1-(ACRIDIN-9'-YL)-PYRAZOLIN-3 AND 5-ONES. A NEW CLASS OF HETEROCYCLES WITH POTENTIAL BIOLOGICAL ACTIVITY.

Ioan Cristea*[a], Mariana M. Popovici, Maria T. Mendel[b], Ioan Silaghi-Dumitrescu[a] and Erika Kozma[a]

[a]Department of Organic Chemistry, "Babeş-Bolyai" University, Str. Arany Janoş 11, 3400 Cluj-Napoca, Romania, e-mail: cristea@chem.ubbcluj.ro
[b]Chemical and Pharmaceutical Research Institute, Str. Fabricii 126, 3400 Cluj-Napoca.Romania

Abstract: *1-(Acridin-9'-yl)-3-methylpyrazolin-5-ones 3 a-c were synthesised by cyclocondensation of 9-hydrazinoacridine derivatives 1a-c* with *ethylacetoacetate in NaOH methanolic solution and 1-(acridin-9'-yl)-5-methylpyrazolin-3-ones 4a-c respectively, by arylation of 3-methyl-5-pyrazolone 5 with 9-chloroacridine derivatives 6a-c. The structural assignments and the stereochemistry of these compounds were confirmed by spectroscopic methods (IR, UV, ^{1}H-NMR) and AM1 molecular orbital calculations.*

INTRODUCTION

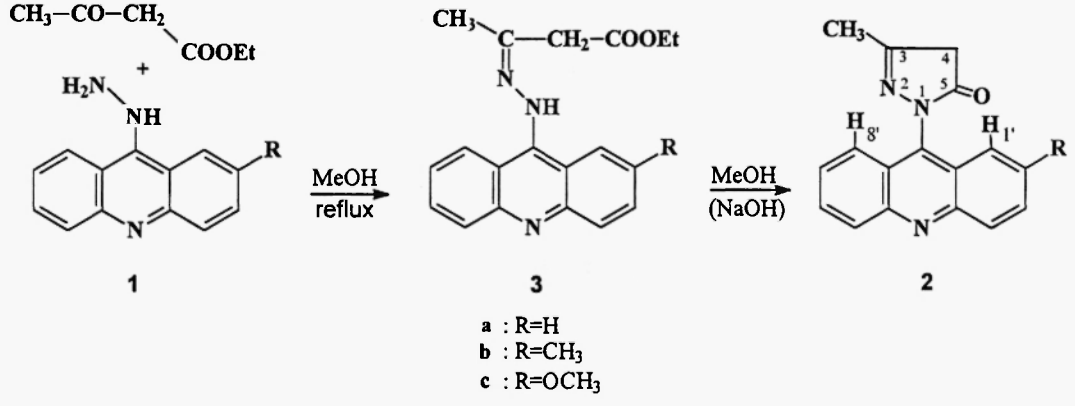
The chemistry of pyrazolinones is well known, 5-pyrazolinones have been by far the most commercially important members of pyrazole type, having been widely used as pharmaceuticals, as dyes, and in colour photography (1,2). Because of the importance of 5-pyrazolinone and of its derivatives, much attention has been devoted to the compounds of this type (3-5). Since the first pyrazolinone was developed by Knorr in 1883, many papers have been published on 1-arylpyrazolin-5-one analgesics and antiinflammatories. In order to find new compounds with biological activity, the phenyl ring from the position 1 of pyrazolinone system was substituted by pyrimidine ring. Thus, 1-pyrimidinylpyrazolin-5-ones, a new class of heterocycles relatively recently discovered (6-8), exhibit less toxicity than 1-phenylpyrazolin-5-ones and present a very high interest by its potent biological activity. There have been several reports (9-11) on the synthesis and pharmacological studies on 1-pyrimidinylpyrazolin-5-ones.

Following our investigations (11,12) on the synthesis of new compounds containing an heterocycle ring in the position 1 of pyrazolinone system, we have obtained a new class of heterocycles: *1-(acridin-9'-yl)-pyrazolinones* .These compounds may prove to be interesting as they contain both pyrazolone system, present in many known drugs, and acridine ring, present in many biologically active substances. These compounds can also be useful intermediates in synthesis of dyes and pigments. 5-Pyrazolinones are very reactive at C-4, and most of the important reactions they undergo occur at that position. Condensation with aromatic aldehydes and ketones can form 4-arylidenepyrazolinones used as colour couplers, the reaction with diazonium salts serves to synthesise the widely used 4-

arylazopyrazolinone dyes. In this paper, we have synthesised some 1-(acridin-9'-yl)-3-metylpyrazolin-5-ones **3a-c** and 3-one **4a-c** , and developed a study concerning the stereochemistry of the new compounds, by IR, UV and ^{1}H-NMR methods. AM1 molecular orbital calculations (13) have been performed in order to establish the structure of these compounds.

RESULTS AND DISCUSSION

In our investigations, 1-(acridin-9'-yl)-3-methylpyrazolin-5-ones **3a-c** were obtained by a Knorr-type cyclocondensation of 9-hydrazinoacridines **1a-c** with ethyacetoacetate in methanol solution under basic catalysis. Thus, when equimolar amounts of the 9-hydrazinoacridines **1a-c** and ethylacetoacetate were heated in methanol under reflux for 1.5 hours, they afforded the hydrazones **2a-c**, as intermediates.



1 3 2

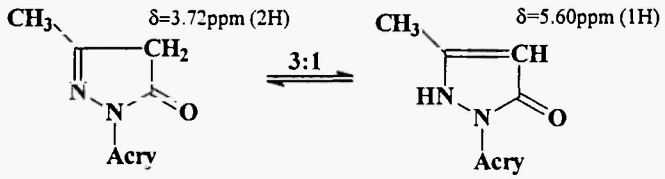
a : R=H
b : R=CH_3
c : R=OCH_3

Scheme 1

For 9-hydrazinoacridine **1a** the corresponding hydrazone was isolated and characterised by elemental analysis and spectral data. For the other compounds the intermediate hydrazones were not isolated, the refluxing methanolic solution was than treated with aq. NaOH 50% at 60^{0}C for 2 hours, to afford the corresponding 1-(acridin-9'-yl)-3-methylpyrazolin-5-ones **3a-c**, in about 60% yields (Scheme 1). The reactions were monitored by TLC using "Merck" silicagel 60 F 254 plates, and chloroform:acetone 9:1 as eluent.

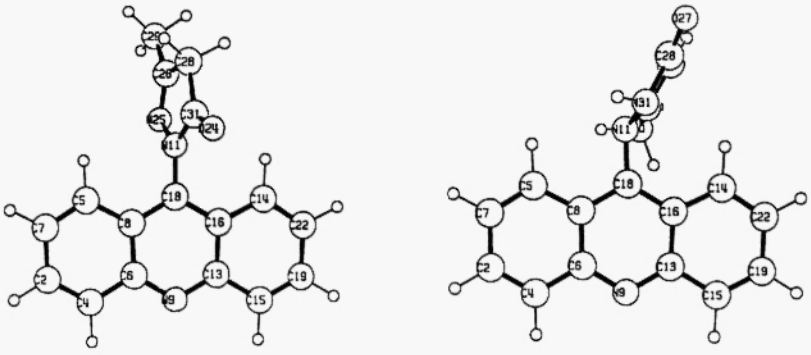
The structural assignments and the stereochemistry for the synthesised compounds were confirmed by ^{1}H-NMR methods. Thus the NMR spectra for all the compounds **3a-c** have the same chemical shifts (δ= 2.32 ppm) for the methyl protons located in position 3 of pyrazolone ring. It's well known that the pirazolone derivatives exist in solution in three tautomeric forms: (A)-methylenic, (B)-iminic, (C)-phenolic (14). The spectral studies on 1(acridin-9'-yl)-3-methylpyrazolin-5-ones revealed that in non-polar or aprotic solvents as carbon tetrachloride or chloroform-d, the only methylenic form (A) was observed. NMR spectra have confirmed the existence of two hydrogen atoms at the 4-position of

pyrazolone ring (δ= 3.72ppm, 2H, $CDCl_3$). IR spectra examined in chloroform and carbon tetrachloride exhibit a sharp band $\nu_{C=O}$ located higher than 1704 cm^{-1}, which corresponds to an unconjugated carbonyl group. NMR spectra in polar solvents as acetone-d_6 and DMSO-d_6 revealed that the methylenic form (A) prevailed and an equilibrium with iminic form (B) is likely to exist (ratio 3:1). The chemical shift for the proton from the position 4 of pyrazolone ring is located at δ= 5.60ppm (acetone-d_6)for the iminic form (Scheme 2).



Scheme 2

The ^{1}H-NMR spectrum for the compound **3a** shows that the acridine protons H1' and H8' are equivalent, having the same chemical shift (δ=7.92 ppm, 2H, dd). The molecular structure of the compound **3a** has also been estimated by full geometry optimisation at the AM1 semiempirical molecular orbital level by using the PCSpartan [PCSpartan, Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370, Irvine, 92612 California] package from Wavefunction. Thus, the two rings (pyrazolone and acridine) are non-coplanar because of interference with the hydrogen atoms from the 1'- and 8'-positions, and the angle between the plane of acridine ring and that of the pyrazolone ring is about 70^0 (Figure 1).



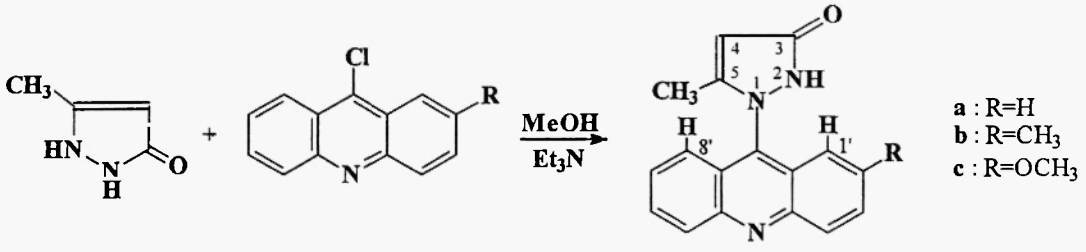
3a **4a**

Figure 1. The AM1 optimised geometries of 1-(acridin-9'-yl)-3-methylpyrazolin-5-one **3a** and 1-(acridin-9'-yl)-5-methylpyrazolin-3-one **4a**.

UV spectra of the compounds **3a-c** similar to that of acridine (λ_{max}= 258, 350 nm, EtOH) suggested that resonance between acridine and pyrazolone rings is diminished by steric hindrance between the pyrazolone ring and the hydrogen atoms in the 1- and 8-positions, leading to the loss of the coplanar-

ity (15). Also, the barrier of rotation around the C_9 -N_1 bond in the compound **3a** is of order of 0.2 kcal/mol which is enough small to allow the flipping of the pyrazolone ring so that the H_1 and H_8 protons become equivalent in NMR. The enthalpy of formation for iminic form (B) is higher by 11.2 kcal/mol than for methylenic form (A). This explains why in nonpolar solvents only methylenic form (A) was observed in ^{1}H-NMR spectra. However this difference is reduced in presence of polar solvents, for exemple, AM1-SM2 model (16) gives a smaller difference between the enthalpies of formation for A and B (7.1 kcal/mol). This, in connection with the greater dipole-moment for B (4.94 D compared to 4.10 D for A) explains the equilibrium between the two tautomers observed by NMR.

1-(Acridin-9'-yl)-5-methylpyrazolin-3-ones **4a-c** were synthesised by arylation of 5-methyl-3-pyrazolone **5** with 9-chloroacridine derivatives **6a-c** in methanolic solution under basic catalysis. The best yields were obtained in about 65% yields, using Et_3N or piperidine as basic catalyst.



5 **6a-c** **4a-c**

Scheme 3

The reactions were monitored by TLC using "Merck" silicagel 60 F 254 plates, and hexane: ethylacetate: chloroform 5:3:1 as eluent. The structural assignments and the stereochemistry for the compounds **4a-c** were studied by ^{1}H-NMR spectroscopy and AM1 molecular orbital calculations for the compound **4a**. The ^{1}H-NMR spectra revealed that in non-polar or polar solvents as carbon tetrachloride, chloroform, acetone -d_6, DMSO-d_6, the only iminic form is observed. Thus, the methyl signals from the 5 position of pyrazolone ring have appeared at δ=1.81-1.85ppm, significantly shielded due to the steric hindrance caused by the acridine ring. The spectra for all the compounds **4a-c** display a singlet for the proton from the 4 position of pyrazolone ring located at δ=5.60ppm ($CDCl_3$, 1H). Also, for the acridine ring, the NMR spectrum for the compound **4a** shows that the protons H1'and H8' are non-equivalent (H1'δ=7.80ppm, H8'δ=7.55ppm). This fact is explained by AM1 molecular calculations for the compound **4a** , which shows an envelope conformation for pyrazolone ring where the N1 atom is more pyramidal (Figure 1). IR spectra recorded in carbon tetrachloride and chloroform show that the vibration $\nu_{c=o}$ appears at 1685-1690 cm^{-1} corresponding to a conjugated carbonyl group (17). Details concerning the biological tests for the new compounds obtained will be the topic of a next paper.

EXPERIMENTAL

The melting points were determined in capillaries and are uncorrected. IR spectra were recorded with a FT-IR 5300 JASCO apparatus in solutions or in the solid state (KBr pellets). ^{1}H-NMR spectra were recorded with 300 MHz Varian spectrometer using TMS as an internal standard. Electronic spectra were recorded in MeOH on a "Specord" spectrophotometer. Thin layer chromatography was performed on TLC plastic sheets with silica gel 60 F 254.

General procedure for compounds 3a-c

A mixture of 9-hydrazinoacridine (0.1 mol) and ethylacetoacetate (0.1 mol) in 100 ml methanol was heated under reflux for 1.5 hours. A solution of 6 g NaOH in 10 ml water and 40 ml MeOH was then dropwise added and the mixture refluxed for an extended period of time (2h). The solvent was removed by distillation, and the reaction mixture was diluted with 150 ml water, neutralised with acetic acid to pH = 6.5-7 and allowed to stand at room temperature for two hours. The filtered precipitate was recrystallized from the proper solvent.

General procedure for compounds 4a-c

A mixture of 9-chloroacridine (0.1 mol), 5-methyl-3-pyrazolone (0.1 mol) and 10 ml Et_3N in 400 ml MeOH was heated under reflux for 2 hours. The solvent was removed by distillation, the mixture diluted with 200 ml water was neutralised with HCl 0.1 N, then recrystallized from the proper solvent.

1-(acridin-9'-yl)-3-methylpyrazolin-5-one (3a)

Pale green, m.p. 185^{0}C. Yield 68% (AcOEt). Anal. Calcd. for $C_{17}H_{13}N_3O$: C 74.18, H 4.72, N 15.27; found: C 74.23, H 5.12, N 15.50; ^{1}H-NMR, δppm, ($CDCl_3$): acridine ring: 7.64(H3'=H6',t,2H), 7.75(H2'=H7', t, 1H), 7.92(H1'= H8', d, 2H), 8.26(H4'=H5', d, 2H); pyrazolone ring: 2.32(3-CH_3, s, 3H), 3.72(4-CH_2, s, 2H); IR (cm^{-1}, $CDCl_3$): 680, 875, 1542, 1710, 3425; UV, λ_{max}=258, 350 (EtOH).

1-(2'-methylacridin-9'-yl)-3-methylpyrazolin-5-one (3b)

Brown, m.p. 150^{0}C. Yield 64% (acetone). Anal. Calcd. for$C_{18}H_{15}N_3O$: C 74.74, H 5.19, N 14.53; found: C 73.92, H 4.95, N 14.89; ^{1}H-NMR, δppm, ($CDCl_3$): acridine ring: 7.53(H1', s, 1H), 7.76(H3',d, 1H), 7.90(H6', H7',m, 2H), 8.10(H8', d, 1H), 8.20(H5',d, 1H), 1.95(2'-CH_3 ,s, 3H); pyrazolone ring: 2.30(3-CH_3, s, 3H), 3.82(4-CH_2, s, 2H); IR (cm^{-1}, $CDCl_3$): 690, 845, 1532, 1715, 3415; UV, λ_{max}=258, 355 (EtOH).

1-(2'-methoxyacridin-9'-yl)-3-methylpyrazolin-5-one (3c)

Yellow,m.p. 174^{0}C. Yield 60% (AcOEt). Anal. Calcd. for$C_{18}H_{15}N_3O_2$: C 70.82, H 4.92, N 13.77; found: C 69.80, H 4.50, N 13.25; ^{1}H-NMR, δppm, ($CDCl_3$): acridine ring: 7.56(H1',s,1H), 7.76(H3',d, 1H), 7.90(H6', H7', m, 2H), 8.05(H8', d, 1H), 8.10(H4',d, 1H), 8.20(H5',d, 1H), 3.90(2'-OCH_3, s, 3H); pyrazolone ring: 2.30(3-CH_3, s, 3H), 3.82(4-CH_2, s, 2H); IR (cm^{-1}, $CDCl_3$): 670, 895, 1542, 1725, 3435; UV, λ_{max}=255, 355, 381 (EtOH).

1-(acridin-9'-yl)-5-methylpyrazolin-3-one (4a)

Yellow, m.p. 270°C, Yield 72% (MeOH). Anal. Calcd. for $C_{17}H_{13}N_3O$: C 74.18, H 4.72, N 15.27; found: C 73.98, H 5.00, N 14.95; ^{1}H-NMR, δppm, ($CDCl_3$): acridine ring: 7.50-7.65 (H2',H3`,H6`, H7`, m, 4H), 7.55(H8`, d, 1H), 7.80(H1`, d, 1H), 8.25(H4'=H5`, d, 2H); pyrazolone ring: 1.82(5-CH_3, s, 3H), 5.60(4-CH, s, 1H); IR (cm^{-1}, $CDCl_3$): 670, 754, 855, 1542, 1685, 3425; UV, λ_{max} =250, 345 (EtOH).

1-(2'-methylacridin-9'-yl)-5-methylpyrazolin-3-one (4b)

Green, m.p. 140°C. Yield 72% (EtOH). Anal. Calcd. for$C_{18}H_{15}N_3O$: C 74.74, H 5.19, N 14.53; found: C 73.85, H 5.45, N 14.10; ^{1}H-NMR, δppm, ($CDCl_3$): acridine ring:7.50(H8',d, 1H),7.65-7.78 (H2', H3`,H6`,H7`, m, 4H), 7.70(H1', d, 1H), 8.14(H4'=H5', d, 2H), 2.30(2'-CH_3 , s, 3H); pyrazolone ring: 1.81(5-CH_3 ,s, 3H), 5.62(4-CH, s, 1H); IR (cm^{-1}, $CDCl_3$): 650, 704, 355, 1542, 1690, 3440; UV, λ_{max} =250, 345,367 (EtOH).

1-(2'-methoxyacridin-9'-yl)-5-methylpyrazolin-3-one (4c)

Yellow,m.p. 134°C. Yield 63% (AcOEt). Anal. Calcd. for$C_{18}H_{15}N_3O_2$: C 70.82, H 4.92, N 13.77; found: C 70.12, H 5.20, N 13.45; ^{1}H-NMR, δppm, ($CDCl_3$): acridine ring: 7.52(H8',d, 1H),7.60-7.78 (H2', H3`,H6`,H7`, m, 4H), 7.82(H1', d, 1H), 8.12(H4'=H5', d, 2H), 3.78(2'-OCH_3 , s, 3H); pyrazolone ring: 1.85(5-CH_3 ,s, 3H), 5.58(4-CH, s, 1H); IR (cm^{-1}, $CDCl_3$): 704, 335, 1532, 1687, 3440; UV, λ_{max} =255, 355,367 (EtOH).

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