*Chemistry of Heterocyclic Compounds, Vol. 40, No. 4, 2004*

# SYNTHESIS AND ROTAMERISM OF 9,10-DIARYL-SUBSTITUTED 1,2,3,4,5,6,7,8,9,10-DECAHYDRO-ACRIDINE-1,8-DIONES

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*Condensation of aromatic aldehydes with 5,5-dimethylcylohexane-1,3-dione and primary arylamines gave 9,10-diaryl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones. Several stereochemical features of the synthesized compounds are discussed. Dynamic NMR was used to determine the inversion barriers for the rotamers formed.*

**Keywords:** diaryl-substituted decahydroacridinediones, heterocyclization, rotamerism.

9,10- Disubstituted decahydroacridine-1,8-diones are generally prepared through a Hanztsch synthesis with a wide variety of reaction conditions [1-5]. The synthesis of the target products consists of two stages: the reaction of cyclic ketones with aldehydes and the separation of the Michael adducts followed by their heterocyclization using primary amines. Moreover, the Michael adducts are quite readily cyclized to octahydroxanthones and the second stage of the reaction is almost always accompanied by the formation of quite large amounts of oxygen containing heterocycles.

One of the problems in this work was the development of a single stage method for obtaining the target 9,10-disubstituted decahydroacridine-1,8-diones. Based on general and systematized data [1-8] and certain experimental data we propose a single stage method for the synthesis of diaryl substituted decahydroacridinediones which is more convenient to carry out and gives a higher yield of the final products than does the two stage.

The procedure consists of the reaction of 5,5-dimethylcyclohexane-1,3-dione (**1**, dimedone) with the aldehydes **2a-i** and the primary amines **3a-i**. The selection of reaction conditions (in particular the solvent and the catalyst) appears to the most critical. The reactions in alcohols and slow boiling solvents is independent of the type of catalyst and gives difficult to separate mixtures of the reaction products and the starting materials. The use of the high boiling, polar DMF as solvent appears optimal. It was found that the basic catalysts given in the literature (triethylamine, N-methylmorpholine, piperidine) have little effect and the reaction products are mainly the Michael adducts **4**. At the same time, a large amount of acid catalyst (acetic, trifluroacetic, hydrochloric acid) leads to a heavy contamination of the target compounds **5a-o** by the xanthones **6**. In the method proposed by us a small amount of concentrated hydrochloric acid is used.

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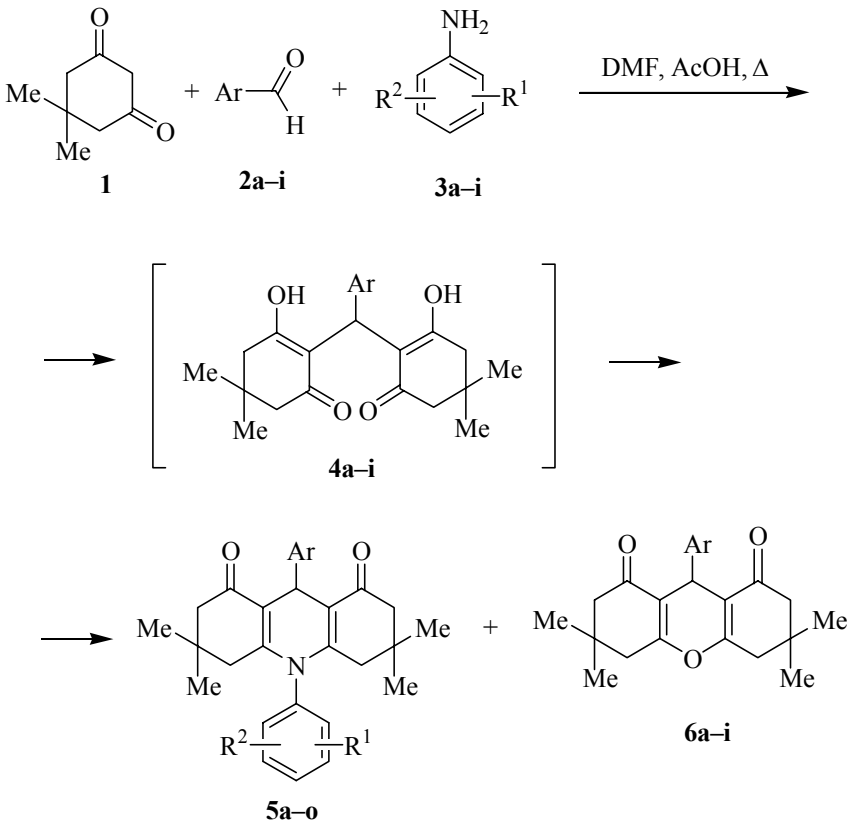
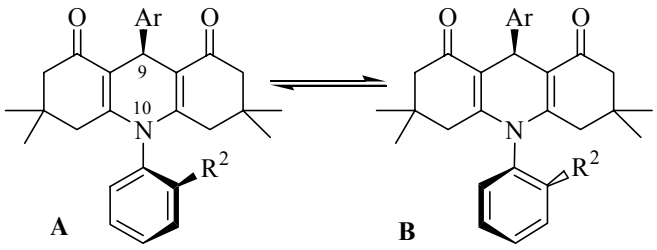



**2, 4, 6 a** Ar = Ph; **b** Ar = 3-$FC_6H_4$; **c** Ar = 4-$MeC_6H_4$; **d** Ar = 4-$BrC_6H_4$; **e** Ar = 4-$ClC_6H_4$;
**f** Ar = 4-$O_2NC_6H_4$; **g** Ar = 2-MeO-5-$BrC_6H_3$; **h** Ar = 4-$FC_6H_4$; **i** Ar = 4-$MeOOCC_6H_4$;
**3 a–c,h,i** $R^1$ = H, **a** $R^2$ = H, **b** $R^2$ = 4-OEt, **c** $R^2$ = 2-F, **h** $R^2$ = 3-$CO_2H$, **i** $R^2$ = 3-F; **d** $R^1$ = 6-F, $R^2$ = 2-F; **e** $R^1$ = 3-Cl, $R^2$ = 2-Cl;
**f** $R^1$ = 4-Cl, $R^2$ = 2-Cl; **g** $R^1$ = 4-OMe, $R^2$ = 2-OMe; **5 a-g,n,o** $R^1$ = H; **a** Ar = Ph, $R^2$ = H, **b** Ar = 3-$FC_6H_4$, $R^2$ = 4-OEt,
**c–g** $R^2$ = 2-F, **c** Ar = Ph, **d,l** Ar = 4-$MeC_6H_4$, **e** Ar = 4-$BrC_6H_4$, **f,i,k,m** Ar = 4-$ClC_6H_4$, **g** Ar = 4-$O_2NC_6H_4$,
**n** Ar = 4-$FC_6H_4$, $R^2$ = 3-$CO_2H$, **o** Ar = 4-$MeOOCC_6H_4$, $R^2$ = 3-F; **h** Ar = 2-MeO-5-$BrC_6H_3$,
$R^1$ = 6-F, $R^2$ = 2-F; **i–l** $R^2$ = 2-Cl, **i**, **j** $R^1$ = 3-Cl, **j** Ar = 2-MeO-5-$BrC_6H_3$, **k,l** $R^1$ = 4-Cl,
**m** $R^1$ = 4-OMe, $R^2$ = 2-OMe

The composition and structure of the synthesized 9,10-diaryl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones **5a-o** were confirmed by elemental analytical data (Table 1) and by $^1$H NMR spectroscopy (Table 2). The reaction products **4a-i** and **6a-i** were not specifically separated from the reaction mixture but their presence was revealed using TLC and $^1$H NMR. Samples of compounds **4a-i** and **6a-i** were prepared for comparison by known methods [2-5].

The $^1$H NMR spectra of compounds **5a-o** show singlets at 0.68 and 0.90 ppm which are assigned to the protons of the four methyl groups in positions 3 and 6, multiplets for the $CH_2$ group protons of the cyclohexane rings in the range 1.42-2.40 ppm, a singlet for the methine proton at 4.93-5.28 ppm, and signals for the aromatic protons in the range 6.60-8.10 ppm, and also for the substitutent in Ar and $R^1$, $R^2$.

At room temperature the spectra of the compounds **5c-g, i-m** with one *ortho* substituent in N–Ar ($R^1$ = H, 2-$R^2 \neq$ H) show a doubling of virtually all of the signals, in particular the methine proton and the methyl group protons. This led us to infer the presence of two diastereomers differing in the relative orientation of the substituents Ar and $R^2$ relative to the plane of the acridine framework, hence showing that the rotamers **A** and **B** have quite a high inversion barrier:




In order to verify this proposal we have studied the dependence of the $^1$H NMR spectra for the synthesized compounds on temperature. With a temperature increase we have found that the plotted doubling of the signals in the spectra of the acridinediones **5c-g, i-m** is gradually lost until they coalesce completely. Measurement of the spectra at -60°C for the acridinediones **5n,o** ($R^1$ = H and 3-$R^2$ ≠ H) gives a doubling of the signals which is not seen at room temperature. In the case of compounds **5a,b** an increase (from -60 to 160°C) and lowering of the temperature does not affect the appearance of the spectrum. For compound **5h** (2-$R^1$ = 6-$R^2$ ≠ H) the existence of rotamers is not possible and a doubling of signals is not observed in the temperature range indicated above.

The dependence of the $^1$H NMR spectra of compounds **5c-g** on temperature allowed an experimental determination of their energetic inversion barriers $\Delta G_1$ in kJ/mol as 82±5 (**5c,d**), 82±6 (**5e**), 81±6 (**5f**), and 84±5 (**5g**). This high barrier is not typical of biphenyls and its hetero analogs [9]. In particular, they allow observation of doubled signals even for compounds **5n,o** which contain the $R^2$ substituent in a *meta* position.

TABLE 1. Parameters for Compounds **5a-o**

| Com-pound | Empirical formula | Found N, % / Calculated N, % | mp, °C | Yield, % |
|---|---|---|---|---|
| **5a** | $C_{29}H_{31}NO_2$ | 3.21 / 3.29 | 209-210 | 67 |
| **5b** | $C_{31}H_{34}FNO_3$ | 2.82 / 2.87 | 219-221 | 92 |
| **5c** | $C_{29}H_{30}FNO_2$ | 3.15 / 3.16 | 192-194 | 78 |
| **5d** | $C_{30}H_{32}FNO_2$ | 3.10 / 3.06 | 178-179 | 58 |
| **5e** | $C_{29}H_{29}BrFNO_2$ | 2.62 / 2.68 | 212-214 | 62 |
| **5f** | $C_{29}H_{29}ClFNO_2$ | 3.01 / 2.93 | 275-276 | 69 |
| **5g** | $C_{29}H_{29}FN_2O_4$ | 5.72 / 5.70 | 273-274 | 89 |
| **5h** | $C_{30}H_{30}BrF_2NO_3$ | 2.50 / 2.46 | 262-264 | 75 |
| **5i** | $C_{29}H_{28}Cl_3NO_2$ | 2.61 / 2.65 | 274-275 | 70 |
| **5j** | $C_{30}H_{30}BrCl_2NO_3$ | 2.40 / 2.32 | 260-262 | 76 |
| **5k** | $C_{29}H_{28}Cl_3NO_2$ | 2.71 / 2.65 | 280-281 | 62 |
| **5l** | $C_{30}H_{31}Cl_2NO_2$ | 2.81 / 2.75 | 248-250 | 80 |
| **5m** | $C_{31}H_{34}ClNO_4$ | 2.73 / 2.69 | 229-230 | 68 |
| **5n** | $C_{30}H_{30}FNO_4$ | 2.91 / 2.87 | 305-308 | 55 |
| **5o** | $C_{31}H_{32}FNO_4$ | 2.83 / 2.79 | 268-270 | 81 |

TABLE 2. $^1$H NMR Spectra of Compounds **5a-o**

| Com-pound* | Chemical shift, δ, ppm (spin-spin coupling, *J*, Hz) | | | | |
|---|---|---|---|---|---|
| | $(CH_3)_2C$*$^2$ | $4CH_2$ (8H, m) | CH (s / two s) | $H_{arom}$, m | $R^1$, $R^2$ |
| **5a** | 0.70; 0.87 | 1.62-2.36 | 5.06 | 6.97-7.72 (10H) | — |
| **5b** | 0.72; 0.87 | 1.8-2.32 | 5.05 | 6.75-7.45 (8H) | 1.37 (3H, t, *J* = 7.3, $CH_3$)<br>4.01 (2H, q, *J* = 7.3, $CH_2$) |
| **5c** | 0.73; 0.88; 0.89; | 1.56-2.35 | 5.01; 5.04 | 6.95-7.74 (9H) | — |
| **5d** | 0.72; 0.75; 0.89 | 1.57-2.37 | 4.97; 5.00 | 6.92-7.75 (8H) | 2.21 (3H, s, $CH_3$) |
| **5e** | 0.72; 0.75; 0.89 | 1.59-2.36 | 4.97; 5.00 | 7.16-7.76 (8H) | — |
| **5f** | 0.71; 0.74; 0.88 | 1.57-2.35 | 5.01; 5.02 | 7.13-7.76 (8H) | — |
| **5g** | 0.72; 0.74; 0.90 | 1.61-2.40 | 5.14 | 7.36-8.22 (8H) | — |
| **5h** | 0.76; 0.88 | 1.69-2.29 | 5.10 | 6.76-7.86 (6H) | 3.77 (3H, s, $OCH_3$) |
| **5i** | 0.75; 0.88; 0.90 | 1.46-2.30 | 5.00; 5.02 | 7.14-7.98 (7H) | 2.15 (3H, s, $CH_3$) |
| **5j** | 0.73; 0.86 | 1.42-2.26 | 4.97; 5.28 | 6.76-7.97 (6H) | 3.80 and 3.84 (3H, two s, $OCH_3$) |
| **5k** | 0.73; 0.87; 0.89 | 1.42-2.33 | 4.98 | 7.10-8.10 (7H) | — |
| **5l** | 0.71; 0.73; 0.86; 0.88 | 1.45-2.28 | 5.02 | 6.83-8.00 (7H) | 2.75 and 2.78 (3H, two s, $CH_3$) |
| **5m** | 0.68; 0.73; 0.86 | 1.53-2.29 | 4.93; 4.99 | 6.60-7.50 (7H) | 3.85 and 3.90 (3H, two s, $OCH_3$) |
| **5n** | 0.75; 0.89 | 1.45-2.35 | 5.02 | 6.88-7.78 (H) | — |
| **5o** | 0.68; 0.87 | 1.63-2.35 | 5.06 | 7.25-8.04 (8H) | 3.79 (3H, s, $OCH_3$) |

* Compounds **5c-g, i-m** are a mixture of rotamers.

*$^2$ Singlet signals observed with an overall intensity corresponding to 12 protons.

To explain the results obtained we have carried out a quantum-chemical analysis of the process of the conformational transformation of the rotamers. Calculation of equilibrium geometries and the geometry of the transition state using the AM1 method showed that the cyclohexanone ring sterically hinders the rotation of the aryl substituent around the C–N bond. The high steric loading for compounds **5c-g, i-m** infers that, in the process of the conformational transition, simultaneously with rotation of the 10-Ar substituent the dihydropyridine ring has to undergo a complete inversion. The initially planar disposition of bonds around the nitrogen atoms becomes pyramidal and the cyclohexanone rings are strongly distorted. A direct result of the occurrence of this combination of energetically unfavored processes is the high (~82 kJ/mol) barrier to inversion.

## EXPERIMENTAL

$^1$H NMR spectra were measured on a Varian Mercury VX-200 spectrometer (200 MHz) using DMSO-$d_6$ solvent and TMS internal standard. The purity of the compounds prepared was monitored using TLC on Silufol UV-254 plates with chloroform, ethyl acetate or their mixture as solvent. Melting points were measured on a Koffler stage. The nitrogen content in the prepared compounds corresponded with that calculated (Table 1).

Determination of the rotational barriers was carried out using an overall line shape method and its comparison with the practical, least squares numerical value as in the method [10]. To determine the effective time $T_2$ in solution an equimolar amount of the corresponding 9-aryl-3,3,6,6-tetramethyl-2,3,4,5,6,7,8,9-octahydro-1H-1,8-xanthenedione was added (for which $T_2$ had been measured). Calculations were carried out on the methyl group signals. The obtained values for the rate of rotation constant were used for calculation of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ as line shape coefficients in the Eyring equation.

Quantum-chemical calculations were performed using the GAMESS program package [11]. The parameters for the different atoms used in the AM1 calculation method were taken from [12, 13].

**3,3,6,6-Tetramethyl-9,10-diphenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (5a).** Two drops of concentrated hydrochloric acid were added to a solution of dimedone **1** (0.42 g, 3 mmol), benzaldehyde **2a** (0.16 g, 1.5 mmol), and aniline (0.14 g, 3 mmol) in dry DMF (1 ml) and the mixture was refluxed for 3 h. The precipitate formed on cooling was filtered off and crystallized from aqueous ethanol (80%) to give compound **5a** (0.43 g).

**Compounds 5b-o** were prepared similarly from dimedone **1**, the aldehydes **2b-i**, and the amines **3b-i**.

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