Acta Pharmaceutica Turcica
XLIII (2) (117-120) 2001

STUDIES ON THE SYNTHESIS OF SOME NEW ANTIPYRINE DERIVATIVES

BAZI YENİ ANTİPİRİN TÜREVLERİNİN SENTEZLERİ ÜZERİNE ÇALIŞMALAR

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Some new 4-(4,5-diarylimidazole-2-yl) antipyrine, 4-(5-substituted benzimidazole-2-yl) antipyrine and 4-(phenantroimidazole-2-yl) antipyrine derivatives were synthesised. The structure elucidations of the compounds were performed by IR and ^{1}H-NMR spectroscopic data and elemental analyses results.

Bazı yeni 4-(4,5-diarilimidazol-2-il) antipirin, 4-(5-sübstitüe benzimidazol-2-il) antipirin ve 4-(fenantroimidazol-2-il)antipirin türevleri sentezlendi. Elde edilen bileşiklerin yapıları IR ve ^{1}H-NMR spektroskopik; yöntemleri ve elementel analiz sonuçları yardımıyla aydınlatıldı.

Keywords: *Antipyrine; 1,2-Diketone; 1,2-Diaminobenzene; Synthesis*

Anahtar Kelimeler: *Antipirin; 1,2-Diketon; 1,2-Diaminobenzen; Sentez*

Introduction

Antipyrine, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, was the first pyrazolone derivative, especially known with analgesic, antipyretic and anti-inflammatory effects (1). One of the authors' previous works on the analgesic activity of some 4-(2-phenyloxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones from 4-(aroyloxyalkanoyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones (2-4), 4-(benzazol-2-yl)thioacetylantipyrines (5), antipyrinyloxoalkylthioquinazolinones (6) and many other studies on obtaining new antipyrine derivatives (7-11) encouraged us for the synthesis of some new antipyrine derivatives. In this study, we aimed to combine the well-known antipyrine with another ring system that we think should be helpful on enhancing the activity of the new derivatives. For this purpose, another well known ring system, imidazole residue has been chosen since there have been reports on its analgesic and anti-inflammatory activities (11-15).

Materials and Methods

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded using the following instruments: IR: Shimadzu 435 IR spectrophotometer, ^{1}H-NMR: Jeol JNM-EX 90A FT NMR spectrometer, DMSO-d_6, TMS as internal standards. Analyses for C, H, N were within 0.4 % of the theoretical values.

4-Formylantipyrine(16) and phenantro-9,10-dione(17) were prepared as described in the literature. Benzil derivatives, furil and thienil were obtained by oxydating the corresponding benzoines, furoine and thienoine. Some characteristics of the compounds obtained were given in table.

* Correspondence:

Table. Some characteristics of the compounds.

Comp.	M. P. (°C)	Yield (%)	Formulae	Mol. Weight (g)
1	221-2	72	$C_{26}H_{22}N_4O$	406.47
2	208-9	76	$C_{28}H_{26}N_4O$	434.52
3	193-5	82	$C_{28}H_{26}N_4O_3$	466.52
4	177-8	75	$C_{26}H_{20}Cl_2N_4O$	475.36
5	125-8	68	$C_{22}H_{18}N_4O_3$	386.39
6	163-5	70	$C_{22}H_{18}N_4OS_2$	418.51
7	196-8	72	$C_{26}H_{20}N_4O$	404.45
8	290-3	52	$C_{18}H_{15}N_4O$	303.33
9	218-9	48	$C_{19}H_{18}N_4O$	318.36
10	232-5	44	$C_{18}H_{15}ClN_4O$	338.783

Synthesis of the compounds

Method 1. 4-Formylantipyrine (5 mmol) and an appropriate derivative of 1,2-diketone (5 mmol) were refluxed for 3 hours with ammonium acetate (50 mmol) in acetic acid. The mixture was poured into ice water and ammonium hydroxide solution was added to adjust the pH to 6-6.5. The precipitate was filtered and recrystallised from ethanol.

Method 2. 4-Formylantipyrine (5 mmol), an appropriate derivative of 1,2-diaminobenzene (5 mmol) and $NaHSO_3$ (5 mmol) were refluxed for 6 hours in methanol. The solvent was evaporated and the precipitate so formed was filtered and crystallised from ethanol. The IR spectrum of these compounds were as;

1: **IR** (KBr)ν_{max} (cm^{-1}): 3200-2500 (N-H), 1645 (C=O), 1602-1450 (C=N, C=C). **^{1}H-NMR** σ(ppm): 2.65 (3H, s), 3.44 (3H, s), 7.1-8.2 (15H, m), 12.90 (1H, bs).

2: **IR** (KBr)ν_{max} (cm^{-1}): 3260-2450 (N-H), 1642(C=O), 1595-1480(C=N, C=C). **^{1}H-NMR** σ(ppm): 2.45(6H, s), 2.66(3H, s), 3.46(3H, s), 7.2-7.7(13H, m), 12.95(1H, bs).

4: **IR**(KBr)ν_{max} (cm^{-1}): 3250-2450 (N-H), 1645(C=O), 1605-1450(C=N, C=C). **^{1}H-NMR** σ(ppm): 2.66(3H, s), 3.45(3H, s), 7.2-7.62(5H, m), 7.82(4H, d, j:8.10), 8.07(4H, d, j:8.12), 13.00(1H, bs).

6: **IR**(KBr)ν_{max} (cm^{-1}): 3290-2500 (N-H), 1645(C=O), 1600-1445(C=N, C=C). **^{1}H-NMR** σ(ppm): 2.64(3H, s), 3.44(3H, s), 7.15-7.72(11H, m), 12.95(1H, bs).

7: **^{1}H-NMR** σ(ppm): 2.65(3H, s), 3.45(3H, s), 7.25-7.82(9H, m), 8.45-8.67(2H, m), 8.81-8.90(2H, m), 12.90(1H, bs).

8: **IR**(KBr)ν_{max} (cm^{-1}): 3200-2500 (N-H), 1640(C=O), 1590-1480(C=N, C=C). **^{1}H-NMR** σ(ppm): 2.62(3H, s), 3.40(3H, s), 7.02-7.72(9H, m), 12.95(1H, bs).

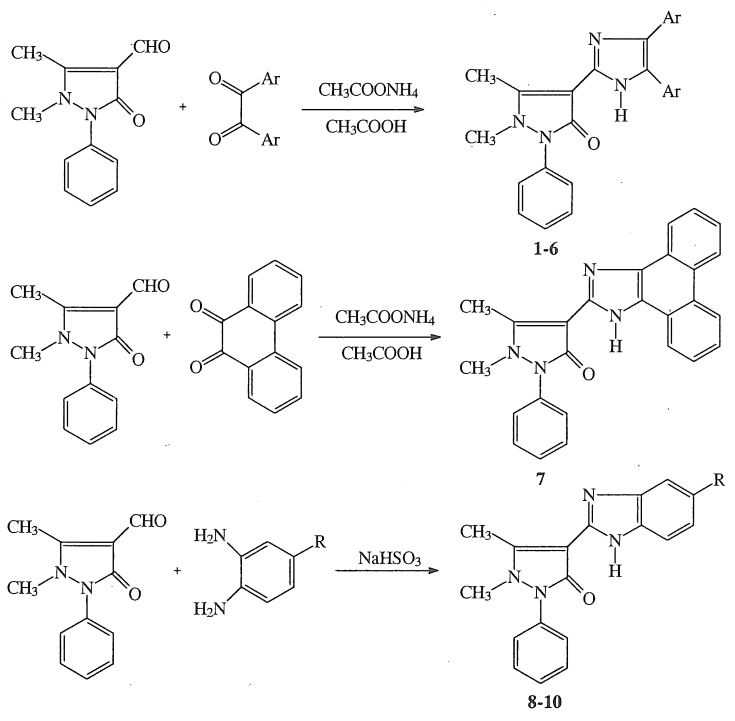
10: **IR**(KBr)ν_{max} (cm^{-1}): 3250-2460 (N-H), 1652(C=O), 1595-1450(C=N, C=C). **^{1}H-NMR** σ(ppm): 2.62(3H, s), 3.45(3H, s), 7.2-7.84(8H, m), 12.90(1H, bs).

Results And Discussion

Some 4-(4,5-diarylimidazole-2-yl) antipyrine **[1-6]**, and 4-(phenantroimidazole-2-yl) antipyrine **[7]** 4-(5-substituted benzimidazole-2-yl) antipyrine **[8-10]** derivatives were prepared using the synthetic methods outlined on the Scheme.

Synthesis of imidazole and phenantroimidazole derivatives, **[1-7]**, using 4-formylantipyrine and appropriate 1,2-diketo compound have been performed according to the general method of the literature(18). In this method, an aldehyde and a 1,2-diketo compound in acetic acid were heated in the presence of ammonium acetate.

Benzimidazole derivatives **[8-10]** were prepared by reacting 4-formylantipyrine and an appropriate 1,2-diaminobenzene derivative. In this general method, 1,2-diaminobenzene and aldehyde bisulfite adduct were heated in methanol(19).



Comp.	Ar
1	
2	
3	
4	
5	
6	

Comp.	R
8	H
9	CH_3
10	Cl

Scheme-Synthesis of the compounds

The structures of the compounds were elucidated by spectral data and elemental analyses. In the IR spectra, some significant stretching bands due to N-H, C=O, C=N and C=C were observed at about 3200-2450, 1640-1652 and 1590-1445 cm^{-1} regions respectively. As was expected the carbonyl stretching band at the fourth position of 4-formylantipyrine was no longer present in our compounds. Also, the C=N bands of the newly constructed imidazole residues at 1590-1445 cm^{-1} were observed.

In the NMR spectra, the signals due to 2-CH_3 and 3-CH_3 of the pyrazole nucleus appeared at 2.62-2.66 and 3.40-3.46 ppm and N-H in the imidazole nucleus appeared at 12.90-13.00 ppm regions respectively. The signals of other alkyl or aryl groups were also observed as expected.

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Accepted: 01.02.2001