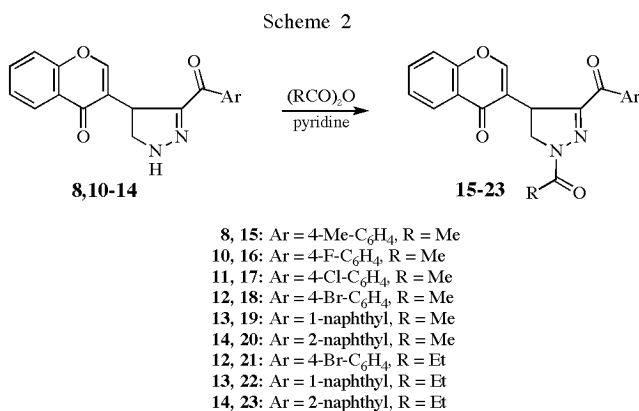
3-(3-Aryl-3-oxopropenyl)chromen-4-ones **1-6** were allowed to react with diazomethane in a 1:1 mixture of anhydrous methylene chloride and diethyl ether at *ca.* 0°. 3-Aroyl-4-(3-chromonyl)-2-pyrazolines **7-12** have been obtained as sole isolable products (Scheme 1), the structures of which have been elucidated by means of elemental analyses and spectroscopic measurements (*vide infra*).



In the ¹H nmr spectra of compounds **7-12**, the three protons attached to the C-4 and C-5 carbon atoms of the pyrazoline ring gave an ABX spin system. Both the chemical shifts and the coupling constant values (*cf.* Experimental) reveal a 2-pyrazoline structure. ¹³C chemical shift data of

the carbon atoms of the pyrazoline ring also prove the 2-pyrazoline character deduced from the ^1H nmr data. The 2-pyrazoline structure was further corroborated by their ir spectra measured in potassium bromide discs. A characteristic NH band was observed between 3232 and 3288 cm^{-1} while the C=N band was detected between 1589 and 1598 cm^{-1} . The two carbonyl bands at around 1640 and 1610 cm^{-1} also confirm the presence of an aroyl and chromonyl units in the molecule.

All these spectroscopic data prove that the 1,3-dipolar cycloaddition of the 3-(3-aryl-3-oxopropenyl)chromen-4-ones **1-6** with diazomethane is completely regioselective providing 1-pyrazolines, as initial cycloadducts which rearrange into 2-pyrazolines **7-12**, where the methylene moiety of the diazomethane is attached to the α -carbon atom of the α,β -enone. The double bond of the 3-chromonyl unit may also react with diazomethane as found by Ghosh *et al.* [29] for similar chromone derivatives. However, no traces of such cycloadducts could be detected or isolated in the case of our substrates.



As a further proof of the 2-pyrazoline structure, N-acylation of selected examples of 3-aroaryl-4-(3-chromonyl)-2-pyrazolines described in our previous [8] and present papers has also been performed. Compounds **8** and **10-14** were allowed to react with a mixture of anhydrous pyridine and acetic anhydride or propionic anhydride to afford their N-acylated derivatives **15-23** (Scheme 2). Structures of these new 2-pyrazolines have been elucidated by elemental analyses, ir and ^1H and ^{13}C nmr spectroscopic measurements (*cf.* Experimental). Moreover, molecular ions detected in their EI-ms spectra also corroborated their structures determined by the above-mentioned techniques. All these data prove that neither the 2-pyrazoline nor the chromone ring suffered any rearrangement under these acylating conditions.

In conclusion, it has been established that the 1,3-dipolar cycloaddition of 3-(3-aryl-3-oxopropenyl)chromen-4-ones with diazomethane provides 3-aroaryl-4-(3-chromonyl)-2-

pyrazolines as sole isolable products similarly to the related α,β -unsaturated ketones. N-Acylation of these 2-pyrazolines can easily be performed to get new pyrazoline derivatives for drug research

EXPERIMENTAL

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. ^1H 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, $\delta = 0.0$) at room temperature. The ir spectra (KBr discs) were obtained with a Perkin-Elmer 16 PC instrument. Mass spectra were recorded on a VG Trio-2 instrument. Elemental analyses were measured in-house with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F₂₅₄ (Merck) layer using hexane:acetone (7:3 v/v) as eluent. Starting materials **1-6, 13, 14** were synthesized according to known procedures [8, 30-32].

Synthesis of 3-Aroyl-4-(3-chromonyl)-2-pyrazolines **7-12** by the Reaction of 3-(3-Aryl-3-oxopropenyl)chromen-4-ones **1-6** with Diazomethane. General Procedure.

A mixture of 3-(3-aryl-3-oxopropenyl)chromen-4-one (**1-6**, 5.0 mmoles), diazomethane (15.0 mmoles), anhydrous methylene chloride (30.0 ml) and diethyl ether (30.0 ml) was allowed to stand in refrigerator for 48 hours, then the solvent was evaporated under reduced pressure and the residue was crystallized from methanol to obtain 3-aroaryl-4-(3-chromonyl)-2-pyrazolines **7-12** (Scheme 1).

3-Benzoyl-4-(3-chromonyl)-2-pyrazoline (**7**).

This compound was obtained as white needles in 78% yield, mp 193-194°; ir: 3232 (NH), 1636 (C=O), 1608 (C=O), 1598 (C=N) cm^{-1} ; ^1H nmr (DMSO-d_6): 3.68 (1H, dd, $J = 12.3, 3.1$ Hz, 5-H), 3.97 (1H, dd, $J = 12.3, 10.1$ Hz, 5-H), 4.68 (1H, dd, $J = 10.1, 3.1$ Hz, 4-H), 7.32-8.20 (m, 9 arom. H); ^{13}C nmr (DMSO-d_6): 40.5 (C-4), 54.8 (C-5), 153.1 (C-3), 177.2 (C=O), 187.5 (C=O).

Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_3$: C, 71.69; H, 4.43; N, 8.79. Found: C, 71.72; H, 4.41; N, 8.76.

4-(3-Chromonyl)-3-(4-methylbenzoyl)-2-pyrazoline (**8**).

This substance was isolated as white crystals in 61% yield, mp 164-165°; ir: 3246 (NH), 1640 (C=O), 1604 (C=O), 1596 (C=N) cm^{-1} ; ^1H nmr (DMSO-d_6): 2.34 (3H, s, Me), 3.54 (1H, dd, $J = 12.4, 3.0$ Hz, 5-H), 3.98 (1H, dd, $J = 12.4, 10.1$ Hz, 5-H), 4.54 (1H, dd, $J = 10.1, 3.0$ Hz, 4-H), 7.07-8.18 (m, 8 arom. H); ^{13}C nmr (DMSO-d_6): 40.7 (C-4), 54.6 (C-5), 153.9 (C-3), 176.1 (C=O), 186.1 (C=O).

Anal. Calcd. for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3$: C, 72.28; H, 4.85; N, 8.42. Found: C, 72.33; H, 4.83; N, 8.44.

4-(3-Chromonyl)-3-(4-methoxybenzoyl)-2-pyrazoline (**9**).

This compound was prepared as white needles in 75% yield, mp 108-109°; ir: 3388 (NH), 1644 (C=O), 1604 (C=O), 1598 (C=N) cm^{-1} ; ^1H nmr (DMSO-d_6): 3.62 (1H, dd, $J = 12.7, 3.2$ Hz, 5-H), 3.78 (3H, s, Me), 3.94 (1H, dd, $J = 12.7, 9.9$ Hz, 5-H), 4.66 (1H, dd, $J = 9.9, 3.2$ Hz, 4-H), 6.51-7.86 (m, 8 arom. H); ^{13}C nmr (DMSO-d_6): 25.1 (OMe), 40.6 (C-4), 55.0 (C-5), 153.2 (C-3), 176.9 (C=O), 185.7 (C=O).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.92; H, 4.65; N, 8.07.

4-(3-Chromonyl)-3-(4-fluorobenzoyl)-2-pyrazoline (**10**).

This compound was isolated as pale yellow plates in 73% yield, mp 217-218°; ir: 3258 (NH), 1636 (C=O), 1608 (C=O), 1598 (C=N) cm^{-1} ; 1H nmr (DMSO- d_6): 3.58 (1H, t, J = 12.5 Hz, 5-H), 3.98 (1H, t, J = 12.5 Hz, 5-H), 4.54 (1H, dd, J = 8.7, 4.1 Hz, 4-H), 7.24-8.16 (m, 8 arom. H); ^{13}C nmr (DMSO- d_6): 40.3 (C-4), 54.8 (C-5), 154.0 (C-3), 176.1 (C=O), 184.8 (C=O).

Anal. Calcd. for $C_{19}H_{13}FN_2O_3$: C, 67.86; H, 3.89; N, 8.33. Found: C, 67.85; H, 3.91; N, 8.30.

3-(4-Chlorobenzoyl)-4-(3-chromonyl)-2-pyrazoline (**11**).

This substance was prepared as pale yellow needles in 66% yield, mp 235-236°; ir: 3240 (NH), 1632 (C=O), 1614 (C=O), 1598 (C=N) cm^{-1} ; 1H nmr (DMSO- d_6): 3.59 (1H, t, J = 12.8 Hz, 5-H), 4.01 (1H, t, J = 12.8 Hz, 5-H), 4.56 (1H, dd, J = 8.6, 3.9 Hz, 4-H), 7.44-8.16 (m, 8 arom. H); ^{13}C nmr (DMSO- d_6): 40.7 (C-4), 54.8 (C-5), 154.1 (C-3), 176.1 (C=O), 185.0 (C=O).

Anal. Calcd. for $C_{19}H_{13}ClN_2O_3$: C, 64.69; H, 3.71; N, 7.94. Found: C, 64.71; H, 3.69; N, 7.97.

3-(4-Bromobenzoyl)-4-(3-chromonyl)-2-pyrazoline (**12**).

This compound was obtained as pale yellow needles in 89% yield, mp 232-233°; ir: 3252 (NH), 1629 (C=O), 1605 (C=O), 1589 (C=N) cm^{-1} ; 1H nmr (DMSO- d_6): 3.58 (1H, t, J = 12.8 Hz, 5-H), 4.02 (1H, t, J = 12.8 Hz, 5-H), 4.54 (1H, dd, J = 8.8, 4.1 Hz, 4-H), 7.47-8.17 (m, 8 arom. H); ^{13}C nmr (DMSO- d_6): 40.7 (C-4), 54.8 (C-5), 154.1 (C-3), 176.1 (C=O), 185.2 (C=O).

Anal. Calcd. for $C_{19}H_{13}BrN_2O_3$: C, 57.45; H, 3.30; N, 7.05. Found: C, 57.48; H, 3.28; N, 7.08.

N-Acylation of 3-Aroyl-4-(3-chromonyl)-2-pyrazolines **8**, **10-14** in a Mixture of Anhydrous Pyridine and Acetic anhydride or Propionic anhydride. General Procedure.

A mixture of 3-aryol-4-(3-chromonyl)-2-pyrazoline (**8**, **10-14**, 2.0 mmoles), anhydrous pyridine (5.0 ml) and acetic anhydride (10.0 ml) or propionic anhydride (10.0 ml) was heated at 80° for 3 hours, then poured into water. The precipitate was collected by filtration, washed with water, and crystallized from methanol to afford 2-pyrazolines **15-23** (Scheme 2).

1-Acetyl-4-(3-chromonyl)-3-(4-methylbenzoyl)-2-pyrazoline (**15**).

This compound was isolated as white plates in 71% yield, mp 130-131°; ir: 1682 (C=O), 1644 (C=O), 1606 (C=O), 1588 (C=N) cm^{-1} ; 1H nmr (CDCl₃): 2.43 (3H, s, Me), 2.49 (3H, s, Me), 4.09 (1H, dd, J = 12.6, 3.9 Hz, 5-H), 4.34 (1H, t, J = 12.6 Hz, 5-H), 4.60 (1H, dd, J = 8.5, 3.9 Hz, 4-H), 7.24-8.18 (m, 8 arom. H); ^{13}C nmr (CDCl₃): 21.5 (Me), 29.5 (Me), 43.5 (C-4), 50.1 (C-5), 154.1 (C-3), 170.4 (C=O), 176.9 (C=O), 187.4 (C=O); EI-*ms*: m/z 374 (M⁺).

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.84; N, 7.48. Found: C, 70.61; H, 4.83; N, 7.50.

1-Acetyl-4-(3-chromonyl)-3-(4-fluorobenzoyl)-2-pyrazoline (**16**).

This substance was isolated as white needles in 69% yield, mp 202-203°; ir: 1682 (C=O), 1648 (C=O), 1610 (C=O), 1598

(C=N) cm^{-1} ; 1H nmr (CDCl₃): 2.45 (3H, s, Me), 4.07 (1H, dd, J = 12.0, 4.0 Hz, 5-H), 4.34 (1H, t, 12.0 Hz, 5-H), 4.57 (1H, dd, J = 8.9, 4.0 Hz, 4-H), 7.06-8.26 (m, 8 arom. H); ^{13}C nmr (CDCl₃): 21.2 (Me), 43.5 (C-4), 50.2 (C-5), 152.2 (C-3), 170.3 (C=O), 177.0 (C=O), 186.2 (C=O); EI-*ms*: m/z 378 (M⁺).

Anal. Calcd. for $C_{21}H_{15}FN_2O_4$: C, 66.67; H, 3.99; N, 7.40. Found: C, 66.65; H, 3.98; N, 7.42.

1-Acetyl-3-(4-chlorobenzoyl)-4-(3-chromonyl)-2-pyrazoline (**17**).

This compound was isolated as pale yellow needles in 67% yield, mp 212-213°; ir: 1684 (C=O), 1644 (C=O), 1610 (C=O), 1586 (C=N) cm^{-1} ; 1H nmr (CDCl₃): 2.44 (3H, s, Me), 4.06 (1H, dd, J = 11.7, 4.1 Hz, 5-H), 4.33 (1H, t, J = 11.7 Hz, 5-H), 4.54 (1H, dd, J = 8.7, 4.1 Hz, 4-H), 7.27-8.15 (m, 8 arom. H); ^{13}C nmr (CDCl₃): 21.2 (Me), 43.5 (C-4), 50.3 (C-5), 154.2 (C-3), 170.4 (C=O), 177.0 (C=O), 186.3 (C=O); EI-*ms*: m/z 394 (M⁺).

Anal. Calcd. for $C_{21}H_{15}ClN_2O_4$: C, 63.88; H, 3.83; N, 7.09. Found: C, 63.85; H, 3.84; N, 7.11.

1-Acetyl-3-(4-bromobenzoyl)-4-(3-chromonyl)-2-pyrazoline (**18**).

This substance was prepared as white plates in 84% yield, mp 190-191°; ir: 1682 (C=O), 1646 (C=O), 1610 (C=O), 1582 (C=N) cm^{-1} ; 1H nmr (CDCl₃): 2.44 (3H, s, Me), 4.06 (1H, dd, J = 12.5, 4.0 Hz, 5-H), 4.34 (1H, t, J = 12.5 Hz, 5-H), 4.54 (1H, dd, J = 8.5, 4.0 Hz, 4-H), 7.29-8.17 (m, 8 arom. H); ^{13}C nmr (CDCl₃): 21.2 (Me), 43.5 (C-4), 50.3 (C-5), 154.2 (C-3), 170.4 (C=O), 177.0 (C=O), 186.8 (C=O); EI-*ms*: m/z 440/442 (M⁺).

Anal. Calcd. for $C_{21}H_{15}BrN_2O_4$: C, 57.42; H, 3.44; N, 6.37. Found: C, 57.44; H, 3.42; N, 6.39.

1-Acetyl-4-(3-chromonyl)-3-(1-naphthoyl)-2-pyrazoline (**19**).

This compound was isolated as white needles in 69% yield, mp 155-156°; ir: 1680 (C=O), 1644 (C=O), 1610 (C=O), 1592 (C=N) cm^{-1} ; 1H nmr (CDCl₃): 2.28 (3H, s, Me), 4.14 (1H, dd, J = 12.6, 3.7 Hz, 5-H), 4.37 (1H, t, 12.6, 5-H), 4.64 (1H, dd, J = 8.8, 3.7 Hz, 4-H), 7.27-8.40 (m, 11 arom. H); ^{13}C nmr (CDCl₃): 21.1 (Me), 43.3 (C-4), 50.7 (C-5), 154.5 (C-3), 170.6 (C=O), 177.2 (C=O), 190.7 (C=O); EI-*ms*: m/z 410 (M⁺).

Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.82. Found: C, 73.19; H, 4.44; N, 6.80.

1-Acetyl-4-(3-chromonyl)-3-(2-naphthoyl)-2-pyrazoline (**20**).

This substance was obtained as pale yellow needles in 63% yield, mp 149-150°; ir: 1674 (C=O), 1644 (C=O), 1609 (C=O), 1684 (C=N) cm^{-1} ; 1H nmr (CDCl₃): 2.49 (3H, s, Me), 4.12 (1H, dd, J = 12.3, 3.4 Hz, 5-H), 4.38 (1H, t, J = 12.3 Hz, 5-H), 4.63 (1H, dd, J = 8.5, 3.4 Hz, 4-H), 7.26-8.87 (m, 11 arom. H); ^{13}C nmr (CDCl₃): 21.3 (Me), 43.7 (C-4), 50.3 (C-5), 154.2 (C-3), 171.0 (C=O), 177.1 (C=O), 187.6 (C=O); EI-*ms*: m/z 410 (M⁺).

Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.82. Found: C, 73.12; H, 4.40; N, 6.85.

3-(4-Bromobenzoyl)-4-(3-chromonyl)-1-propionyl-2-pyrazoline (**21**).

This compound was prepared as white plates in 76% yield, mp 142-143°; ir: 1680 (C=O), 1644 (C=O), 1610 (C=O), 1582 (C=N) cm^{-1} ; 1H nmr (CDCl₃): 1.26 (3H, t, J = 7.3 Hz,

CH_2CH_3), 2.81 (2H, m, CH_2CH_3), 4.06 (1H, dd, $J = 12.5, 3.9$ Hz, 5-H), 4.34 (1H, t, $J = 12.5$ Hz, 5-H), 4.53 (1H, dd, $J = 8.5, 3.9$ Hz, 4-H), 7.28-8.13 (m, 8 arom. H); ^{13}C nmr (CDCl_3): 8.6 and 27.0 (Et), 43.1 (C-4), 50.5 (C-5), 154.2 (C-3), 173.8 (C=O), 176.9 (C=O), 186.8 (C=O); EI-*ms*: m/z 452/454 (M^+).

Anal. Calcd. for $\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{O}_4$: C, 58.29; H, 3.78; N, 6.18. Found: C, 58.32; H, 3.76; N, 6.20.

4-(3-Chromonyl)-3-(1-naphthoyl)-1-propionyl-2-pyrazoline (22).

This compound was isolated as pale yellow plates in 68% yield, mp 116-117°; ir: 1678 (C=O), 1644 (C=O), 1610 (C=O), 1592 (C=N) cm^{-1} ; ^1H nmr (CDCl_3): 1.16 (3H, t, $J = 7.5$ Hz, CH_2CH_3), 2.69 (2H, m, CH_2CH_3), 4.12 (1H, dd, $J = 11.8, 3.9$ Hz, 5-H), 4.38 (1H, t, $J = 11.8$ Hz, 5-H), 4.61 (1H, dd, $J = 8.7, 3.9$ Hz, 4-H), 7.33-8.41 (m, 11 arom. H); ^{13}C nmr (CDCl_3): 8.5 and 26.9 (Et), 42.9 (C-4), 50.9 (C-5), 154.3 (C-3), 174.0 (C=O), 177.1 (C=O), 190.7 (C=O); EI-*ms*: m/z 424 (M^+).

Anal. Calcd. for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_4$: C, 73.57; H, 4.75; N, 6.59. Found: C, 73.61; H, 4.73; N, 6.61.

4-(3-Chromonyl)-3-(2-naphthoyl)-1-propionyl-2-pyrazoline (23).

This substance was prepared as pale yellow needles in 67% yield, mp 162-163°; ir: 1678 (C=O), 1640 (C=O), 1612 (C=O), 1584 (C=N) cm^{-1} ; ^1H nmr (CDCl_3): 1.29 (3H, t, $J = 11.4$ Hz, CH_2CH_3), 2.86 (2H, m, CH_2CH_3), 4.12 (1H, dd, $J = 11.5, 4.0$ Hz, 5-H), 4.38 (1H, t, $J = 11.7, 5\text{-H}$), 4.62 (1H, dd, $J = 8.5, 4.0$ Hz, 4-H), 7.27-8.21 (m, 11 arom. H); ^{13}C nmr (CDCl_3): 8.7 and 27.1 (Et), 43.3 (C-4), 50.4 (C-5), 154.2 (C-3), 173.9 (C=O), 177.0 (C=O), 187.6 (C=O); EI-*ms*: m/z 424 (M^+).

Anal. Calcd. for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_4$: C, 73.57; H, 4.75; N, 6.59. Found: C, 73.54; H, 4.76; N, 6.57.

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