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FACILE SYNTHESIS OF 3,5-DI-BENZYLIDENE(2-MORPHOLIN/PIPERIDIN-4-YL-1-YL-ACETYL) PIPERIDIN-4-ONES

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Abstract: The Claisen-Schmidt condensation of 3,5-dibenzylidene-1-(2-chloro-acetyl)-piperidin-4-one**(5a-f)** react with morpholine**(6)** in presence of K_2CO_3 to gave 3,5-dibenzylidene-1-(2-morpholin-4-yl-acetyl)piperidin-4-ones**(7a-f)**, and **(5a-f)** react with piperidin**(8)** in presanced K_2CO_3 to gave 3,5-dibenzylidine-1-(2-piperidin-1-yl-acetyl)-piperidin-4-ones **(9a-f)** in good yields.

Keywords: - Claisen-Schmidt condensation, 3, 5-dibenzylidene-piperidine-4-one, chloroacetyl chloride, piperidine, morpholine, K_2CO_3

INTRODUCTION

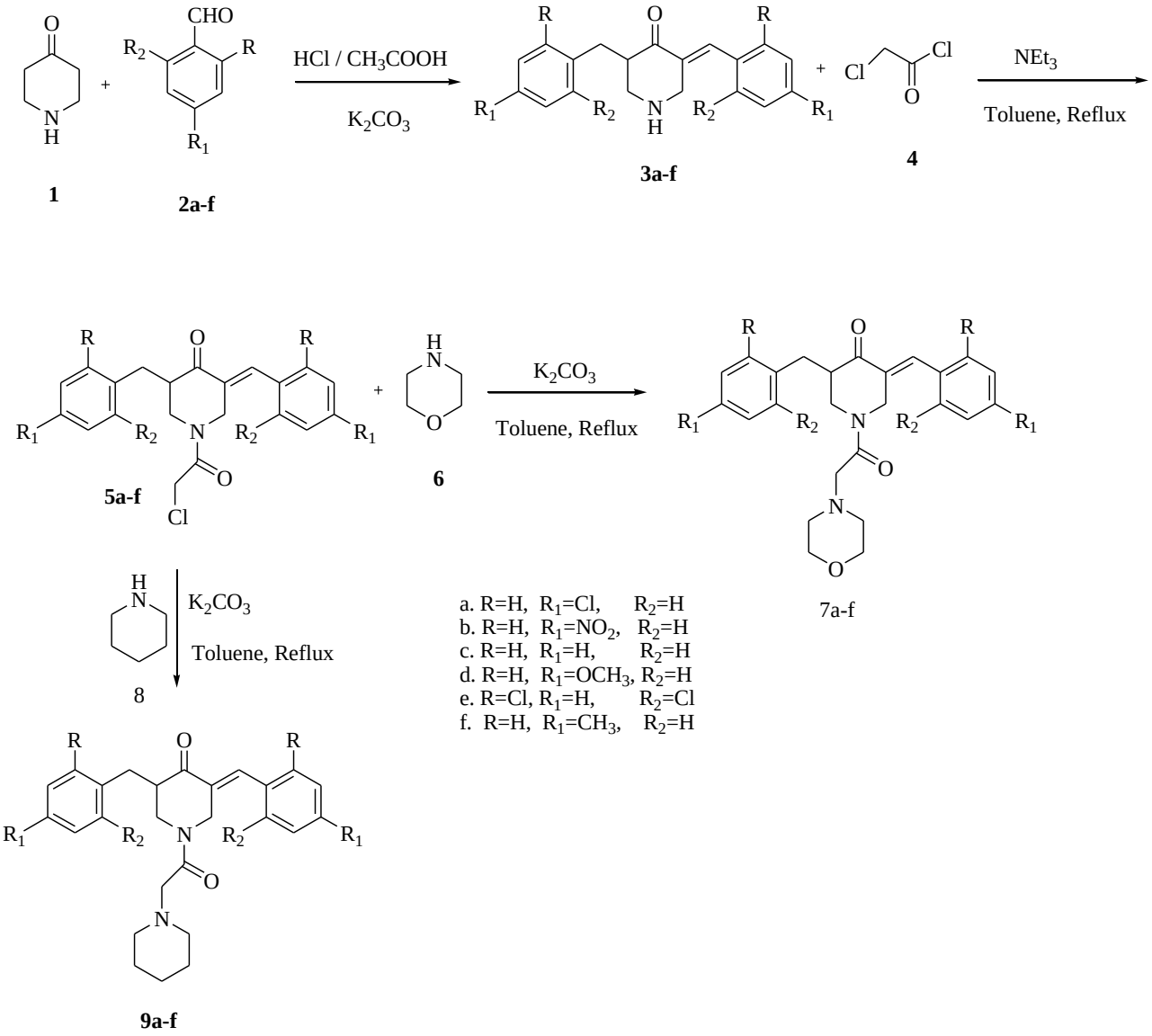
Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, chromone,flavones, Is flavones etc[I-V]. The natural heterocyclics are plant secondary metabolites, which protect the plant from attack by pathogens, fungi, bacteria and insects. Several synthetic analogs of these heterocyclic's show different bioactivity[V-VIII]. More than 50% of the drugs used in the modern medicine are either derived from synthetic or natural heterocyclic systems.

Heterocyclic ring systems having piperidin-4-one nucleus have aroused great interest in the past and present years due to their wide range of biological activity such as anti viral, and anti microbial activity and their derivative piperidines are also biologically important and act as neurokinin receptor antagonists[IX-X]. The bis(substituted benzyliden) cycloalkanones are very important precursors to potentially bioactive pyrimidine derivatives intermediates of agrochemicals, pharmaceuticals, and perfumes new organic materials for nonlinear optical applications, cytotoxic analogues and the units of liquid-crystalline polymers. In addition these compounds undergo double 1,3-dipolar cycloaddition reaction with azomethine to give bis-spiropyrrolidines, which are often the central ring system of numerous natural products. N-substituted piperidinone derivatives are the most successfully employed for a wide range of biological activity. Perusal of the literature has been found that the 1-(2-morpholin/piperidine-4-yl/1-yl-acetyl)-3,5-bis-(2,4,6-try substituted arylidene)-piperidin-4-ones moiety has significant biological activity. Therefore we propose to prepare a few target molecules and investigate their antioxidant and prooxidant assay of these molecules in liver and blood.

RESULT AND DISCUSSIONS:

A mixture of 3, 5-dibenzylidene-1-(2-chloro-acetyl)-piperidin-4-one **(1a)** K_2CO_3 and piperdine **(8)** in toluene was refluxed for about 8 hours to give 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one (**9a**). Formation of the synthesized compounds 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one is confirmed by the ^1H NMR (400 MHz) the piperidine protons appeared as multiplet at δ1.38 and 2.18. 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one δ 2.14 (t, 4H, morpholine), 2.99 (s, 2H, -COC<u>H</u>$_2$), 3.38 (t, 4H, morpholine), 4.85 (s, 2H, piperidinone ring-H), 5.00 (s, 2H, piperidinone ring-H) ,7.40 (m,8H, Ar-H), 7.77 (s,1H, arylidirle-H),7.81 (s, lH, arylidine-H).

Scheme-1



EXPERIMENTAL SECTION

General Methods. Melting points were determined on a Polmon instrument (model no. MP 96).IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer, and ^{1}H NMR (200 MHz) and ^{13}C NMR (100.6) were recorded on spectrometer using TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument.

I) General procedure for the Synthesis of 3,5-dibenzylidene-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one (7a-f).

A mixture of 3, 5-Dibenzylidene-1-(2-chloro-aceryl)-piperidin-4-one **(5a)** (3.52 gr, 10 mmol), K_2CO_3 (2.48 gr, 18 mmol) and morpholine **(6)** (1.55 mL, 18 mmol) in toluene was refluxed, for about 6 h. After completion of the reaction, K_2CO_3 was removed by filtration and the solvent was removed under reduced pressure. The crude product was subjected for column chromatography purification using silica gel (60-120) with hexane/ethyl acetate (1:1) as eluent to give 3,5-Dibenzylidene-1-(2-morpholin-4- yl-acetyl)-piperidin-4-one **(7a)** in good yield.

3,5-Bis-(4-chloro-benzylidene)-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one(7a).

Yield: 81%, mp: 179 ºC.

IR (KBr) (cm^{-1} (υ): 2966, 2916, 1658,1633,1493,1406, 1259, l122, 814.

^{1}H NMR ($CDCl_3$): δ 2.14 (t, 4H, morpholine), 2.99 (s, 2H, -COC$\underline{H}_2$), 3.38 (t, 4H, morpholine), 4.85 (s, 2H, piperidinone ring-H), 5.00 (s, 2H, piperidinone ring-H) ,7.40 (m,8H, Ar-H), 7.81 (s, lH, arylidine-H).

^{13}C NMR ($CDCl_3$): δ 51.0 (CH), 47.9(CH_2), 44.6 (CH_2), 137.6 (C′), 127.6(CH), 136.0(CH), 128.8(CH), 133.5 (C′), 55.3 (CH_2), 55.3 (CH_2), 52.7(CH_2), 52.7 (CH_2), 66.1(CH_2), 33.8 (CH_2), 147.6(C′).

MS (EI): m/z (%) 471 (96) $[M+H]^+$.

Employing the similar procedure as mentioned for **7a,** compounds **7b-f** were obtained from **5b-f** as solids in 70-85% yield.

1-(2-Morpholin-4-yl-acetyl)-3,5-bis-(4-nitro-benzylidene)-piperidin-4-one(7b).

Yield: 79%, mp: 236 ºC.

IR (KBr) cm^{-1}: 2918, 2851, 1726, 1651, 1595, 1518, 1259, 1172, 1113, 856.

^{1}H NMR ($CDCl_3$) δ 2.19 (t, 4H, morpholine), 3.02 (s, 2H, -COCH_2-), 3.35 (t, 4H, morpholine), 4.86 (s, 2H, piperidinone ring-H), 5.08 (s, 2H, piperidinone ring-H) ,7.65 (m,8H, Ar-H),8.35 (s, 1H, arylidine-H),8.40 (s, 1H, arylidine-H).

^{13}C NMR ($CDCl_3$): δ 53.0 (CH), 45.9(CH_2), 45.6 (CH_2), 137.6 (C′), 125.6(CH), 138.0(CH), 127.8(CH), 135.5 (C′), 55.3 (CH_2), 55.3 (CH_2), 52.7(CH_2), 52.7 (CH_2), 66.1(CH_2), 33.8 (CH_2), 147.6(C′).

MS (EI): m/z (%) 493 (44) $[M+H]^+$.

3,5-Dibenzylidene- 1 -(2-morpholin-4-yl-acetyl)-piperidin-4-one(7c).

Yield: 84 %, mp: 142 ºC.

IR (KBr) cm^{-1}: 2964, 2918, 1643, 1606, 1493, 1444, L275, l171, 1111, 864, 771, 688.

^{1}H NMR ($CDCl_3$) δ 2.16 (t, 4H, morpholine), 3.02 (s, 2H, -COCH_2-), 3.39 (t, 4H, morpholine), 4.96 (s,2H, piperidinone ring-H),5.09 (s,2H, piperidinone ring-H) ,7.50 (m, 10H, Ar-H), 7.85 (s, lH, arylidine-H), 7.92 (s,lH, arylidine-H).

^{13}C NMR ($CDCl_3$): δ 50.0 (CH), 49.9(CH_2), 44.6 (CH_2), 135.6 (C′), 125.6(CH), 138.0(CH), 126.8(CH), 130.5 (C′), 55.3 (CH_2), 55.3 (CH_2), 52.7(CH_2), 52.7 (CH_2), 66.1(CH_2), 33.8 (CH_2), 147.6(C′).
MS (EI): m/z (%) 403 (98) $[M+H]^+$.

3,5-Bis-(4-methoxy-benzylidene)-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one(7d).
Yield: 93%, mp: 156 ºC.
IR (KBr) cm^{-1}: 2930, 2837, 1647, 1597, 1510, 1255, 1167, 1113, 866, 829.
^{1}H NMR ($CDCl_3$) δ 2.17 (t, 4H, morpholine), 3.01 (s, 2H, -COC$\underline{H}_2$-), 3.35 (t, 4H, morpholine), 3.86 (s, 6H, two methoxy protons),4.89 (s,2H, piperidinone ring-H) ,4.89 (s,2H, piperidinone ring-H),6.95 (d,4H, Ar-H), 7.42 (m,4H, Ar-H),7J4 (s, lH, arylidine-H), 7.80 (s, lH, arylidine-H).
^{13}C NMR ($CDCl_3$): δ 52.0 (CH), 50.9(CH_2), 44.6 (CH_2), 133.6 (C′), 129.6(CH), 135.0(CH), 128.8(CH), 133.5 (C′), 55.3 (CH_2), 55.3 (CH_2), 52.7(CH_2), 52.7 (CH_2), 66.1(CH_2), 33.8 (CH_2), 147.6(C′).
MS (EI): mlz (%) 463 (50) $[M+H]^+$.

3,5-Bis-(2,6-dicholoro-benzylidene).1-(2-morpholin-4-yl-acetyl)-piperidin-4-one(7e).
Yield: 75%, mp: 162 ºC.
IR (KBr) cm^{-1}: 2918, 2851, 1682, 1651, 1554, 1427, 1263, lll4, 866, 8l2, 78l.
H NMR ($CDCl_3$) δ 2.19 (t, 4H, morpholine), 2.83 (s, 2H, -COC$\underline{H}_2$-), 3.48 (t, 4H, morpholine), 4.40 (s, 2H, piperidinone ring-H), 4.59 (s, 2H, piperidinone ring-H) ,7.98 (m,6H, Ar-H),7.65 (s, 1H, arylidine-H), 7.68 (s, lH, arylidine-H).
^{13}C NMR ($CDCl_3$): δ 50.0 (CH), 49.9(CH_2), 45.6 (CH_2), 135.6 (C′), 126.6(CH), 135.0(CH), 129.8(CH), 130.5 (C′), 55.3 (CH_2), 55.3 (CH_2), 52.7(CH_2), 52.7 (CH_2), 66.1(CH_2), 33.8 (CH_2), 147.6(C′).
MS (EI): m/z (%) 541 (99) $[M+H]^+$.

3,5-Bis-(4-methyl-benzylidene)-1-(2-morpholin-4-y1-acety1)-piperidin-4-one(7f).
Yield: 88%, mp: 187 ºC.
IR (KBr) cm^{-1}: 2918, 2852, 1568, 1344,981,912.
^{1}H NMR ($CDCl_3$) δ 2.15 (t, 4H, morpholine), 2.39 (s, 6H, two methyl protons), 2.99 (s, 2H, -COC$\underline{H}_2$-), 3.37 (t, 4H, morpholine), 4.91 (s, 2H, piperidinone ring-H), 5.03 (s,2H, piperidinone ring-H), 7.33 (m, 8H, Ar-H), 7.79 (s, lH, arylidine-H), 7.80 (s, lH,arylidine-H).
^{13}C NMR ($CDCl_3$): δ 54.0 (CH), 50.9(CH_2), 45.6 (CH_2), 135.6 (C′), 125.6(CH), 135.0(CH), 123.8(CH), 133.5 (C′), 55.3 (CH_2), 55.3 (CH_2), 52.7(CH_2), 52.7 (CH_2), 66.1(CH_2), 33.8 (CH_2), 147.6(C′).
MS (EI): m/z (%) 430 (97) $[M+H]^+$.

II) Synthesis of 7,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-ones (9a-f)
A mixture of 3, 5-dibenzylidene-1-(2-chloro-acetyl)-piperidin-4-one **(1a)** (3.52 gr, l0 mmol), K_2CO_3 (2.48 gr, 18 mmol) and piperdine (**8**) (1.77 mL, 18 mmol) in toluene was refluxed for about 8 h. After the completion of reaction, K_2CO_3 was removed by filtration and the solvent was removed under reduced pressure and the crude product was subjected for column chromatography purification using silica gel (60-120) with hexane/ethyl acetate (1:1) as eluent to give 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one (**9a**) in good yield.

3,5-Bis-(4-chloro-benzylidene)-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one(9a)
Yield: 85%, mp: 173 ºC.
IR (KBr) cm^{-1}: 2918, 2849, 1672, 1635, 1491, 1406, 1277, 1244, 1170, 1093, 979, 814,761,694.
^{1}H NMR ($CDCl_3$) δ 1.28 (m, 6H, piperidine protons), 2.93 (s, 2H, -$COCH_2$-), 4.84 (s, 2H, piperidinone ring-H),7.41 (m, 8H, Ar-H),7.75 arylidine-H)-protons), 2.10 (m, 4H, piperidine piperidinone ring-H), 5.07 (s, 2H, piperidinone ring-H), 7.41 (m, 8H, Ar-H), 7.75 (s, 1H, arylidine-H), 7.78 (s, 1H, arylidine-H).
^{13}C NMR ($CDCl_3$): δ 55.0 (CH), 50.9(CH_2), 48.6 (CH_2), 138.6 (C′), 127.6(CH), 135.0(CH), 124.8(CH), 135.5 (C′), 33.8 (CH_2), 55.3 (CH_2), 53.6(CH_2), 25.2 (CH_2), 25.2(CH_2), 53.8 (CH_2), 133.5(C′).
MS (EI): m/z (%) 470 (62) $[M+H]^+$

3,5-Bis-(4-nitro-benzylidene)-1-(2-piperidin-1-y1-acetyl)-piperidin-4-one(9b)
Yield: 78%, mp: l79 ºC.
IR (KBr) cm^{-1}: 2928, 2846, 1650, 1620, 1492, 1388, 1250, 1232, 1154, 1055, 958, 811,757,660.
^{1}H NMR ($CDCl^3$) δ 1.32 (m, 6H, piperidine protons), 2.13 (m, 4H, piperidine protons), 3.00 (s, 2H, -$COCH_2$-), 4.85 (s, 2H, piperidinone ring-H), 5.09 (s, 2H, piperidinone ring-H),7.63 (m, 8H, Ar-H), 8.01 (s, lH, arylidine-H), 8.06 (s, 1H,arytidine-H).
^{13}C NMR ($CDCl_3$): δ 53.0 (CH), 50.9(CH_2), 45.6 (CH_2), 138.6 (C′), 125.6(CH), 135.0(CH), 125.8(CH), 133.5 (C′), 33.8 (CH_2), 55.3 (CH_2), 53.6(CH_2), 25.2 (CH_2), 25.2(CH_2), 53.8 (CH_2), 133.5(C′).
MS (EI): m/z (%) 491(70) $[M+H]^+$.

3,5-Dibenzylidene- 1 -(2-piperidin- 1 -yl-acetyl)-piperidin-4-one (9c)
Yield: 80%, mp: 138 ºC.
IR (KBr) cm^{-1}: 2922, 2843, 1651, 1614, 1444, 1165, 1263, 79 4,752,688.
^{l}H NMR ($CDCl_3$) δ 1.38 (m, 6H, piperidine protons), 2.18 (m, 4H, piperidine protons), 3.00 (s, 2H, -$COCH_2$)-), 4.99 (s, 2H, piperidinone ring-H), 5.16 (s, 2H, piperidinone ring-H),7.02 (m, 10H, Ar-H), 7.87 (s, 1H, arylidine-H), 7.93 (s, 1H,arylidine-H).
^{13}C NMR ($CDCl_3$): δ 50.0 (CH), 51.9(CH_2), 44.6 (CH_2), 133.6 (C′), 127.6(CH), 137.0(CH), 126.8(CH), 137.5 (C′), 33.8 (CH_2), 55.3 (CH_2), 53.6(CH_2), 25.2 (CH_2),25.2(CH_2), 53.8 (CH_2), 133.5(C′).
MS (EI): m/z (o/o) 400 (87) [M+H]r.

3,5-Bis-(4-methoxy-benzylidene)-l-(2-piperidin-1-yl-acetyl)-piperidin-4-one(9d)
Yield: 87%, mp: 149 ºC.
IR (KBr) cm^{-1}: 2953, 2916, 1666, 1604, 1508, 1298, 1251, 1772, 1030, 873, 827, 754.
^{1}H NMR ($CDCl_3$) δ 1.24 (m, 4H, piperidine protons), 1.61 (m, 4H, piperidine Protons), 2.17 (s,2H, piperidine protons), 3.85 (s, 6H, two methyl protons), 4.15 (s, 2H, -$COCH_2$), 4.91 (s,2H, piperidinone ring-H),5.04 (s, 2H, piperidinone rirg-H), 6.93 (d, 4H, Ar-H), 7.35 (m, 4H, Ar-H),7.37 (s, lH, arylidine-H),7.76 (s, lH, arylidine-H).

^{13}C NMR ($CDCl_3$): δ 55.0 (CH), 53.9(CH_2), 47.6 (CH_2), 135.6 (C′), 127.6(CH), 135.0(CH), 127.8(CH), 134.5 (C′), 33.8 (CH_2), 55.3 (CH_2), 53.6(CH_2), 25.2 (CH_2),25.2(CH_2), 53.8 (CH_2), 133.5(C′).
MS (EI): m/z (%) 461 (7) $[M+H]^+$.

3,5-Bis-(2,5-dichloro-benzylidene)-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one(9e)
Yield: 73%, mp: 150 ºC.
IR (KBr) cm^{-1}:2932, 2851, 1724, 7651. 1556, 1427, 1253, 1186, 1122,848,779.
^{1}H NMR (CDCls) (d): 1.29 (m, 4H, piperidine protons), 2.03 (m, 4H, piperidine protons), 2.16 (bs, 2H, piperidine protons), 2.83 (S, 2H, -COGHz-),4.42 (s, 2H, piperidinone ring-H),4.62 (s, 2H, piperidinone ring-H) ,7.35 (m, 6H, A1--U), 7.42 (s, lH, arylidine-H), 7.67 (s, lH, arylidine-H).
^{13}C NMR ($CDCl_3$): δ 50.0 (CH), 51.9(CH_2), 42.6 (CH_2), 133.6 (C′), 121.6(CH), 133.0(CH), 125.8(CH), 133.5 (C′), 33.8 (CH_2), 55.3 (CH_2), 53.6(CH_2), 25.2 (CH_2),25.2(CH_2), 53.8 (CH_2), 133.5(C′).
MS (EI): m/z (%) 538 (97) $[M+H]^+$.

3,5-Bis-(4-methyl-benzylidene)-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one(9f)
Yield: 76%, mp: 161 ºC.
IR (KBr) cm^{-1}: 3414, 1572,513.
H NMR ($CDCl_3$) δ 1.30 (m, 4H, piperidine protons), 1.44 (bs, 2H, piperidine protons), 2.10 (bs, 4H, piperidine protons),2.42 (s, 6H, two methyl protons), 2.91 (s, 2H, -$COCH_2$-), 4.88 (s, 2H, piperidinone ring-H), 5.04 (s, 2H, piperidinone ring-H), 7.23 (m,4H, Ar-H) , 7.29 (d, 2H, Ar-H), 7.37 (d,2H, Ar-H) , 7.71 (s, 1H, arylidine-H), 7 .78 (s, 1H, arylidine-H).
^{13}C NMR ($CDCl_3$): δ 50.0 (CH), 53.9(CH_2), 43.6 (CH_2), 133.6 (C′), 127.6(CH), 137.0(CH), 123.8(CH), 133.5 (C′), 33.8 (CH_2), 55.3 (CH_2), 53.6(CH_2), 25.2 (CH_2),25.2(CH_2), 53.8 (CH_2), 133.5(C′).
MS (EI): m/z (%) 428 (99) $[M+H]^+$.

REFERENCES

I. McElvain, S. M., I. Am. Chem. Soc., 1924,46,1721.
II. McElvain, S. M., I. Am. Chem. Soc., 1926,48,2179.
III. McE1vain,'S. M., L Am. Chem. Soc., 1926,48,2239.
IV. Kuettel, G. M.; McElvain, S. M., I.Am.Chem.Soc. 1931, 53, 2692.
V. Smith, P. J.; Dimmock,. R.; Taylor, W. G., Can. /. Chem., 1972, 50, 871..
VI. Smith, P. J.; Dimmock, f. R.; Turner, W. A, Can. /. Chem., L973, 51, 1458.
VII. Dimmock, J. R.; Hamon, N. W.; Hindmarsh, K. W.; Sellar, A. P.; Turner, W. A'; Rank, G. H.;Robertson, A. I., I Pharm- Sci.,1976,65,538.
VIII. Dimmock,.R.;Arora, V. K.; Wonko, S. L.; Hamon, N. W.; Quail.J.W.; Jia, Z; Warrington, R. C.;Fang, W. D.; Lee, J.S., Drug Des. Discov. 1990, 6, 183'
IX. Dimmock, J.R.;Arora, V. K.; Semple, H.A.; Lee, J. S.; A1len, T. M.; Kao, G. Y., Pharmazie" L992, 47, 246.
X. Dimmock, J. R.;Arora, V. K.; Chen, M.;A1len, T. M.; Kao, G. Y., Drug Des. Discou, 1994, 12, 19.
XI. Dimmock, J.. R.;Arora, V. K.; Duffy, M. I.; Reid, R. S.;Allen, T. M.; Kao, G. Y., Drug

Des. Discov., 1992, 8, 291.
XII. El-Subbagh, H. I.;Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.;A}-Obaid, A.M.,l Med. Chem., 2000, 27, 2915.
XIII. Deli,. Lorand, T.; Szabo, D.; Foldesi, A., Pharmaz, 1984, 39, 539.
XIV. Ogawa, M.; Ishii, Y.; Nakano, T.; Irifune, S.; Inventors, S.; Jpn. Kohai Tokkyo, JP, 63192446, Chem. Abstr., 1988, 63, 238034.
XV. Kawamah, I.; Inoue, K.; Inabe, T.; Kiguchi, M.; Kato, M.;Taniguchi, Y., Chem. Phys. Lett., 1996, 249, 29.

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