Arch. Pharm. Res. **15**(1), 1-4 (1992)

Synthesis of Some New 4-Substituted Antipyrines as Potential Antipyretic Analgesics

M. Hammouda
Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt
(Received November 2, 1991)

Abstract □ 4-Acetylantipyrine **1** underwent condensation with 4-formyl-antipyrine **2** to give **3**. Condensation of either **3** with **1** or **1** with **2** in a molar ratio of (2 : 1) afforded **4**. Cyclization of **4** in the presence of PPA and ammonium acetate or 4-aminoantipyrine in the presence of glacial acetic acid gave **5-7**, respectively. Claisen condensation of **1** with ethyl acetate and diethyl oxalate afforded compounds **8-10**. The reaction of **1** and **2** with indole in ethanol/conc. hydrochloric acid was also investigated.

keywords □ Antipyrine, antipyretic, polyphosphoric acid.

Antipyrine was one of the first major synthetic compound to be used in medicine as an analgesic and antipyretic drug[1]. The 4-substituted derivatives of antipyrine were reported to be more active and less toxic than the parent drug[2-4].

In the present work, the interest emphasized the synthesis of some new 4-substituted antipyrine as potential antipyretic-analgesics.

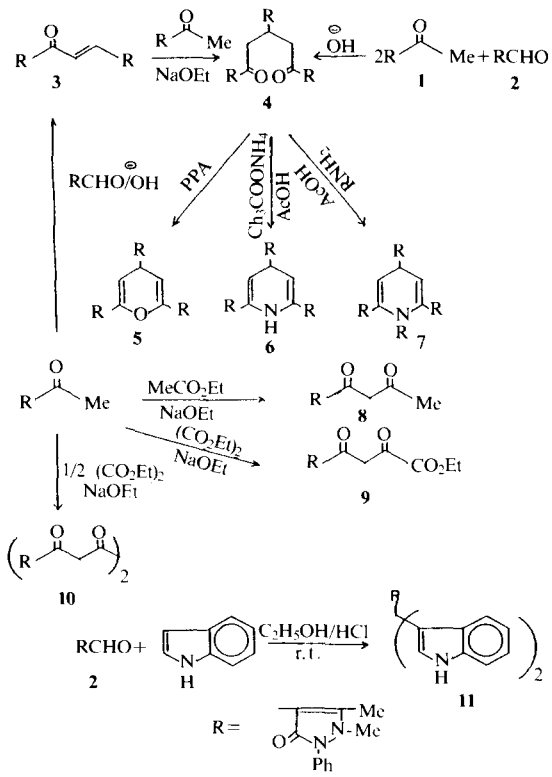
Thus, 4-acetylantipyrine **1** having an active methyl group easily, underwent condensation with 4-formyl-antipyrine **2** to give 1,3-di(antipyrin-4-yl)-prop-1-ene-3-one **3**. On the other hand, condensation of **1** with **2** in 2 : 1 molar ratio, lead to the formation of 1,3,5-tri(antipyrin-4-yl)-pentan-1,5-dione **4**. The IR spectrum of **3** showed absorption bands at 1715 cm^{-1} ($-CH_2-CO$), 1670 cm^{-1} (CO-antipyrine) and 1640 cm^{-1} (C=N), its ^{1}H-NMR showed signal at δ 3.2 ($-CH_2-CO-R$). In order to obtain a further proof of the structure of **4**, this compound was prepared independently by condensation of **3** with **1**.

The accessibility of the compound **4**, and the behaviour of 1,5-diketones towards dehydrating agents and ammonia, as routes to 1,4-pyran[5,6] and 1,4-dihydropyridine[6] derivatives, respectively motivated me to study its behaviour towards polyphosphoric acid (PPA), ammonium acetate and 4-aminoantipyrine. Thus, compound **4** was subjected to cyclization in the presence of PPA to give 4H-2,4,6-tri(antipyrin-4-yl)-pyran **5**. Its IR spectrum showed absorption bands at 1670 cm^{-1} (CO-antipyrine) and 1640 cm^{-1} (C=N) and lacked the absorption of ($-CH_2-CO$). On the other hand, treatment of compound **4** with ammonium acetate and 4-aminoantipyrine in glacial acetic acid afforded **6** and **7**, respectively.

In the present study the Claisen condensation of 4-acetylantipyrine **1** with ethyl acetate and diethyl oxalate have been utilized to obtain some new 4-substituted-antipyrine. Therefore, compound **1** was subjected to Claisen condensation with ethyl acetate to give 4-acetoacetylantipyrine **8** in poor yield, the structure of which was supported by the IR spectrum which showed bands at 3480-3420 cm^{-1} (OH, enolic) and 1685 cm^{-1} (CO, β-diketone).

Condensation of **1** with dietyl oxalate in the presence of sodium ethoxide afforded ethyl (4-oxaloacetyl)-antipyride **9**, its structure was confirmed by IR and ^{1}H-NMR spectra. On the other hand, Claisen condensation of **1** with diethyl oxalate in a molar ratio of 2 : 1 yielded **10**. The formation of **10** finds analogy with that reported by Finar[7] on the condensation of diethyl oxalate with acetophenone and with that reported by me on the formation of 2-acetoacetyl-1,3-indandione[8].

It has been reported that indoles react with aldehydes or ketones in the presence of acids to give diindolymethane derivatives[9,10]. To find out a combination between antipyrine and indole, 4-formyl-



antipyrine **2** was subjected to react with indole in ethanol hydrochloric acid mixture (2 : 1) at room temperature to give 4-antipyrinyl-3,3′-diindolylmethane **11**. The ^{1}H-NMR of **11** showed singletes at δ 2.1 (3H, antipyrinyl $C^3C\underline{H}_3$), 3 (3H, antipyrinyl N^2 $C\underline{H}_3$), 5.7 (1H, methine) and 10.8 (2H, indolic N<u>H</u>). On the other hand, attempts to apply the same reaction using 4-acetylantipyrine **1** was unsuccessful.

EXPERIMENTAL

All mp.'s are uncorrected and were taken in a Gallenkamp electric melting point apparatus. IR spectra were performed on a Unicam SP 2000 IR spectrophotometer using KBr. ^{1}H-NMR, spectra were obtained on a varian Gemini-200 (200 MHz).

1,3-Di (antipyrin-4-yl)-prop-1-ene-3-one, 3

Method A : To a solution of **1** (0.01 mol, 2.3 g) and **2** (0.01 mol, 2.16 g) in ethanol (40 m*l*) was added NaOH (50%, 0.5 m*l*). The reaction mixture was stirrd at room temperature for 4 h., left to stand overnight, poured onto water (100 m*l*), acidified with dil. HCl and the precipitated solid was recrystallized from aq. ethanol to give yellow crystals (1.7 g, 43%). mp. 176℃.

Method B : A mixture of **1** (0.01 mol, 2.3 g) and **2** (0.01 mol, 2.16 g) was heated at 160-165℃ for 1.5 h. The reaction mixture was left to cool and recrystallized from aq. ethanol to give **3** (2.4 g, 56%). mp. 176℃ (mixed mp.); IR (cm^{-1}): 1680 (α, β-unsaturated ketone), 1670 (CO, antipyrine) and 1640 (C=N); $C_{25}H_{24}N_4O_3$ (428.5); calcd.: C 70.07, H 5.65, N 13.08; Found: C 70.0, H 5.5, N 12.9.

1,3,5-Tri (antipyrin-4-yl)-pentan-1,5-dione, 4

Method A : To a mixture of **1** (0.01 mol, 2.3 g) and **2** (0.005 mol, 1.08 g) in ethanol (50 m*l*) was added few drops NaOH (50%). The reaction mixture was refluxed for 3 h., on a steam bath, left to cool, poured onto water, acidified with dil. HCl, and the precipitated solid was recrystallized from aq. ethanol to give a buff powder (1.7 g, 52%). mp. 221-225℃; IR (cm^{-1}): 1710 (CO), 1670 (CO, antipyrine) and 1640 (C=N); ^{1}H-NMR ($CDCl_3$): δ 2.5 (s, 9H, antipyrinyl C^3 $C\underline{H}_3$), 3.0 (s, 9H, antipyrinyl N^2 $C\underline{H}_3$), 3.2 (d, 4H, $2C\underline{H}_2$-CO), 3.4 (m, 1H, methine) and 7.2-7.6 (m, 15H, aromatic protons); $C_{38}H_{38}N_6O_5$ (658.7); calcd: C 69.28, H 5.81, N 12.76; Found: C 69.2, H 5.6, N 12.5.

Method B : To a solution of **3** (0.002 mol, 0.86 g) in 20 m*l* 3% $NaOCH_3$, **1** (0.002 mol, 0.46 g) was added. The reaction mixture was refluxed for 6 h, left to cool, diluted with H_2O (30 m*l*), acidified with dil. HCl and the precipitated solid was recrystallized from aq. ethanol to give **4** (0.8 g, 61%). mp. 222-224℃ (mixed mp.).

4H-2,4,6-Tri (antipyrin-4-yl)-pyran, 5 : A mixture of **4** (1 g) and polyphosphoric acid (10 g) was heated for 1.5 h. at 130-40℃. The reaction mixture was diluted with water (100 m*l*), the solid obtained was filtered and recrystallized from ethanol to give brown powder (0.4 g, 41%). mp. 125℃; IR (cm^{-1}): 1670 (CO, antipyrine) and 1640 (C=N); $C_{38}H_{36}N_6O_4$ (640.7); calcd: C 71.23, H 5.66, N 13.12; Found: C 71.2, H 5.6, N 13.0.

1,4-Dihydro-2,4,6-tri (antipyrin-4-yl) pyridine, 6 and 1,4-dihydro-1,2,4,6-tetra (antipyrin-4-yl) pyridine, 7

To a solution of **4** (0.001 mol, 0.66 g) in glacial acetic acid (10 m*l*) was added amm. acetate (0.002

mol, 0.15 g) and/or 4-aminoantipyrine (0.0013 mol, 0.26 g). The reaction mixture was refluxed for 10 h, left to cool, diluted with water (50 m*l*) and the precipitated solid recrystallized from ethanol. Compound **6**: Pale yellow powder, mp. 245℃ (0.4 g, 63%); IR (cm^{-1}): 3390-3320 (NH), 1660 (10, antipyrine) and 1630 (C=N); calcd: C 71.34, H 5.83, N 15.33; Found: C 71.2, H 5.6, N 15.2. Compound **7**: Grey powder, mp. 258℃ (0.6 g, 73%); IR (cm^{-1}): 1680 (CO, antipyrine) and 1640 (C=N); $C_{49}H_{47}N_9O_4$ (825.9); calcd: C 71.25, H 5.74, N 15.26; Found: C 71.1, H 5.5, N 15.1.

4-Acetoacylantipyrine*, *8

A suspension of **1** (0.005 mol, 1.15 g) in ethylacetate (25 m*l*) was slowly added to sodium sand (2 g). The reaction mixture was refluxed for 5 h. and the excess ethylacetate was distilled. The reaction mixture was poured onto ice-cold water, acidified with dil. HCl and the resulting solid was recrystallized from aq. ethanol to give pale yellow powder (0.16 g, 12%). mp.>300℃; IR (cm^{-1}): 3480-3420 (OH, enolic), 1685 (β-diketone), 1660 (CO, antipyrine) and 1630 (C=N); $C_{15}H_{16}N_2O_3$ (272.3); calcd: C 66.16, H 5.92, N 10.29; Found: C 65.8, N 6.1, N 10.1.

Ethyl (4-oxaloacetyl)-antipyrine*, *9

To a stirred solution of **1** (0.01 mol, 2.3 g) and diethyl oxalate (0.04 mol, 5.4 m*l*) was added dropwise a solution of sodium ethoxide (0.02 mol, 1.36 g). The reaction mixture was refluxed for 4 h, cooled and then acidified with acetic acid (3%) to give yellow crystals (2.4 g, 73%). mp. 174℃ dec; IR (cm^{-1}): 1725 (α-keto ester), 1690 (β-diketone), 1665 (CO, antipyrine) and 1640 (C=N); ^{1}H-NMR ($CDCl_3$): δ 1.4 (t, 3H, $COOCH_2C\underline{H}_3$), 2.7 (s, 3H, C-$C\underline{H}_3$), 3.1 (s, 3H, N-$C\underline{H}_3$), 3.4 (s, 2H, -CO·$C\underline{H}_2$·CO-), 4.4 (q, 2H, $COOC\underline{H}_2CH_3$) and 7.3-7.6 (m, 5H, aromatic protons); $C_{17}H_{18}N_2O_5$ (330.3); calcd: C 61.81, H 5.49, N 8.48; Found: C 62.1, H 5.6, N 8.3.

1,6-Bis (antipyrin-4-yl)-1,3,4,6-hexantetrone*, *10

To a stirred solution of **1** (0.01 mol, 2.3 g) and diethyl oxalate (0.005 mol, 0.7 m*l*) was added dropwise a solution of sodium ethoxide (0.02 mole, 1.36 g). The reaction mixture was refluxed for 4 h, then worked up as described for compound **9** to give a yellow powder (1.6 g, 62%). mp. 215℃ dec; IR (cm^{-1}): 1705 (α-diketone), 1685 (β-diketone), 1675 (CO, antipyrine) and 1635 (C=N); $C_{28}H_{26}N_4O_6$ (514.5); calcd: C 65.36, H 5.09, N 10.89; Found: C 65.1, H 5.2, N 10.7.

4-Antipyrinyl-3,3'-diindolymethane*, *11

A mixture of **2** (0.01 mol, 2.16 g) and indole (0.02 mol, 2.3 g) in ethanol (10 m*l*) and conc. HCl (5 m*l*) was stirred at room temperature for 3 h., left to stand overnight. The reaction mixture was poured onto water (100 m*l*), basified with NaOH solution and the precipitated solid was recrystallized from ethanol to give a buff powder. (1.6 g, 37%), mp. 269 ℃; IR (cm^{-1}): 3320 (NH, indolic), 1660 (CO, antipyrine) and 1625 (C=N): ^{1}H-NMR [$(C\underline{D}_3)_2SO$]: δ 2.1 (s, 3H, C-$C\underline{H}_3$), 3.0 (s, 3H, N-$C\underline{H}_3$), 5.7 (s, 1H, methine), 6.9-7.6 (m, 15H, aromatic protons) and 10.8 (s, 2H, indolic N$\underline{H}$); $C_{28}H_{24}N_4O$ (432.5); calcd: C 77.75, H 5.59, N 12.96; Found: C 77.7, H 5.7, N 12.8.

LITERATURE CITED

1. Wilson, C. O., Gisvold, O. and Doerge, R. F.: Textbook of *Organic medicinal and pharmaceutical chemistry*, 6th ed., p. 746, 1971, Lippincott Co., Philadelphia, Toronto.
2. Erlenmeyer, H. and Willi, E.: Relation between constitution and physiological activity of pyrazolone derivatives. *Helv. Chem. Acta.* **18**, 740 (1935).
3. Prishchep, T. P.: Comparative pharmacological properties of some acylated 4-aminoantipyrine and of 1-phenyl-3-methyl-4-amino-5-pyrazolone. Farmakol. I Toksikol. 25, 55 (1962); C. A. 57, 13859 (1962).
4. Mario R. and Silvio Checchi (Univ. Florence): New derivatives of antipyrine, isoantipyrine and pyrazolidine. *Ann. Chim.* (Rome) **43**, 816 (1953). C. A. **49**, 6235 (1955).
5. Acheson, R. M.: *An introduction to the chemistry of heterocyclic compounds*, 2nd. ed., p. 239, 1967, John Wiley and Sons, Inc., New York, London, Sydney and Toronto.
6. Kataritzky, A. R.: *Handbook of heterocyclic chemistry*, 1st ed. pp. 404, 1985, Pergamon Press, Oxford, New York, Toronto, Sydney and Frankfurt.
7. Finar, I. L.: Preparation and properties of some bipyrazolyls. *J. Chem. Soc.*, 1208 (1955).
8. Hamama, W. S., Hammouda, M. and Afsah,

E. M.: Synthesis of 2-acetoacetyl-and 2-oxaloacetyl-1,3-indandiones and related compounds. Z. Naturforsch. 43b, 897 (1988).
9. Thesing, J.: Chemistry of indole III. The effect of alkali on quaternary salts of gramine. *Chem. Ber.*, **87**, 692 (1954).
10. Gray, A. P. and Archer, W. L.: Pyridylethylation of indole and related reactions. *J. Am. Chem. Soc.* **79**, 3554 (1957).