Behavior of 3(2-Pyridinylmethylene)-5-aryl-2(3*H*)-furanones and 3(3-Pyridinylmethylene)-5-aryl-2(3*H*)-furanones as Alkylating Agents: A Comparative Study

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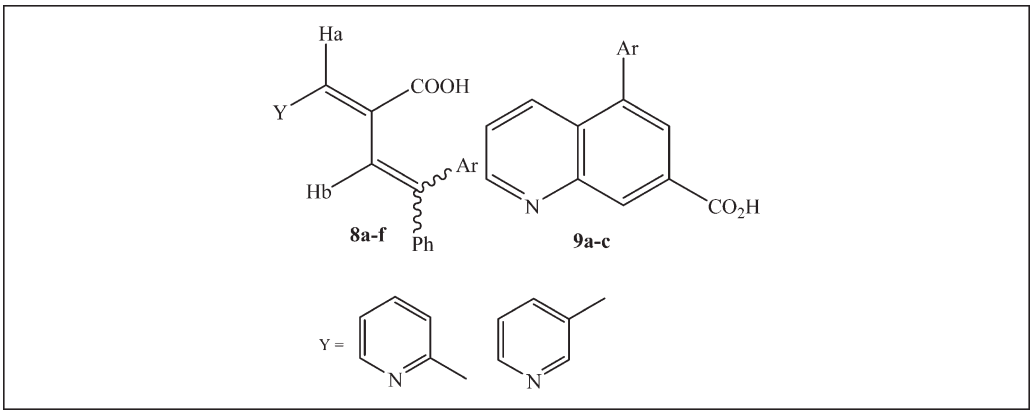

3(2-pyridinylmethylene)-5-aryl-2(3*H*)-furanones and 3(3-pyridinylmethylene)-5-aryl-2(3*H*)-furanones were prepared as a mixture of (E) and (Z) stereoisomers by condensing pyridine-2-carboxaldehyde and pyridine-3-carboxaldehyde with 3-aroylpropionic acids. The reaction of the furanones **6** and **7** with anhydrous aluminium chloride in benzene led to the formation of 4,4-diaryl-1-(2-pyridinyl)but-1,3-diene (**8**) and 4,4-diaryl-1-(3-pyridinyl)but-1,3-diene (**9**) as mixtures of geometrical (E,E- and E,Z-) stereoisomers *via* an intermolecular alkylation mode. When the reaction was carried out in tetrachloroethane as a solvent, the reaction of **6** gave 5-arylquinoline-7-carboxylic acid *via* intramolecular alkylation mode. This may be considered as a novel method for the synthesis of quinoline derivatives.

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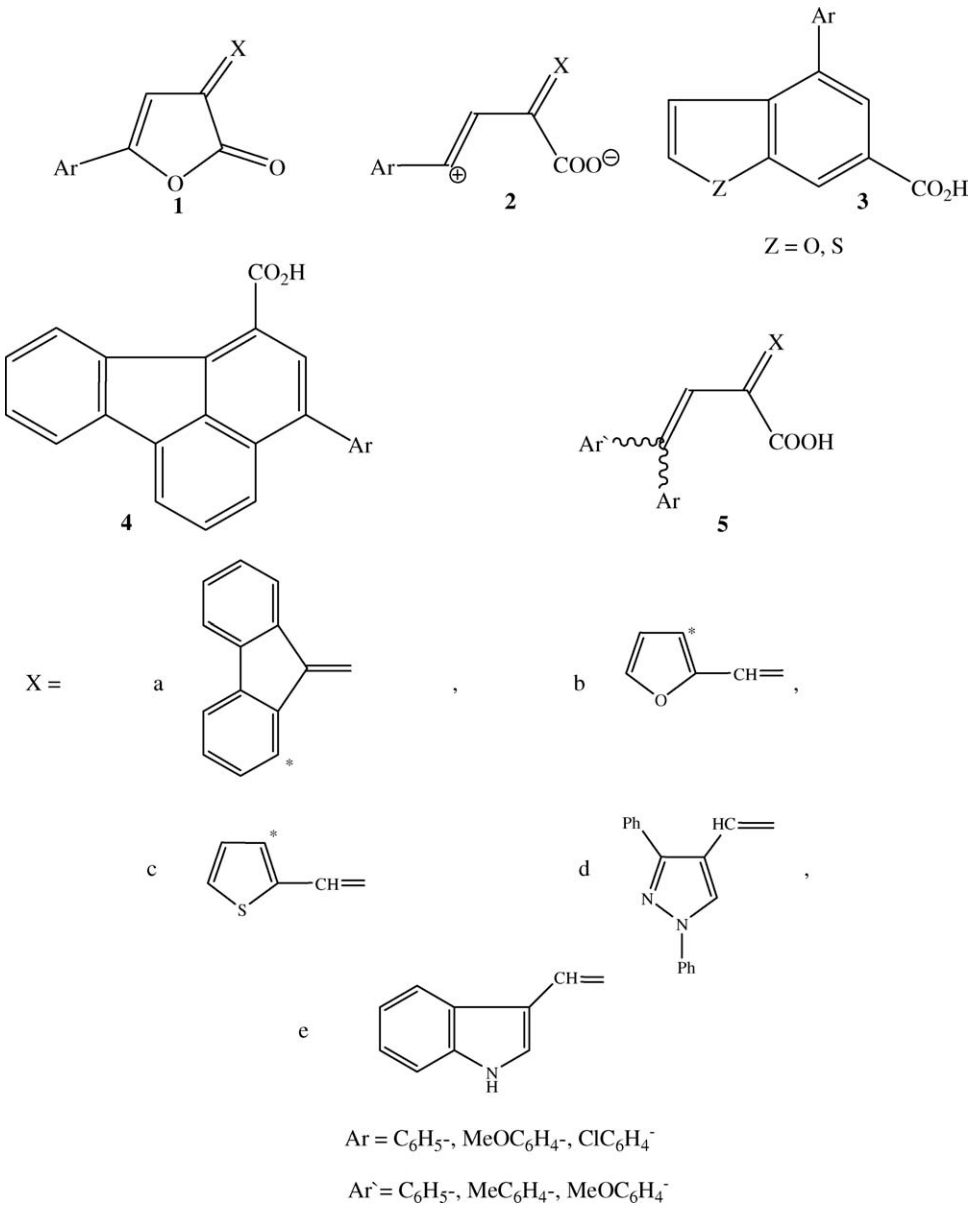
INTRODUCTION

Our research group was interested in studying the behavior of 2(3*H*)-furanones **1** as alkylating agents. It was found that the Lewis acid, $AlCl_3$, affects carbon-oxygen bond breaking of the furanone ring to give a resonance stabilized carbocation **2**. The reaction is completed through two distinct routes: either the carbocation formed attacks the o-position (*) of X group situated at position 3 intramolecularly or the solvent attacks the carbocation to give the intermolecular reaction product. It was found that the reaction course is affected by two main factors namely: (a) the nature of X group; thus when X was 2-furyl or 2-thienyl, the corresponding benzofuran [1] and benzothiophene [2] carboxylic acids **3** were formed, respectively. However, when X was pyrazolyl [3] or indolyl [4] groups, the products of intermolecular alkylations, butadienecarboxylic acids **5d and e**, were formed exclusively. (b) The nucleophilicity of the solvent, thus when X was fluorenyl and the reaction was conducted in benzene, fluoranthene carboxylic acids **4** were obtained as the products of intramolecular alkylation [5]. However, using toluene or anisole as solvents changed the mode of the reaction from intra- to intermolecular with the formation of the corresponding butadienecarboxylic acids **5a** [6].

It was of interest to the author to investigate the behavior of two newly synthesized 2(3*H*)-furanones namely 5-aryl-3(2-pyridinylmethylene)-2(3*H*)-furanones **6** and 5-aryl-3-(3-pyridinylmethylene)-2(3*H*)-furanones **7** to verify the possibility of intramolecular alkylation mode at positions 2 and 3 of the pyridine nucleus.

RESULTS AND DISCUSSION

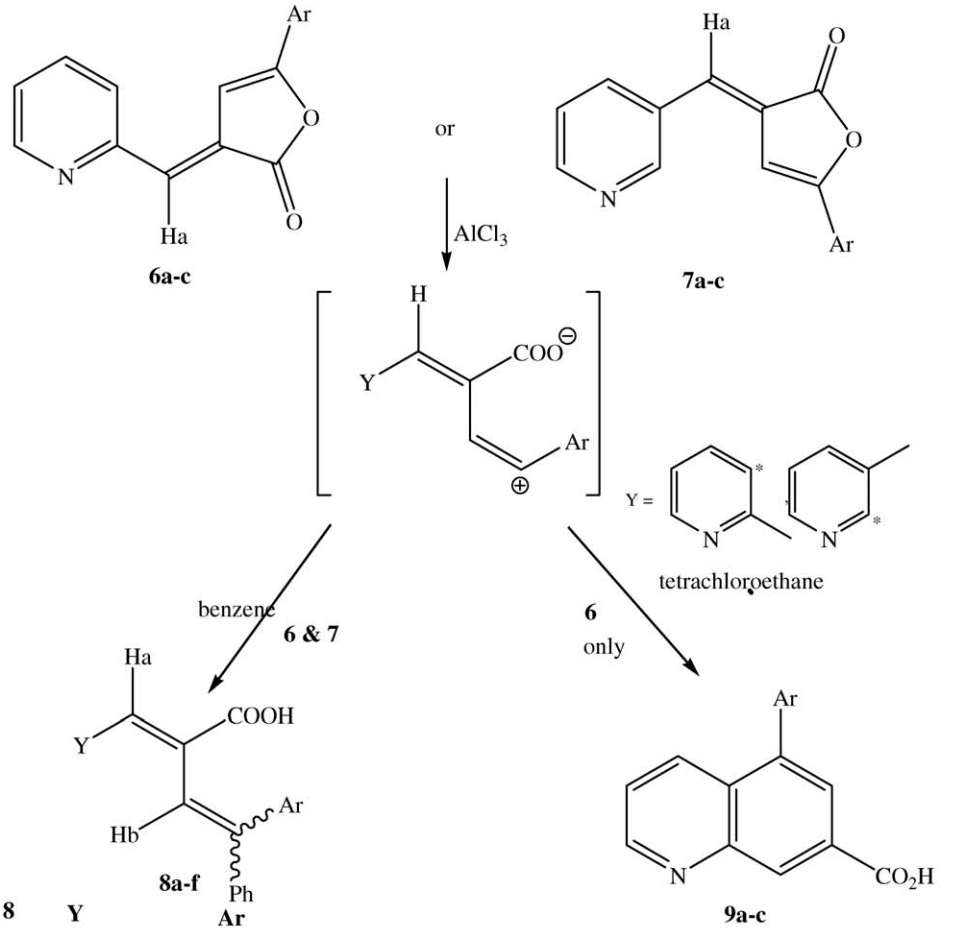
In this investigation, some 2(3*H*)-furanones bearing 2-pyridinyl and 3-pyridinyl groups at position 3 were synthesized with a study of their behavior as alkylating agents. Thus, pyridine-2-carboxaldehyde and pyridine-3-carboxaldehyde condense with 3-aroylpropionic acids applying the procedure described by Khan and Rastogi



[7], to give the corresponding furanones **6** and **7**. The structures of the furanones were inferred from their analytical and spectral data (*cf.*, Experimental section). The infrared spectra of these products show $\nu_{C=O}$ at 1775 cm^{-1} characteristic of the carbonyl moiety of 2(3*H*)-furanones. The ^{1}H-NMR spectra of compounds **6** and **7** showed two singlets for the olefinic proton Ha and two singlets for OCH_3 protons in case of **6c** and **7c**. This showed that compounds **6** and **7** were formed as a mixture of two geometrical (E- and Z-) isomers in which the E-isomers predominates. The furnaones **6** and **7** reacted with $AlCl_3$ in excess benzene to give the butadienecarboxylic acids **8a–f** *via* intermolecular alkylation mode in which the solvent benzene undergoes nucleophilic attack on the intermediate carbocation (Scheme 1). This may be attributed to the small charge density on pyridinyl group compared with the solvent(benzene). The structure of these acids was inferred from their analytical and spectral data (*c.f.*, Experimental section). The analytical and mass spectroscopic data indicate the incorporation of phenyl group.

The ^{1}H-NMR spectra of compound **8b,c,e,f** showed two singlets for the olefinic protons and two singlets for OCH_3 protons in case of **8c,f**. This showed that compounds **8b,c,e,f** exist as a mixture of two geometrical (E,E) and (E,Z) stereoisomers in which the latter predominates due to steric factor. The deshielding of the olefinic proton Hb in case of (E,E)-isomers when

Scheme 1



8	Y	Ar
a	2-pyridinyl	Ph
b	2-pyridinyl	4-ClC_6H_4
c	2-pyridinyl	4-$OMeC_6H_4$
d	3-pyridinyl	Ph
e	3-pyridinyl	4-ClC_6H_4
f	3-pyridinyl	4-$OMeC_6H_4$

Ar = a, Ph; b, 4-ClC_6H_4; c, 4-$OMeC_6H_4$

compared with the (E,Z)-counterpart can be rationalized in terms of the ring current of the more activated aryl groups.

Among the compounds of a quinoline series quinolinecarboxylic acids attract the attention of researchers because of their close structure resemblance to alkaloids. Cinchophen (2-phenylquinoline-4-carboxylic acid) was introduced in 1910 as an analgesic, antipyretic, and uricosuric drug [8]. These reports initiated the interest of the author to conduct the above reaction in tetrachloroethane as solvent. Thus, when the reaction of furanones **6** and **7** with aluminium chloride was carried out in tetrachloroethane as solvent, 5-arylquinoline-7-carboxylic acids **9a–c** were isolated in case of **6**. The formation of **9** may be rationalized on the basis of attack of the carbocation intermediate on position 3 of the pyridine moiety.

This reaction may be considered as a versatile route for the synthesis of quinolinecarboxylic acid derivatives. However in case of **7**, the reaction failed and the unreacted furanones were isolated. The failure of **7** to give the intramolecular products, quinolinecarboxylic acids is not unexpected. It is well established that position 2 in the pyridine nucleus is less susceptible to attack by electrophilic reagents than position 3.The structures of **9a–c** were inferred from their analytical and spectral data (*c.f.*, Experimental section).

EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were carried out at the Microanalytical unit, Cairo University. IR spectra were measured on a Unicam SP-1200 spectrometer using KBr wafer technique. ^{1}H-NMR spectra were measured in DMSO-d_6 on a Varian plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP1000 EX instrument operating at 70 eV.

General procedure for the preparation of 5-aryl-3-(2-pyridinylmethylene)-2(3*H*)-furanones 6a–c and 5-aryl-3-(3-pyridinylmethylene)-2(3*H*)-furanones 7a–c.

i. (Chlorosulfinyloxy)-*N*,*N*-dimethylmethaniminium chloride (the cyclodehydrating agent): Into a 25-mL dropping funnel containing benzene (5 mL) and *N*,*N*-dimethylformamide (1 mL, 10.2 mmol), followed by thionyl chloride (0.8 mL, 11 mmol). After 5 min, the two phases were separated, and the reagent (lower layer) was used in the next step.

ii. To a stirred solution of 3-aroylpropionic acid (10 mmol) in dichloromethane (25 mL) at 0°C, the cyclodehydrating agent (10 mmol) prepared in step (i) was added. Stirring was continued for 15 min. Pyridine-2-carboxaldehyde or pyridine-3-carboxaldehyde (10 mmol) was added followed by triethylamine (30 mmol) in dichloromethane (15 mL). The resulting mixture was stirred at room temperature for 5 h. The organic layer was washed with water (2 × 50 mL) and dried over anhydrous sodium sulfate. Removal of the solvent left a residue that formed golden yellow crystals, which were recrystallized from ethanol to give 5-aryl-3-(2-pyridinylmethylene)-2(3*H*)-furanone **6** or 5-aryl-3-(3-pyridinylmethylene)-2(3*H*)-furanone **7**, respectively.

5-Phenyl-3-(2-pyridinylmethylene)-2(3H)-furanone (6a). 90% yield, m.p. 218–219°C.IR: ν_{max} 1770 (C=O), 1650 (C=N), 1600 (C=C).^{1}H-NMR (DMSO-d_6) (E-form, 55%) δ 6.53–7.94 (m, 10H, ArH), 8.60 (s, 1H, H_a); (Z-form, 45%) δ 8.56 (s, 1H, H_a). MS: *m/z* (%) 249 (M^+, 3), 161 (30), 106 (9), 105 (100), 77(26), 51 (9). Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.39; H, 4.01; N, 5.94.

5-(4-Chlorophenyl)-3-(2-pyridinylmethylene)-2(3H)-furanone (6b). 83% yield, m.p. 230–231°C. IR: ν_{max} 1769 (C=O),1650 (C=N), 1610 (C=C).^{1}H-NMR (DMSO-d_6) (E-form, 60%) δ 6.02–7.63 (m, 9H, ArH), 8.80 (s, 1H, H_a); (Z-form, 40%) δ 8.77 (s, 1H, H_a). MS: *m/z* (%) 285 (1.1), 283 (M^+, 3.1), 141 (35), 193 (100), 93 (14), 75 (12). Anal. Calcd. for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.59; H, 3.27; N, 5.02.

5-(4-Methoxyphenyl)-3-(2-pyridinylmethylene)-2(3H)-furanone (6c). 90% yield, m.p. 225–227°C. IR: ν_{max} 1753 (C=O),1645 (C=N), 1605 (C=C).^{1}H-NMR (DMSO-d_6) (E-form, 70%) δ 3.02 (s, 3H, OCH_3), 6.37–8.01 (m, 9H, ArH), 8.62 (s, 1H, Ha); (Z-form, 30%) δ 8.59 (s, 1H, Ha). MS: *m/z* (%) 279 (M^+, 6), 141 (20), 139 (58), 135 (100), 93 (8), 77 (14). Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 74.01; H, 4.40; N, 5.31.

5-Phenyl-3-(3-pyridinylmethylene)-2(3H)-furanone (7a). 87% yield, m.p. 186–187°C. IR: ν_{max} 1775 (C=O), 1625 (C=N), 1599 (C=C).^{1}H-NMR (DMSO-d_6) (E-form, 60%) δ = 6.22–7.30 (m, 10H, ArH), 8.98 (s, 1H, H_a); (Z-form, 40%) δ = 8.94 (s, 1H, H_a). MS: *m/z* 249 (M^+, 4), 193 (6), 144 (67), 105 (100), 77 (39), 51 (12). Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.89; H, 5.01; N, 5.74.

5-(4-Chlorophenyl)-3-(3-pyridinylmethylene)-2(3H)-furanone (7b). 85% yield, m.p. 244–246°C. IR: ν_{max} 1762 (C=O), 1643 (C=N), 1597 (C=C).^{1}H-NMR (DMSO-d_6) (E-form, 60%) δ = 6.90–7.89 (m, 9H, ArH), 8.39 (s, 1H, H_a); (Z-form, 40%) δ = 8.30 (s, 1H, H_a). MS: *m/z* 285 (0.45), 283 (M^+, 1.1), 144 (79), 139 (100), 93 (14), 75 (11). Anal. Calcd. for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.43; H, 3.20; N, 5.19.

5-(4-Methoxyphenyl)-3-(3-pyridinylmethylene)-2(3H)-furanone (7c). 80% yield, m.p. 198–200°C. IR: ν_{max} 1760 (C=O), 1624 (C=N), 1596 (C=C).^{1}H-NMR (DMSO-d_6) (E-form, 78%) δ = 3.89 (s, 3H, OCH_3), 6.62–8.27 (m, 9H, ArH), 8.78 (s, 1H, H_a); (Z-form, 22%) δ = 8.73 (s, 1H, Ha). MS: *m/z* 279 (M^+, 3), 144 (36), 135 (100), 77 (14). Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.65; H, 4.32; N, 5.39.

General procedure for the preparation of 4,4-diaryl-1-(2-pyridinyl)but-1,3-diene-2-carboxylic acids (8a–c) and 4,4-diaryl-1-(3-pyridinyl)but-1,3-diene-2-carboxylic acids (8d–f). To a stirred mixture of anhydrous $AlCl_3$ (0.03 mole) in dry benzene (100 mL), a solution of the furanone **6** or **7** in benzene was added dropwise at 10–20°C. After complete addition, the reaction mixture was stirred at room temperature for an additional 15 h. The complex formed was decomposed with 15% aqueous HCl and then steam-distilled to remove the excess of benzene. The solid remaining was filtered off, dissolved in aqueous sodium carbonate (25 mL, 20%), cooled well, and reprecipitated by dropwise addition of conc. HCl. The solid product obtained was recrystallized from benzene/ethanol to give 4,4-diaryl-1-(2-pyridinyl)but-1,3-diene-2-carboxylic acids (**8a–c**) in case of **6** and 4,4-diaryl-1-(3-pyridinyl)but-1,3-diene-2-carboxylic acids (**8d–f**) in case of **7**.

4,4-Diphenyl-1-(2-pyridinyl)but-1,3-diene-2-carboxylic acid (8a). Yellowish-white (30% yield), m.p. 260–261°C. IR: ν_{max} 3200–3500 (OH), 1698 (C=O), 1653 (C=N), 1590 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.97 (s, 1H, H_a), 7.14–7.96 (m, 14H, ArH), 8.60 (s, 1H, H_b), 12.82 (br.s, 1H, OH, exchangeable). MS: *m/z* (%) 327 (M^+, 12), 284 (52), 240 (30), 210 (46), 143 (35), 78 (100). Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.23; H, 5.71; N, 4.47.

4-Phenyl-4-(4-chlorophenyl)-1-(2-pyridinyl)but-1,3-diene-2-carboxylic acid (8b). Yellowish white crystals (35% yield),

m.p. 279–280°C. IR: ν_{max} 2900–3450 (OH), 1692 (C=O), 1630 (C=N), 1610 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6) (E,Z-form 55%): δ 6.37 (s, 1H, H_a), 7.02–7.98 (m, 13H, ArH), 8.37 (s, 1H, H_b), 12.20 (br.s, 1H, OH, exchangeable). (E,E-form, 45%), δ 8.34 (s, 1H, H_b). MS: *m/z* (%) 363 (7), 361 (M^+, 18), 163 (25), 185 (17), 130 (67), 78 (100). Anal. Calcd. for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87. Found: C, 72.81; H, 4.03; N, 3.52.

4-Phenyl-4-(4-methoxyphenyl)-1-(2-pyridinyl)but-1,3-diene-2- carboxylic acid (8c). Yellow crystals (30% yield), m.p. 320–321°C. IR: ν_{max} 3150–3420 (OH), 1702 (C=O), 1645 (C=N), 1602 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6) (E,Z-form 57%): δ 3.90 (s, 3H, OCH_3), 6.62 (s, 1H, H_a), 6.82–7.91 (m, 13H, ArH), 8.21 (s, 1H, H_b), 12.50 (br.s, 1H, OH, exchangeable). (E,E-form, 43%), δ 3.92 (s, 3H, OCH_3), 8.24 (s, 1H, H_b). MS: *m/z* (%) 357 (M^+, 27), 340 (30), 250 (30), 180 (12), 141 (42), 130 (54), 78 (100). Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.81; H, 5.60; N, 3.48.

4,4-Diphenyl-1-(3-pyridinyl)but-1,3-diene-2-carboxylic acid (8d). Yellowish white crystals (32% yield), m.p. 354–355°C. IR: ν_{max} 3250–3445 (OH), 1701 (C=O), 1630 (C=N), 1600 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.83 (s, 1H, H_a), 6.93–8.07 (m, 14H, ArH), 8.35 (s, 1H, H_b), 12.57 (br.s, 1H, OH, exchangeable). MS: *m/z* (%) 327 (M^+, 70), 291 (31), 276 (25), 253 (70), 210 (20), 78 (100). Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 79.93; H, 5.49; N, 3.95.

4-Phenyl-4-(4-chlorophenyl)-1-(3-pyridinyl)but-1,3-diene-2-carboxylic acid (8e). Yellow crystals (35% yield), m.p. 327–328°C. IR: ν_{max} 3290–3510 (OH), 1705 (C=O), 1650 (C=N), 1600 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6) (E,Z-form 60%): δ 6.29 (s, 1H, H_a), 6.98–7.87 (m, 13H, ArH), 8.19 (s, 1H, H_b), 12.59 (br.s, 1H, OH, exchangeable). (E,E-form, 40%), δ 8.17 (s, 1H, H_b). MS: *m/z* (%) 363 (20), 361 (M^+, 55), 212 (40),167 (20), 173 (30), 130 (70), 78 (100). Anal. Calcd. for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87. Found: C, 73.41; H, 4.63; N, 4.07.

4-Phenyl-4-(4-methoxyphenyl)-1-(3-pyridinyl)but-1,3-diene-2-carboxylic acid (8f). Yellow crystals (25% yield), m.p. 301–303°C. IR: ν_{max} 3210–3490 (OH), 1705 (C=O), 1647 (C=N), 1595 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6) (E,Z-form 53%): δ 3.90 (s, 3H, OCH_3), 6.70 (s, 1H, Ha), 6.92–8.10 (m, 13H, ArH), 8.23 (s, 1H, H_b), 12.53 (br.s, 1H, OH, exchangeable). (E,E-form, 47%), δ 3.93 (s, 3H, OCH_3), 8.25 (s, 1H, H_b). Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 78.01; H, 4.99; N, 3.69.

General procedure for the reaction of the furanones 6 and 7 with anhydrous $AlCl_3$ in tetrachloroethane. The reaction was carried out as described in the previous experiment by using tetrachloroethane instead of benzene. The product in case of **7** was shown by direct comparison (m.p, mixed m.p and TLC) to be the unreacted furanones but in case of **6** gave 5-arylquinonline-7-carboxylic acids **9**.

5-Phenylquinonline-7-carboxylic acid (9a). Yellow crystals (35% yield), m.p. 250–252°C. IR: ν_{max} 3300–3500 (OH), 1703 (C=O), 1640 (C=N), 1605 (C=C). ^{1}H-NMR 7.22–8.98 (m, 10H, ArH), 13.2 (br.s, 1H, OH, exchangeable). MS: *m/z* (%) 249 (M^+,17), 237(23),232(45),205(40),172(15)128(100), 77(32). Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.73; H, 4.90; N, 5.81.

5-(4-Chlorophenyl)quinonline-7-carboxylic acid (9b). Yellow crystals, (35% yield), m.p. 289–290°C. IR: ν_{max} 3350–3500 (OH), 1695 (C=O), 1628 (C=N), 1600 (C=C). ^{1}H-NMR δ 6.98–7.82 (m, 9H, ArH), 13.25 (br.s, 1H, OH, exchangeable). MS: *m/z* (%) 285(5.3), 283(M^+,14.9),266(30),238(19), 128(100)120(37). Anal. Calcd. for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.39; H, 3.90; N, 4.65.

5-(4-Methoxyphenyl)quinonline-7-carboxylic acid (9c). Yellow crystals (30% yield), m.p. 280–282°C. IR: ν_{max} 3250–3400 (OH), 1698 (C=O), 1650 (C=N), 1598 (C=C). ^{1}H-NMR δ 3.92 (s, 3H, OCH_3), 7.10–8.32 (m, 9H, ArH), 12.95 (br.s, 1H, OH,exchangeable). MS: *m/z*(%) 279(M^+,7),262(40), 248(15), 235(18), 128(100),77(56). Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.90; H, 5.01; N, 5.21.

REFERENCES AND NOTES

[1] Hashem, A. I. J Prakt Chem 1977, 319, 689.

[2] Hashem, A. I.; Elkousy, S. M.; ElTorgoman, A. M.; El-Basiouny, A. E. Int J Chem 1991, 2, 87.

[3] Hashem, A. I.; Kandeel, K. A.; Youssef, A. S. A.; Abou-Elmagd, W. S. I. J Chem Res 2006, 315.

[4] Abou-Elmagd, W. S. I. J Chem Res 2007, 305.

[5] Hashem, A. I.; Ismail, Z. M. Indian J Chem 1974, 12, 902.

[6] Hashem, A. I.; Eid, E. E. Indian J Chem 1978, 16(B), 502.

[7] Khan, R. H.; Rastogi, R. C. J Chem Res 1991, 260.

[8] http://en.wikipedia.org/wiki/Cinchophen (accessed December 2010).