Acid-Catalysed Rearrangement of 1-Oximinoacridine-1,9-diones. Synthesis of Novel 4,5-Dihydro-3*H*-isoxazolo[3,4,5-*kl*]acridines[+]

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[+]Dedicated to Dr. K. Nagarajan on the occasion of his sixtieth birthday

A polyphosphoric acid (PPA) catalysed internal cyclization of 1-oximinoacridine-1,9-diones **2** to novel isoxazolo[3,4,5-*kl*]acridines **3** is reported. Some of the compounds displayed antimalarial activity in animal models.

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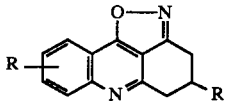
Acridinediones namely Floxacrine **1a** and Deoxyfloxacrine **1b** showed very potent antimalarial activity in the experimental animal models [1,2]. In connection with our work [3,4] to synthesize a structural modification of these acridine derivatives for screening of its antimalarial activities in animal models, we were interested in synthesizing novel isoxazolo[3,4,5-*kl*]acridines of type A.

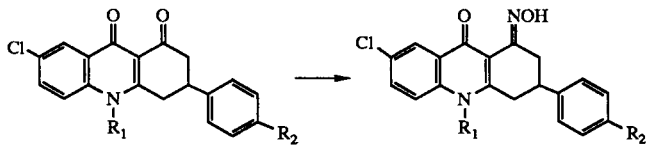


A

Herein we report a simple synthesis of the desired compounds using an acid catalysed rearrangement of acridine oximes **2**.

The acridine oximes **2** required for the present studies

Scheme I



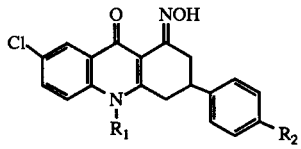
1a-f **2a-f**

a, Floxacrine, $R_1 = OH$, $R_2 = CF_3$
b, Deoxyfloxacrine, $R_1 = H$, $R_2 = CF_3$
c, $R_1 = OH$, $R_2 = Cl$
d, $R_1 = OH$, $R_2 = Cl$
e, $R_1 = OCH_3$, $R_2 = CF_3$
f, $R_1 = OCH_3$, $R_2 = Cl$

were prepared from the corresponding acridinediones [4-6] as shown in Scheme I. The physical data of these oximes are listed in Table 1.

Treatment of the oxime **2c** with polyphosphoric acid (PPA) at 80° for four hours followed by quenching with ice yielded a solid which upon purification on silica gel col-

Table 1
Preparation of Oximes **2**

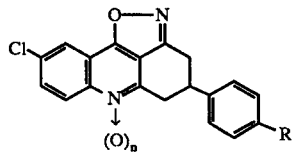


2

Compound No 2	mp °C	Yield %	Molecular Formula	Analysis Found/Calcd. C	H	N	Cl
a	264-265	80	$C_{20}H_{14}ClF_3N_2O_3$	56.93	3.11	6.43	8.58
$R_1 = OH$, $R_2 = CF_3$				56.80	3.30	6.62	8.38
b	265 (266 ref [5])						
$R_1 = OH$, $R_2 = CF_3$							
c	271 dec	84	$C_{19}H_{14}Cl_2N_2O_3$	57.54	4.02	7.06	17.76
$R_1 = OH$, $R_2 = Cl$			1/2 H_2O	57.29	3.80	7.04	17.83
d	294 dec	89	$C_{19}H_{14}Cl_2N_2O_2$	60.90	4.04	7.30	18.76
$R_1 = OH$, $R_2 = Cl$				61.13	3.78	7.50	19.00
e	263-264	87	$C_{21}H_{16}ClF_3N_2O_3$	58.03	3.89	6.18	8.30
$R_1 = OCH_3$, $R_2 = CF_3$				57.74	3.69	6.41	8.12
f	250 dec	79	$C_{20}H_{16}Cl_2N_2O_3$	59.80	4.04	7.26	17.86
$R_1 = OCH_3$, $R_2 = Cl$				59.57	4.00	6.95	17.58

Table 2

Preparation of Isoazolo[3,4,5-*kl*]acridines **3**

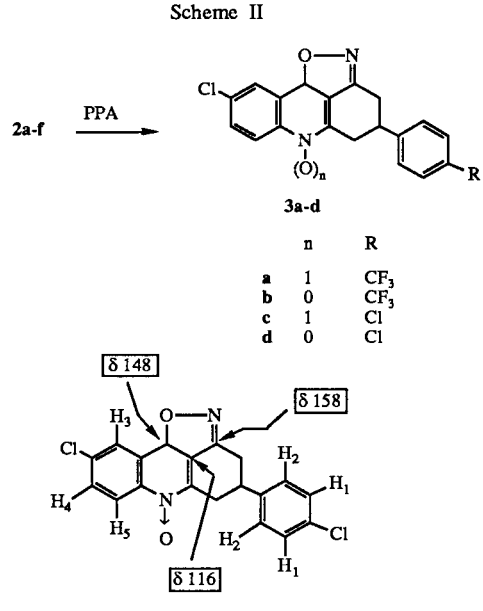


Compound No 3	mp °C	Yield %	Molecular Formula	Analysis Found/Calcd. C	H	N	Cl
a	220-222	94	$C_{20}H_{12}ClF_3N_2O_2$	59.64	2.94	6.78	9.12
n = 1, R = CF_3				59.35	2.97	6.92	8.76
b	206-208	34	$C_{20}H_{12}ClF_3N_2O$	62.02	3.24	6.98	9.35
n = 0, R = CF_3				61.78	3.11	7.21	9.12
c	>250 dec	66	$C_{19}H_{12}Cl_2N_2O_2$	61.09	3.30	7.88	18.80
n = 1, R = Cl				61.47	3.26	7.53	19.10
d	205 dec	60	$C_{19}H_{12}Cl_2N_2O$	64.35	3.09	7.56	20.04
n = 0, R = Cl				64.24	3.41	7.89	19.96

umn afforded the isoxazolo[3,4,5-*kl*]acridine **3c** in 66% yield as a crystalline solid. It analysed for $C_{19}H_{12}Cl_2N_2O_2$. Its ir spectrum showed the absence of the NOH functional group. The ^{1}H nmr (TFA-d) showed peaks at δ 2.8-3.4 (m, 5H, aliphatic H), 6.6 (two d, 4H, H_1 and H_2), 7.42 (dd, J = 9 Hz, J = 2.5 Hz, 1H, H_4), 7.77 (d, J = 2.5 Hz, 1H, H_3), 7.97 (d, J = 9 Hz, 1H, H_5).

The peak at δ 166 (C=O) present in the ^{13}C nmr spectra of the starting oxime **2c** was absent in the ^{13}C nmr spectra of the product **3c**, instead the characteristic peaks of the isoxazole ring were seen as shown in Scheme II. On the basis of the above spectral data the structure **3c** was assigned to the product.

Scheme II



Initial protonation of the oxime, tautomerisation in the ring B of the oxime **2c** followed by an intramolecular cyclization would presumably yield the isoxazolo[3,4,5-*kl*]-acridine **3c**. This type of internal cyclization was found to be general as shown in Scheme II. Interestingly, demethoxylation followed by internal cyclization occurred on treatment of the oximes **2e** and **2f** with PPA yielding the isoxazolo[3,4,5-*kl*]acridine **3b** and **3d** respectively. Physical data of all the isoxazolo[3,4,5-*kl*]acridine synthesized are listed in Table 2

Compounds **3a** and **3b** displayed antimalarial activity in mice when administered orally. Biological test results will be published elsewhere.

EXPERIMENTAL

All the melting points are uncorrected. Infrared spectra were taken in potassium bromide using a Perkin Elmer 157 spectrophotometer. The ^{1}H nmr spectra were run on a Varian T-60 spectrometer. Chemical shifts (δ) are in parts per million relative to tetramethylsilane. The ^{13}C nmr spectra were run on a JEOL-FX 90Q spectrometer.

Preparation of Oxime **2c**.

To the stirred suspension of acridinedione **1c** (5 g, 0.013 mole) in ethanol (100 ml), a warm aqueous solution of hydroxylamine hydrochloride (5 g, 0.072 mole) and sodium acetate (8 g, 0.098 mole) was added. The reaction mixture was stirred at 60° for 4 hours. It was then cooled to room temperature, the precipitate was filtered, the residue washed with water, alcohol and dried at 70° under vacuum. The dried product was suspended in hot methanol, cooled and the product was collected by filtration, mp 271° dec, yield 3 g, 84%; ^{1}H nmr (TFA-d): δ 2.4-3.9 (m, 5H, aliphatic H), 6.85 (two d, 4H, Ar-H), 7.4-8.1 (m, 3H, Ar-H).

Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O_3 \cdot \frac{1}{2}H_2O$: C, 57.29; H, 3.80; N, 7.04; Cl, 17.83. Found: C, 57.54; H, 4.02; N, 7.06; Cl, 17.76.

Similarly the other oximes **2a-f** were prepared (Table 1).

Rearrangement of Oxime **2c**.

A mixture of the oxime (1 g, 0.003 mole) and polyphosphoric acid (10 g) was heatd at 80° for four hours. The reaction mixture was mixed thoroughly with the help of a glass rod. Ice water was then added to the reaction mixture and it was stirred for fifteen minutes. The solid obtained was filtered and dried under vacuum. Purification of the product by chromatography over silica gel using benzene and chloroform (3:7) as the eluant gave the product **3c**. It was crystallized from chloroform and ether, mp >250° dec, yield 0.63 g, 66%; ^{1}H nmr (TFA-d): δ 2.8-3.4 (m, 5H, aliphatic H), 6.6 (two d, 4H, H_1 and H_2), 7.42 (dd, J = 9 Hz, J = 2.5 Hz, 1H, H_4), 7.77 (d, J = 2.5 Hz, 1H, H_3), 7.97 (d, J = 9 Hz, 1H, H_5).

Anal. Calcd. for $C_{19}H_{12}Cl_2N_2O_2$: C, 61.47; H, 3.26; N, 7.53; Cl, 19.10. Found; C, 61.09; H, 3.30; N, 7.88; Cl, 18.80.

Similarly, the isoxazolo[3,4,5-*kl*]acridines **3a-d** were prepared (Table 2).

Acknowledgement.

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