Conversion of 3-Carbethoxy-4-methyl Coumarin Derivatives into Several New Annelated Coumarin Derivatives

BAKEER, Hadeer Mohammed *

Department of Chemistry, Faculty of Science at El-Fayoum, Cairo University, El-Fayoum, Egypt

The reaction of ethyl esters of 4-methyl-2-oxo-2*H*-1-benzo (naphtho) pyran-3-carboxylic acids (1) with aromatic aldehydes in the presence of piperidine yielded 4-styryl-3-carboxamidopiperidyl coumarin derivatives 4. The reaction of hydrazine hydrate with 1 gave acetophenone hydrozone derivatives 5 and acetophenone azine derivatives 6. The reaction of 1 with primary amines afforded compounds 7—9. And the treatment of 1a with Grignard reagents afforded 3-aroyl-4-methyl coumarin derivatives 10.

Keywords coumarin derivative, condensation, Grignard addition

Introduction

Coumarin and its annelated derivatives are reported to possess significant antibacterial,[1] coronary dilatory[2] and hybothermal[3,4] activities. Therefore, it became of interest to synthesize new derivatives of these compounds with expected biological activities. The use of the readily obtainable 3-ethoxycarbonyl coumarin derivatives seemed to be a logic and easy route for the synthesis.

The condensation of α,β-unsaturated ester containing a methyl group at β-position with aromatic aldehydes and ketones leads directly to the corresponding 2,4-dienoic acids.[5-7] It was previously reported[8,9] that the methyl group at the β-position of α,β-unsaturated ester could react with aromatic aldehydes and ketones. Ivanov *et al*.[5-11] found that the ethyl ester of 4-methyl-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (**1a**) upon heating at about 170 ℃ in the presence of sodium amide in hexamethyl phosphoric triamide (HMPT), reacted not only with aromatic aldehydes and ketones but also with aldehydes and ketones containing α-hydrogen atoms such as acetaldehyde, cyclohexanone or acetophenone.[11] In all cases, however, instead of the expected lactone-acids **2**, the corresponding 6′-substituted-2,2′-dioxo-5′,6′-dihydro-2*H*,2′*H*-pyrano [3,4-*c*]-1-benzopyrans (**3**) have been obtained.

In continuation of our research program,[12-15] we found that the same condensation could be carried out with the ethyl ester of 4-methyl coumarin derivatives **1a** and **1b**, as well when heating at 160 ℃ with aromatic aldehydes (*p*-anisaldehyde, *N*,*N*-dimethyl-*p*-aminobenzaldehyde and *p*-nitrobenzaldehyde) in the presence of small amount of piperidine to give the corresponding 4-substituted styryl-3-carboxamidopiperidyl coumarin derivatives **4a—4f**, respectively (Scheme 1). The structures of compounds **4a—4f** were confirmed by their correct analytical data and spectral data. When compound **1a** was heated in an oil-bath of 160 ℃ with piperidine for 2 h, the 3-carboxamidopiperidyl-4-methyl-coumarin was isolated, and in the case of *p*-methoxy-benzaldehyde in the presence of piperidine compound **4a** was yielded.

It has been reported that the reaction of coumarins with hydrazine affects the fission of the heterocyclic ring.[12-17] In the present investigation, the study of reaction behaviour of 4-methyl-3-carbethoxy coumarin derivatives **1a** and **1b** with hydrazine hydrate was extended. Thus compound **1a** reacted with hydrazine hydrate to give 2-hydroxy acetophenone hydrazone (**5a**), 2-hydroxyacetophenone azine (**6a**) and malonic acid hydrazide. On the other hand, compound **1b** reacted with hydrazine hydrate to give both 1-hydroxy-2-acetyl naphthalene hydrazone (**6a**) and 1-hydroxy-2-acetyl naphthalene azine (**6b**) (Scheme 1). The structures of **5** and **6** were confirmed by their spectral data.

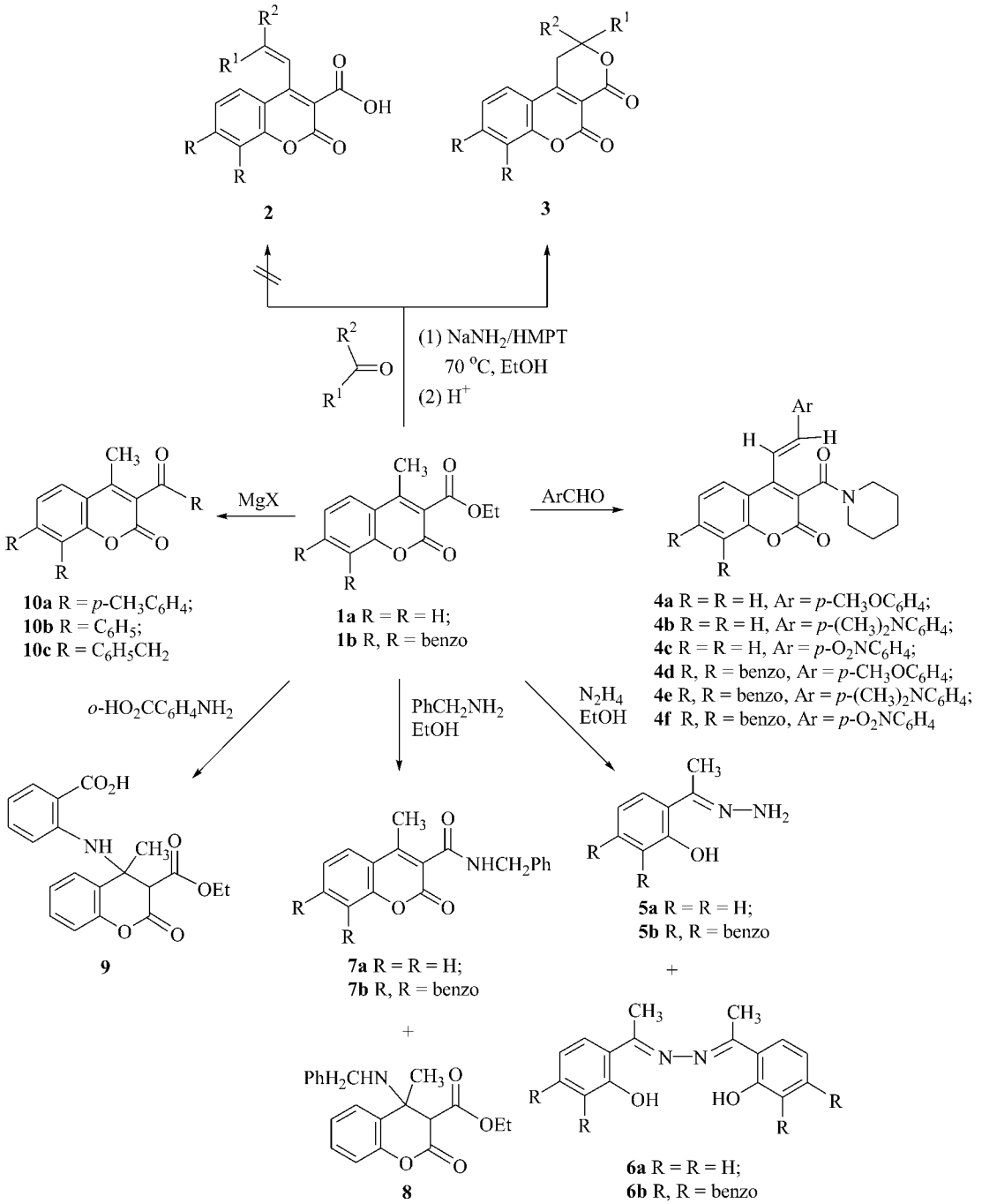
The reaction of **1a** with benzyl amine in boiling ethanol afforded 4-methyl-3-(*N*-benzyl) carboxamidocoumarin (**7a**) as a main product and the other was identified as 4-benzylamino-4-methyl-3-carbethoxy-3,4-dihydro-coumarin (**8**) as aminor product, while the reaction of **1b** gave only 4-methyl-3-(*N*-benzyl) carboxamido-benzo-7,8-coumarin (**7b**). The addition of amino group to the olefinic double in **1b** failed due to the higher stability of heterocyclic ring increased in compound **1b**. Similarly, anthranilic acid underwent 1,4-nucleophilic addition on coumarin **1a** to give *N*-(4-methyl-3-carbethoxy-3,4-dihydrocoumarin-4-yl) anthranilic acid (**9**).

The Grignard addition of **1a** was also examined in the present work. Thus[12-17], the reaction of **1a** with Grignard reagents, such as *p*-tolyl-, phenyl-magnesium bromide and benzyl magnesium chloride, afforded the corresponding 3-aroyl-4-methyl coumarin (**10a—10c**), respectively.

* E-mail: mhadeerbakeer@yahoo.com

Received March 14, 2002; revised July 10, 2002; accepted May 18, 2003.

Scheme 1



Experimental

Melting points were measured by a Gallen Kamp melting point apparatus and uncorrected. IR spectra were recorded on a Pye-Unicam SP 1200 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were measured on a Varian EM 390 instrument operating at 90 MHz in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. Elemental analyses were carried out at the Microanalytical units, at Cairo and Ain Shams Universities. The purity of the synthesized compounds was checked by TLC.

Condensation of **1** *with aromatic aldehydes*: *formation of 4-substituted styryl-3-carboxamidopiperidyl coumarin and benzocoumarin* **(4a—4f)**

A mixture of **1a** or **1b** (0.01 mol), appropriate aromatic aldehydes (0.01 mol) and piperidine (3 mL) was heated in an oil-bath at 160 ℃ for 20 h. The mixture was cooled and acidified with dilute hydrochloric acid (20 mL, 2%). The solid product precipitated was filtered off, washed several times with water, dried and then recrystallized from the appropriate solvent to get **4a—4f.**

4a Yield 40%, pale yellow crystals, m.p. 127—129 ℃ from light petroleum ether (60—80 ℃). ^{1}H NMR ($CDCl_3$) δ: 7.9—7.0 (m, 8H, ArH), 6.15 (d, J = 11.2 Hz, 2H, olefinic *trans* protions), 3.8 (s, 3H, OCH_3), 2.6—1.9 (m, 10H, piperidyl group); IR (KBr) ν: 1740 (C = O lactone), 1660 (C = O amide) cm^{-1}. Anal. calcd for $C_{24}H_{23}NO_4$: C 74.02, H 5.95, N 3.60; found C 74.07, H 6.05; N 3.63.

4b Yield 45%, pale yellow crystals, m. p. 200—202 ℃ from ethanol. ^{1}H NMR (DMSO-d_6) δ: 7.8—7.2 (m, 8H, ArH), 6.2 (d, J = 11.2 Hz, 2H, olefinic *trans* protons), 2.84 (s, 6H, NMe), 2.0—1.36 (m, 10H, piperidyl group); IR (KBr) ν: 1732 (C = O lactone), 1651 (C = O amide) cm^{-1}. Anal. calcd for $C_{25}H_{26}N_2O_3$: C 74.60, H 6.51, N 6.96; found C 74.50, H 6.35, N 7.14.

4c Yield 52%, brown crystals, m.p. 220—222 ℃ from methanol. ^{1}H NMR ($CDCl_3$) δ: 8.1—7.2 (m, 8H, ArH), 6.3 (d, J = 11.6 Hz, 2H, olefinic *trans* protons), 2.2—1.65 (m, 10H, piperidyl group); IR (KBr) ν: 1736 (C = O lactone), 1655 (C = O amide) cm^{-1}. Anal. calcd for $C_{23}H_{20}N_2O_5$: C 68.31, H 4.98, N 6.93; found C 68.46, H 4.96, N 6.88.

4d Yield 16%, brown crystals, m.p. 160—162 ℃ from benzene. ^{1}H NMR (DMSO-d_6) δ: 7.9—7.1 (m, 10H, ArH), 6.7 (d, J = 13 Hz, 2H, olefinic *trans* protons), 3.85 (s, 3H, OCH_3), 2.2—1.42 (m, 10H, piperidyl group); IR (KBr) ν: 1722 (C = O lactone), 1666 (C = O amide) cm^{-1}. Anal. calcd for $C_{28}H_{25}NO_4$: C 76.52, H 5.73, N 3.19; found C 76.22, H 5.73, N 3.38.

4e Yield 18%, brown crystals, m.p. 148—149 ℃ from benzene. ^{1}H NMR (DMSO-d_6) δ: 7.9—7.3 (m, 10H, ArH), 6.56 (d, J = 11.6 Hz, 2H, olefinic *trans* protons), 3.1 (s, 6H, NMe_2), 2.0—1.2 (m, 10H piperidyl group); IR (KBr) ν: 1726 (C = O lactone), 1660 (C = O amide) cm^{-1}. Anal. calcd for $C_{29}H_{28}N_2O_3$: C 76.97, H 6.24, N 6.19; found C 77.01, H 5.78, N 6.16.

4f Yield 20%, pale brown crystals, m.p. 165—167 ℃ from benzene. ^{1}H NMR ($CDCl_3$) δ: 8.2—7.2 (m, 10H, ArH), 6.3 (d, J = 1.9 Hz, 2H, olefinic *trans* protons), 2.4—1.7 (m, 10H, piperidyl group); IR (KBr) ν: 1725 (C = O δ-lactone) and 1660 cm^{-1}(C = O amide) cm^{-1}. Anal. calcd for $C_{27}H_{22}N_2O_5$: C 71.35, H 4.88, N 6.16; found C 71.33, H 5.16, N 6.20.

Formation of **5a** *and* **6a** *via hyazinolysis of* **1a**

A solution of **1a** (0.005 mol) in absolute ethanol (50 mL) was stirred with hydrazine hydrate (0.02 mol) and then the mixture was refluxed for 3 h. After concentration and cooling, the solid formed was filtered off and washed with dilute hydrochloric acid, dried and triturated with light petroleum (40—60 ℃). The petroleum soluble part was concentrated, and the colourless crystals were separated, recrystallized from light petroleum (40—60 ℃) to give 2-hydroxy acetophenone hydrazone (**5a**), yield 25%, m.p. 81—82 ℃ (compound **5a** was confirmed by independent synthesis, m.p. and mixed m.p. determination with an authentic sample and with literature)[12]. ^{1}H NMR ($CDCl_3$) δ: 13.1 (s, 1H, OH), 8.9 (s, 2H, NH_2), 7.9—7.1 (m, 4H, ArH), 2.62 (s, 3H, CH_3); IR (KBr) ν: broad band ranged from 2313—3500 (OH, NH_2, CH_3), 1620 (C = N), 1600 (C = C) cm^{-1}. Anal. calcd for $C_8H_{10}N_{20}$: C 63.98, H 6.71, N 18.65; found C 63.83, H 6.6, N 18.37.

The insoluble product was treated with light petroleum (80—100 ℃). The soluble fraction gave colourless crystals of malonic acid hydrazide, yield 18%, m.p. 132 ℃. Anal. calcd for $C_3H_8N_4O_2$: C 27.27, H 6.06, N 42.42; found C 27.0, H 6.01, N 42.33. The insoluble fraction from light petroleum (90—100 ℃) was recrystallized from benzene to give 2-hydroxy acetophenone azine (**6a**) as yellow crystals, yield 31%, m.p. 190 ℃. ^{1}H NMR (DMSO-d_6) δ: 13.3 (s, 2H, 2 × OH), 8.1—7.1 (m, 8H, ArH), 2.81 (s, 6H, 2 × CH_3); IR (KBr) ν: broad band ranged from 2500—3500 (OH, CH_3), 1625 (C = N), 1600 (C = C) cm^{-1}. Anal. calcd for $C_{16}H_{16}N_2O_2$: C 71.62, H 6.01, N 10.44; found C 71.98, H 6.13, N 10.34.

Formation of **5b** *and* **6b**

A solution of 4-methyl-3-carbethoxy-7,8-benzocoumarin (**1b**) (0.005 mol) in absolute ethanol (50 mL) was treated with hydrazine hydrate (0.02 mol) as described before. The solid separated was triturated with light petroleum (60—80 ℃). The soluble fraction after concentration gave 1-hydroxy 2-acetyl naphthalene hydrazone (**5b**) as yellow crystals, yield 35%, m.p. 135—137 ℃. ^{1}H NMR ($CDCl_3$) δ: 13.27 (s, 1H, OH), 9.1 (s, 2H, NH_2), 8.0—7.1 (m, 6H, ArH), 2.72 (s, 3H, CH_3); IR (KBr) ν: broad band ranged from 2400—3500 (OH, NH_2, CH_3), 1625 (C = N), 1610 (C = C) cm^{-1}. Anal. calcd for $C_{12}H_{12}N_2O$: C 71.98, H 6.04, N 13.99; found C 72.13, H 6.01, N 14.02.

The insoluble fraction was crystallized from benzene to give 1-hydroxy-2-acetyl naphthalene azine (**6b**) as pale yellow crystals, yield 30%, m.p. 199 ℃. ^{1}H NMR (DMSO-d_6) δ: 13.35 (s, 2H, 2 × OH), 8.0—7.1 (m, 12H, ArH), 2.63 (s, 6H, 2 × CH_3); IR (KBr) ν: broad band ranged from 2550—3500 (OH, CH_3), 1625 (C = N), 1600 (C = C) cm^{-1}. Anal. calcd for $C_{24}H_{20}N_2O_2$: C 78.24, H 5.47, N 7.60; found C 78.89, H 5.5, N 7.61.

Reaction of **1a** *with benzylamine*: *formation of* 4-*methyl*-3-(*N-benzyl*)*carboxamido-coumarin* (**7a**) *and* 4-(*benzylamino*)-4-*methyl*-3-*carbethoxy*-3,4-*dihydro-coumarin* (**8**)

A solution of **1a** (0.01 mol) in absolute ethanol (50

mL) was stirred with benzylamine (0.02 mol) and the mixture was refluxed for 3 h. After concentration and cooling, the solid formed was filtered off, washed several times with water, dried and triturated with light petroleum (40—60 ℃). The light petroleum insoluble fraction was recrystallized from benzene to give **7a** as yellow crystals, yield 40%, m.p. 138—140 ℃. ^{1}H NMR ($CDCl_3$) δ: 8.8 (brs, 1H, NH), 7.8—7.1 (m, 9H, ArH), 4.5 (d, J = 4.3 Hz, 2H, CH_2Ph), 2.4 (s, 3H, CH_3); IR (KBr) ν: 1730 (C = O lactone), 1670 (C = O amide), 1605 (C = C) cm^{-1}. Anal. calcd for $C_{18}H_{15}NO_3$: C 73.71, H 5.15, N 9.55; found C 73.41, H 5.24, N 9.71.

The soluble fraction was evaporated *in vacuo* and left a solid product which recrystallized from light petroleum ether (40—60 ℃) to give **8** as yellow crystals, yield 16%, m.p. 70—71 ℃. ^{1}H NMR (DMSO-d_6) δ: 8.25 (s, 1H, NH), 7.9—7.3 (m, 9H, ArH), 4.5 (q, J = 4.6 Hz, 2H, C**H**$_2$CH$_3$), 3.6 (brs, 1H, methine proton), 2.5 (s, 3H, CH_3), 2.25 (s, 2H, CH_2Ph), 1.4 (t, J = 5.1 Hz, 3H, CH_2C**H**$_3$); IR (KBr) ν: 1742 (C = O lactone), 1715 (C = O ester). Anal. calcd for $C_{20}H_{21}NO_4$: C 70.78, H 6.24, N 4.13; found C 70.71, H 5.78, N 4.22.

4-Methyl-3-(N-benzyl) carboxamido-benzo-7,8-coumarin **(7b)**

A solution of 4-methyl-3-carbethoxy-benzo-7,8-coumarin (**1b**, 0.01 mol) in absolute ethanol (50 mL) was treated with benzylamine (0.02 mol) as described above to give **7b** as pale yellow crystals from light petroleum ether (80—100 ℃), yield 46%, m.p. 170—172 ℃. ^{1}H NMR ($CDCl_3$) δ: 8.6 (s, 1H, NH), 7.9—7.1 (m, 11H, ArH), 4.0 (d, J = 4.4 Hz, 2H, CH_2Ph), 2.3 (s, 3H, CH_3); IR (KBr) ν: 1738 (C = O lactone), 1662 (C = O amide) cm^{-1}. Anal. calcd for $C_{22}H_{17}NO_3$: C 76.95, H 4.99, N 4.08; found C 76.45, H 5.42, N 3.95.

N-(4-Methyl-3-carbethoxy-3,4-dihydrocoumarin-4-yl) anthranilic acid **(9)**

A solution of **1a** (0.01 mol) in *n*-butanol (30 mL) was stirred with anthranilic acid (0.01 mol) for 30 mim. and then refluxed for 6 h. After cooling, the solid formed was filtered off and recrystallized from light petroleum ether (b.p. 80—100 ℃) to give **9** as colourless crystals, yield 17%, m.p. 126—128 ℃. ^{1}H NMR ($CDCl_3$) δ: 10.3 (s, 1H, COOH), 9.1 (brs, 1H, NH), 7.9—7.4 (m, 8H, ArH), 6.3 (brs, 1H, 3-CH), 3.8 (q, J = 5.2 Hz, 2H, C**H**$_2$CH$_3$), 2.44 (s, 3H, CH_3), 1.1 (t, J = 5.8 Hz, 3H, CH_2C**H**$_3$); IR (KBr) ν: 1738 (C = O lactone), 1712 (C = O ester), 1696 (C = O acid), 2500—3480 (OH, NH) cm^{-1}. Anal. calcd for $C_{20}H_{19}NO_6$: C 65.03, H 5.18, N 3.79; found C 65.48, H 5.3, N 4.0.

Formation of 3-aroyl-4-methyl coumarin **(10a—10c)** *via reaction of Grignard reagents with* **1a**

An ethereal solution of Grignard reagent (0.03 mol) was added dropwise to the solution of **1a** (0.01 mol) in dry benzene (30 mL). The reaction mixture was heated under reflux for 6 h, and then left overnight at room temperature and decomposed by shaking with a saturated solution of ammonium chloride. The organic layer was separated, dried over anhydous sodium sulphate, concentrated and left to cool. The solid formed was filtered off and recrystallized from the proper solvent to give **10a—10c.**

10a Yield 40%, colourless crystals, m.p. 200—202 ℃ from ethanol. ^{1}H NMR ($CDCl_3$) δ: 7.6—7.0 (m, 8H ArH), 2.4 (s, 3H, CH_3), 1.9 (s, 3H, CH_3Ar); IR (KBr) ν: 1732 (C = O lactone), 1684 (C = O ketone) cm^{-1}. Anal. calcd for $C_{18}H_{14}O_3$: C 77.68, H 5.07; found C 77.96, H 5.30.

10b Yield 55%, pale green crystals, m.p. 157—159 ℃ from toluene. ^{1}H NMR ($CDCl_3$) δ: 7.9—7.3 (m, 9H, ArH), 2.6 (s, 3H, CH_3); IR (KBr) ν: 1741 (C = O lactone), 1682 (C = O ketone) cm^{-1}. Anal. calcd for $C_{17}H_{12}O_3$: C 77.26, H 4.58; found C 77.37, H 4.50.

10c Yield 45%, greem crystals, m.p. 170—172 ℃ from benzene. ^{1}H NMR ($CDCl_3$) δ: 7.8—7.2 (m, 9H, ArH), 4.6 (d, J = 5.6 Hz, 2H, CH_2Ph), 2.1 (s, 3H, CH_3); IR (KBr) ν: 1738 (C = O lactone), 1686 (C = O ketone) cm^{-1}. Anal. calcd for $C_{18}H_{14}O_3$: C 77.68, H 5.07; found C 77.37, H 5.18.

References

1 Cingolani, G. M.; Gualtieri, F.; Pigini, M. *J. Med. Chem.* **1969**, *12*, 531.

2 Mathur, C. N.; Mitra, G. R.; Krishnaswamy, N. R.; Kulshreshtha, R. K.; Arora, R. B. *Arc. Int. pharm.* **1965**, *153*, 218 [*Chem. Abstr.* **1965**, *63*, 1254].

3 Kitagawa, H.; Lwaki, R. *Yakugaku Zasshi* **1959**, *79*, 639 [*Chem. Abstr.* **1959**, *53*, 19158].

4 Derives, J. X.; Voelker, U. *J. Chromatographic Determination of Plasma Protein Binding of Coumarin* (*Netherland*) **1990**, *529*(2), 479.

5 Angheloba, Y.; Ivanov, C.; Gouneva, V. *C. R. Acad. Bulg. Sci.* **1968**, *21*, 1185 [*Chem. Abstr.* **1969**, *71*, 12764].

6 Anghelova, Y.; Ivanov, C. *C. R. Acad. Bulg. Sci.* **1970**, *23*, 1377 [*Chem. Abstr.* **1971**, *74*, 99588].

7 Anghelova, Y.; Ivanov, C. *Chem. Ber.* **1974**, *106*, 2643.

8 Anghelova, Y.; Ivanov, C.; Metsov, S. *Chem. Ber.* **1977**, *110*, 1594.

9 Anghelova, Y.; Spirova, S.; Ivanov, C. *Synthesis* **1977**, 313.

10 Ivanov, C.; Anghelova, Y.; Spirova, S. *Synthesis* **1979**, 732.

11 Wiener, C.; Schroeder, C.; Link, K. *J. Am. Chem. Soc.* **1957**, *79*, 5301.

12 Sammour, A.; Abdalla, M.; El-Kady, M. *Acta Chem.* **1974**, *82*, 369.
13 Soliman, A. Y.; El-Assy, N. B.; El-Shahed, F.; El-Kady, M.; Mohy El-Deen, I. M. *Indian J. Chem.* **1990**, *29B*, 236.
14 Soliman, A. Y. *Bull. Fac. Sci., Assiut Univ.* **1998**, *27B*, 19 [*Chem. Abstr.* **2000**, *132*, 151648].
15 Soliman, A. Y.; El-Kafrawy, A. F.; Mohamed, F. K.; Bakeer, H. M.; Abdel Gawad, A. M. *Indian J. Chem.* **1991**, *30*, 477.
16 El-Kafrawy, A. F.; Soliman, A. Y.; Bakeer, H. M.; Mohamed, F. K.; Abdel Gawad, A. M. *Egypt. J. Chem.* **1992**, *30*, 253.
17 Soliman, A. Y.; Bakeer, H. M.; Attia, I. A. *Chin. J. Chem.* **1996**, *14*, 532.

(E0203146 LI, L. T.; FAN, Y. Y.)