Chemistry of Heterocyclic Compounds, Vol. 37, No. 10, 2001

SYNTHESIS OF 9-R^1-10-R-1,8-DIOXO-DECAHYDROACRIDINES AND DIOXIMES BASED ON THEM

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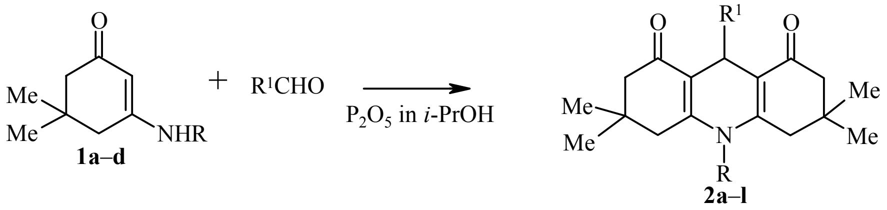
3,3,6,6-Tetramethyl-9-R^1-10-R-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridines were synthesized through the intermediate α-R-methylenebisenamino ketones by the condensation of 5,5-dimethyl-3-N-R-aminocyclohex-2-enones with aliphatic, aromatic, and furan aldehydes (2-propanol, phosphorus pentoxide). It was found that the degree of substitution of the heterocycle in decahydroacridinediones has an effect on the direction of their transformations during oximation.

Keywords: 3-aminocyclohex-2-enone, 1,8-dioxodecahydroacridine dioxime, 1,8-dioxooctahydroacridinium chloride dioxime, methylenebis-3-aminocyclohex-2-enone, condensation, oximation.

The condensation of 5,5-dimethyl-3-methylamino-2-cyclohex-1-one (**1a**) with various aldehydes in a 20% solution of phosphorus pentoxide in isopropyl alcohol is a preparative method for the synthesis of 9-R^1-10-methyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridines [1]. In the present work we give new data on the analogous reaction of the cyclic enaminoketones **1b-d**, containing primary and secondary N-phenyl- and N-benzylamino groups, with formaldehyde, aromatic aldehydes (benzaldehyde, 4-methoxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde), and 5-nitrofurfural and also of the enamino ketone **1a** with acetaldehyde. It was established that in all cases, irrespective of the structure of the reagents, the reaction products are the substituted 9-R^1-10-R-1,8-dioxodecahydroacridines **2a-l**. The yields of compounds **2** are 79-97% with the aliphatic and aromatic aldehydes and 61-69% with 5-nitrofurfural. The new 1,8-dioxodecahydroacridines **2c**,**d**,**g-l** and the previously known compounds **2a**,**b**,**e**,**f** were obtained with yields 1.5-3 times higher than presented in [2-5].



1a–d **2a–l**

1a R = Me, **b** R = H, **c** R = Ph, **d** R = PhCH$_2$; **2a-d** R = H, **a** R^1 = H, **b** R^1 = Ph,
c R^1 = 4-HO-3-MeO-C$_6$H$_3$, **d** R^1 = 5-NO$_2$-2-Fur; **e** R = R^1 =Me; **f–h** R = Ph, **f** R^1 = H,
g R^1 = 4-MeOC$_6$H$_4$, **h** R^1 = 5-NO$_2$-2-Fur; **i-l** R = PhCH$_2$, **i** R^1 = H, **j** R^1 = Ph;
k R^1 = 4-MeOC$_6$H$_4$, **l** R^1 = 5-NO$_2$-2-Fur

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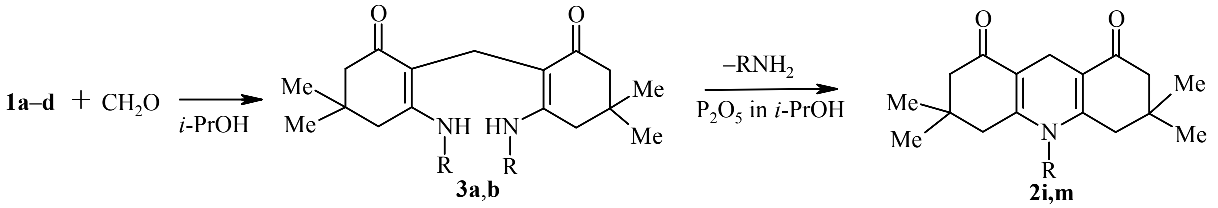
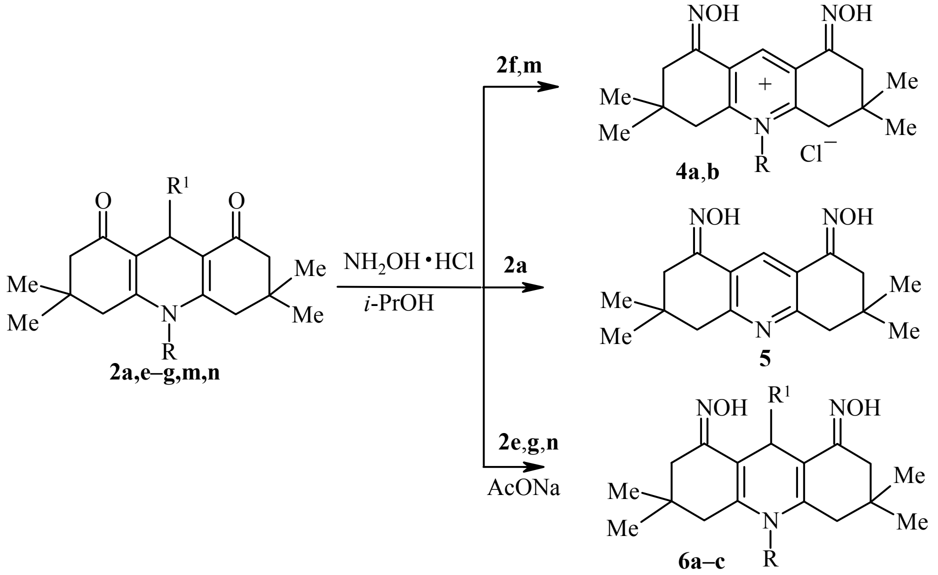
The intermediates of the reaction are α-R-methylenebisenamino ketones **3**. Thus, the bisenamino ketones **3a**,**b** were isolated with yields of 68-71% in the reaction of the enamino ketones **1a**,**d** with formaldehyde in isopropyl alcohol. When subsequently heated in a 20% solution of phosphorus pentoxide in isopropyl alcohol the products underwent cyclization with the formation of the decahydroacridinediones **2i**,**m** with yields of 91-95%.



2i, **3a** R = $PhCH_2$, **2m**, **3b** R = Me

The functional derivatives of the 1,8-dioxodecahydroacridines have hardly been described at all in the literature. The only example is the paper [3], in which it was pointed out that the formation of the dioximes of 9,10-unsubstituted and 9-aryl-substituted 1,8-dioxodecahydroacridines is accompanied by oxidation of the 1,4-dihydropyridine fragment. Dry pyridine was used as solvent. We studied the special features of the oximation of the 10- and 9,10-substituted decahydroacridinediones **2e**-**g**,**m**,**n** on heating in isopropyl alcohol. It was found that under these conditions the dioximes are formed with oxidation or with retention of the 1,4-dihydropyridine ring, depending on the number of substituents at positions 9 and 10 of the substrate.

A special feature of the oximation of the 10-substituted decahydroacridinediones **2f**,**m**, as also of the analogs unsubstituted at the nitrogen atom [3], is aromatization of the 1,4-dihydropyridine ring, leading to the dioximes of 10-R-1,8-dioxo-*sym*-octahydroacridinium chlorides **4a**,**b** (yields 80-82%). In the case of decahydroacridinedione **2a** unsubstituted at positions 9, 10 for comparison it was shown that its dioxime is formed with an identical result both in dry pyridine [3] and in isopropyl alcohol solution (yield 76%). The reaction of 9-R^1-10-R-1,8-dioxodecahydroacridines **2e**,**g**,**n** with hydroxylamine hydrochloride takes place with retention of the heterocycle; the presence of the 9,10 substituents probably increases its resistance to oxidation. Dioximes **6a-c** are formed with yields of 79-88%. During their preparation it is advisable to add sodium



2n R = Me, R^1 = 4-$MeOC_6H_4$; **4a** R = Ph, **b** R = Me;
6a R^1 = 4-$MeOC_6H_4$, R = Ph; **b** R = R^1 = Me; **c** R = Me, R^1= 4-$MeOC_6H_4$

acetate to the reaction mixture in order to combine with the released hydrogen chloride, and this reduces the reaction time by half. The structure of the decahydroacridinediones **2a-m**, bisenaminoketones **3a**,**b**, and dioximes **4a**,**b**, **6a-c** was confirmed by the IR and ^{1}H NMR spectra, and in the case of compounds **2a**,**b**,**e**,**f**,**i**,**m**, **3b**, **5** it was also confirmed by comparison of their melting points with published data.

The IR spectra of compounds **2a-m** are characterized by the presence of two strong absorption bands in the regions of 1590-1615 and 1640-1660 cm^{-1}, corresponding to the stretching vibrations of the C=C–C=O system of bonds. In the spectra of 9-(5-nitro-2-furyl)decahydroacridinediones **2d**,**h**,**l** the stretching vibrations of the nitro group are at 1500 and 1358 cm^{-1}, while those of the furan ring are at 3100-3116 cm^{-1}. The spectra of the dioximes **4-6** contain a broad strong absorption band in the region of 3200-3400 cm^{-1}, which confirms the presence of the associated hydroxyl group. The stretching vibrations of the C=C–C=N fragment appear in the spectra of the dioximes **6a-c** in the form of two bands at 1560-1580 and 1600-1610 cm^{-1}.

The ^{1}H NMR spectra of the 1,8-dioxodecahydroacridines **2a-l** and the dioximes **4a**,**b** and **6a-c** correspond to their structures (Table 1).

TABLE 1. The ^{1}H NMR Spectra of 9-R^1-10-R-Decahydroacridine-1,8-diones **2a-l** and Dioximes **4a**,**b**, **6a-c**

Compound	Chemical shifts, δ, ppm, SSCC (*J*), Hz				
	2,2-H_2, 7,7-H_2, s	4,4-H_2, 5,5-H_2, 4H, s	9,9-H_2 / 9-H	$C(CH_3)_2$, s	Other signals
1	2	3	4	5	6
2a	2.30 (4H)	2.19	3.21 (2H, s)	1.06 (12H)	9.12 (1H, s, NH)
2b	2.35 (4H)	2.19	5.07 (1H, s)	0.97 (6H), 1.08 (6H)	8.17 (1H, br. s, NH); 7.20-7.30 (5H, m, H_{Ph})
2c	2.45 (4H)	2.20	4.66 (1H, s)	1.00 (6H), 1.10 (6H)	9.47 (1H, br. s, OH); 8.18 (1H, s, NH); 6.69-6.98 (3H, m, H_{Ar}); 3.88 (3H, s, OMe)
2d	2.37 (4H)	2.20	5.34 (1H, s)	0.98 (6H), 1.06 (6H)	8.28 (1H, br. s, NH); 7.21 (1H, d, *J* = 4.0, H_{Het}); 6.50 (1H, d, *J* = 4.0, H_{Het})
2e	2.35 (2H), 2.45 (2H)	2.23	4.05 (1H, m)	1.06 (6H), 1.10 (6H)	3.21 (3H, s, NMe); 0.84 (3H, d, *J* = 6.5; 9-Me)
2f	2.21 (4H)	1.92	3.25 (2H, s)	0.97 (12H)	7.20-7.43 (5H, m, H_{Ph})
2g	2.45 (4H)	2.16	5.22 (1H, s)	0.99 (6H), 1.09 (6H)	7.29-7.54 (5H, m, H_{Ph}); 7.23 (2H, d, *J* = 8.4, 3',5'-H_{Ar}); 6.76 (2H, d, *J* = 8.4, 2',6'-H_{Ar}); 3.74 (3H, s, OMe)
2h	2.22 (4H)	2.05	5.52 (1H, s)	0.83 (6H), 0.97 (6H)	7.51-7.59 (5H, m, H_{Ph}); 7.21 (1H, d, *J* = 3.7, H_{Het}); 6.55 (1H, d, *J* = 3.7, H_{Het})
2i	2.30 (4H)	2.17	3.45 (2H, s)	1.00 (6H), 1.05 (6H)	7.23-7.29 (5H, m, H_{Ph}); 4.65 (2H, s, NCH_2)
2j	2.36 (2H), 2.43 (2H)	2.20	5.34 (1H, s)	0.89 (6H), 0.99 (6H)	7.11-7.41 (10H, m, H_{Ph}); 4.90 (2H, s, NCH_2)
2k	2.35 (2H), 2.42 (2H)	2.18	5.26 (1H, s)	0.88 (6H), 0.98 (6H)	7.31 (2H, d, *J* = 8.8, 3',5'-H_{Ar}); 7.15-7.23 (5H, m, H_{Ph}); 6.71 (2H, d, *J* = 8.8, 2',6'-H_{Ar}); 4.89 (2H, s, NCH_2); 3.72 (3H, s, OMe)
2l	2.42 (4H)	2.23	5.54 (1H, s)	0.87 (6H), 1.02 (6H)	7.30-7.41 (5H, m, H_{Ph}); 7.25 (2H, d, *J* = 3.6, H_{Het}); 6.60 (2H, d, *J* = 3.6, H_{Het}); 4.95 (2H, s, NCH_2)
2m	2.36 (4H)	2.24	3.29 (2H, s)	1.06 (12H)	3.21 (3H, s, NMe)

TABLE 1 (continued)

1	2	3	4	5	6
4a	2.90 (4H)	2.76	9.56 (1H, s)	1.12 (12H)	7.90 (3H, m, H_{Ph}); 7.37 (2H, m, H_{Ph})
4b	3.00 (4H)	2.82	9.54 (1H, s)	1.26 (12H)	3.96 (3H, s, NMe)
6a	2.78 (4H)	2.28	5.34 (1H, s)	1.05 (6H), 1.16 (6H)	7.72 (5H, m, H_{Ph}); 7.38 (2H, d, J = 8.4, 3',5'-H_{Ar}); 7.10 (2H, d, J = 8.4, 2',6'-H_{Ar}); 4.02 (3H, s, OMe)
6b	2.76 (4H)	2.40	5.23 (1H, s)	1.22 (12H)	7.29 (2H, d, J = 8.2, 3',5'-H_{Ar}); 7.02 (2H, d, J = 8.2, 2',6'-H_{Ar}); 3.97 (3H, s, OMe); 3.61 (3H, s, NMe)
6c	2.77 (4H)	2.48	4.11 (1H, m)	1.22 (12H)	3.59 (3H, s, NMe); 1.12 (3H, d, J = 6.2, 9-Me)

The most characteristic for these compounds are the signals of the protons at the $C_{(9)}$ atom. In the spectra of the decahydroacridinediones **2a**,**f**,**i**,**m** they are in the region of 3.21-3.29, while for compounds **2b-e**,**g**,**h**,**j-l** and the dioximes **6a-c** they are at 4.05-5.54 ppm. For the dioximes of 1,8-dioxooctahydroacridinium chlorides **4a**,**b** there is a downfield shift of the signal for the proton at the $C_{(9)}$ atom (9.54-9.56 ppm).

Our results [1] make it possible to propose a preparative method for the synthesis of 9-R^1-10-R-1,8-dioxodecahydroacridines and to investigate the special characteristics of their chemical behavior during oximation.

TABLE 2. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, ºC	Yield, %
		C	H	N		
2c	$C_{24}H_{29}NO_4$	72.91 72.73	7.34 7.59	3.54 3.47	226-228	84
2d	$C_{21}H_{24}N_2O_5$	65.57 65.63	6.28 6.25	7.25 7.29	245-247	69
2g	$C_{30}H_{33}NO_3$	79.31 79.12	7.40 7.25	3.29 3.08	225-226	79
2h	$C_{27}H_{28}N_2O_5$	70.75 70.43	6.18 6.09	6.34 6.09	239-241	61
2j	$C_{30}H_{33}NO_2$	82.29 82.00	7.79 7.52	3.65 3.19	184-185	85
2k	$C_{31}H_{35}NO_3$	78.95 79.28	7.61 7.51	3.39 2.98	178-179	81
2l	$C_{28}H_{30}N_2O_5$	71.05 70.89	6.21 6.33	6.07 5.91	243-245	67
3a	$C_{31}H_{38}N_2O_2$	79.57 79.75	8.38 8.09	6.07 5.96	130-132	68
4a*	$C_{23}H_{28}ClN_3O_2$	67.14 66.75	6.62 6.77	10.70 10.16	>350	80
4b*	$C_{18}H_{26}ClN_3O_2$	61.71 61.45	7.56 7.40	12.07 11.95	>350	82
6a	$C_{30}H_{35}N_3O_3$	74.59 74.23	7.46 7.22	9.02 8.66	274-276	82
6b	$C_{19}H_{29}N_3O_2$	69.07 68.88	8.58 8.76	12.34 12.69	264-265	79
6c	$C_{25}H_{33}N_3O_3$	71.38 70.92	7.93 7.80	10.07 9.93	256-257	88

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* For compound **4a**, Cl found, %: 9.00; Cl calculated, %: 8.59.
For compound **4b**, Cl found, %: 10.18; Cl calculated, %: 10.10.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument for suspensions in Vaseline oil or hexachlorobutadiene. The ^{1}H NMR spectra were obtained on a Varian FT-80A spectrometer in deuterochloroform (compounds **2a-m**) and deuterotrifluoroacetic acid (compounds **4a**,**b**, **6a-c**) with TMS as internal standard.

The reactions and the individuality of the compounds were monitored by TLC on Silufol UV-254 plates with 3:1:1 hexane–acetone–chloroform as eluant and iodine vapor as developer.

Enamino ketones **1a-d** were synthesized by the method described in [7], and compound **2n** by the method in [1].

3,3,6,6-Tetramethyl-9-(5-nitro-2-furyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (2d). Enamino ketone **1b** (2.78 g, 0.02 mol) was added to a solution of phosphorus pentoxide (8 g) in isopropyl alcohol (40 ml). The mixture was heated until a transparent solution had formed, and 5-nitrofurfural (1.41 g, 0.01 mol) was added. The reaction mass was boiled with a reflux condenser for 10-12 h and was then poured into 300 ml of cold water. After 12 h the precipitated compound **2d** was filtered off, washed with water, and recrystallized from ethanol.

Decahydroacridinediones **2a-c**,**f-j** were obtained similarly. The characteristics and yields of the compounds **2b**,**d**,**g**,**h**,**j-l** obtained for the first time are presented in Table 2.

The yields, melting points, and published characteristics for the previously described compounds **2a**,**b**,**e**,**f**,**i** are as follows: **2a** yield 79%, mp 301-303°C (52%, 303-306°C [2]); **2b** yield 89%, mp 290-291°C (74%, 290-292°C [3]); **2e** yield 76%, mp 215-217°C (38%, 215-217°C [4]); **2f** yield 86%, mp 289-291°C (43%, 289-291°C [5]); **2i** yield 93%, mp 169-171°C (93%, 168-170°C [1]).

Methylenebis-2,2'-(5,5-dimethyl-3-methylaminocyclohex-2-enone) (3a). A mixture of the enamino ketone **1d** (4.58 g, 0.02 mol), paraform (0.3 g, 0.01 mol), and isopropyl alcohol (40 ml) was boiled under a reflux for 2 h and was then poured into cold water (200 ml). The precipitate was filtered off and recrystallized from isopropyl alcohol, and 3.20 g (68%) of compound **3a** was obtained; mp 130-132°C (ethanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 9.36 (2H, br. s, NH); 7.24 (10H, m, H_{Ph}); 4.48 (4H, d, $J = 6.4$, N–CH_2); 3.44 (2H, s, CH_2); 2.20 (4H, s, 2CH_2); 2.14 (4H, s, 2CH_2); 0.92 (12H, s, 4CMe_2).

Similarly, from the enamino ketone **1a** compound **3b** was obtained. Yield 71%; mp 222-223°C. Published data: mp 223-224°C [6]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm. *J* (Hz): 9.21 (2H, bs, NH); 3.25 (2H, s, CH_2); 2.91 (6H, d, $J = 5.1$, 2NMe); 2.25 (4H, s, 2CH_2); 2.18 (4H, s, 2CH_2); 1.03 (12H, s, 4CMe_2).

3,3,6,6-Tetramethyl-10-benzyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (2i). A sample of compound **3a** (2.35 g, 0.005 mol) was added to a solution of phosphorus pentoxide (4 g) in isopropyl alcohol (20 ml). The mixture was boiled with a reflux condenser for 2 h and was then poured into water (200 ml). The precipitate was filtered off and recrystallized from isopropyl alcohol. We obtained 1.51 g (91%) of compound **2i**; mp 169-171°C. Published data: mp 168-170°C [1].

Compound **2m** was obtained similarly from the bisenamino ketone **3b**. Yield 95%; mp 247-249°C. Published data: 247-249°C [6].

Dioxime of 3,3,6,6-Tetramethyl-10-phenyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridinium Chloride (4a). A mixture of the decahydroacridinedione **2f** (3.49 g, 0.01 mol), hydroxylamine hydrochloride (4.17 g, 0.06 mol), and isopropyl alcohol (50 ml) was boiled with a reflux condenser for 4 h. The precipitated compound **4a** was filtered off, washed with water, and recrystallized from ethanol.

Dioxime **4b** was obtained similarly from the decahydroacridinedione **2m**.

Dioxime of 3,3,6,6-Tetramethyl-9-(*p*-methoxyphenyl)-10-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (6a). A mixture of compound **2g** (4.55 g, 0.01 mol), hydroxylamine hydrochloride (2.78 g, 0.04 mol), sodium acetate (3.28 g, 0.04 mol), and isopropyl alcohol (50 ml) was boiled with a reflux condenser for 4-5 h. It was then cooled and poured into 300 ml of cold water. The precipitated compound **6a** was filtered off, washed with water, and recrystallized from ethanol.

Dioximes **6b**,**c**, **5** were obtained similarly from the decahydroacridinediones **2a**,**e**,**n**.

The characteristics and yields of the dioximes **4a**,**b** and **6a-c** are given in Table 2. The known dioxime **5** was obtained with a yield of 76%. Its melting point (280°C) agreed with published data [3].

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