Chemistry of Heterocyclic Compounds, Vol. 32, No. 1, 1996

SYNTHESIS AND SPECTROSCOPIC PROPERTIES OF NOVEL BENZO[A]PHENANTHRIDINES

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Condensation of arylidene-2-naphthylamines with 5,5-dimethylcyclohexane-1,3-dione (dimedone) gives novel 2,2-dimethyl-5-R-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-4-ones. Treatment of azomethines containing an ortho hydroxyl group in the "aldehyde" fragment gives the corresponding 3,3,6,6-tetramethyl-9-R-1,2,3,4,5,6,7,8-octa-hydroxanthene-1,8-diones. The IR, UV, PMR, and mass spectra of the compounds synthesized have been studied.

The benzophenanthridine ring is the structural basis of many physiologically active compounds including alkaloids [1], enzyme inhibitors [2], dopamine receptor ligands [3], and antibiotics [4].

For a limited number of examples it has been shown that treatment of arylidene-2-naphthylamines with 5,5-dimethylcyclohexane-1,3-dione (dimedone) gives partially hydrogenated aryl substituted benzo[a]phenanthridin-4-ones [5-7]. However, little spectroscopic data was given for these compounds, only the characteristic infrared CO and NH stretching frequencies being reported.

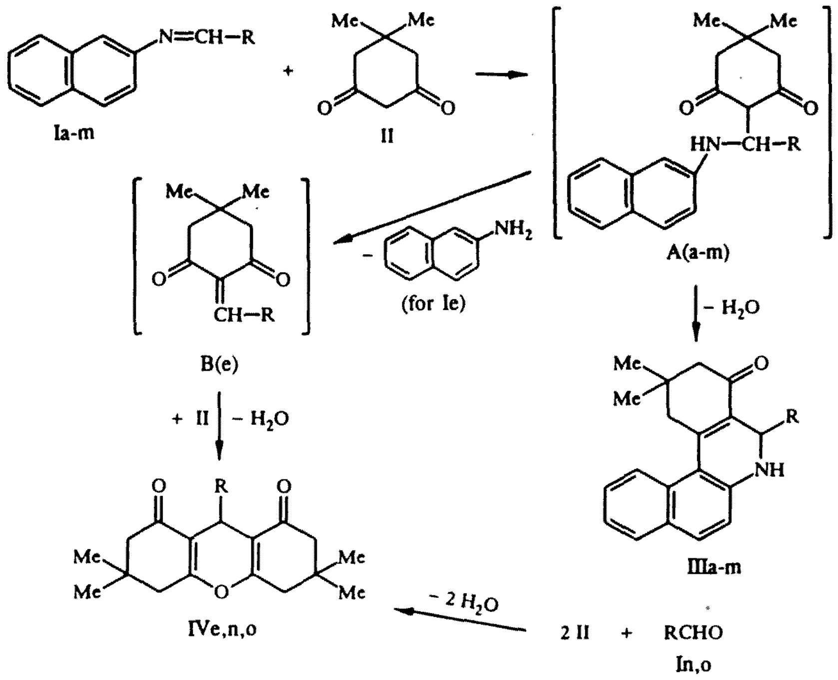
With the object of achieving a synthesis of previously unreported benzo[a]phenanthridin-4-ones we carried out the condensation of arylidene-2-naphthylamines (I) with dimedone (II) and studied the spectroscopic properties of the products.

Thanks to the high reactivity of the β-dicarbonyl compound II, reaction with arylidene-2-naphthylamines occurred readily when heated in ethanol–benzene solution even without a catalyst. We believe that the first stage of the reaction involves addition of the methylene group of the dimedone to the C=N bond of azomethine I to form intermediate aminodiketone A which then loses water and cyclises to the corresponding 2,2-dimethyl-5-R-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-4-one (III).

It was also found that the presence of electron acceptor substituents in the "aldehyde" fragment of the azomethine causes a higher yield of the reaction products (compounds IIIb, *l*, m 68-75%) than in the case of electron donor substituents (IIIf-h 38-53%). This agrees with literature data [8] and involves a change in the polarization of the azomethine bond with an associated increase or decrease in reactivity. A change of the phenyl substituent in the azomethine for pyridine leads to a significant increase in the yield of the desired product (IIIj, 95%), evidently due to the –I effect of the nitrogen atom. On the other hand, with the quinoline azomethine Ii the yield of reaction product (IIIi, 31%) evidently due to steric hindrance caused by the bulky substituent (see also Table 1).

For the ortho-hydroxy analog Ie, both the benzo[a]phenanthridine-4-one IIIe and 3,3,6,6-tetramethyl-9-(*o*-hydroxyphenyl)-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (IVe) are formed. The analogous octahydroxanthenediones IVn,o were prepared by treating dimedone II with 2,4-dihydroxybenylidene-2-naphthylamine In and azomethine Io containing the 2-hydroxy-1-naphthyl "aldehyde" fragment. Evidently the ortho-hydroxyl group causes steric hindrance towards cyclization of the intermediate aminodiketone A as a result of which it undergoes hydramine fission to 2-naphthylamine and α,β-unsaturated diketone B. Subsequent condensation of the latter with the dimedone present in the reaction mixture then gives the octahydroxanthenedione IV. Such a reaction course has only been noted before in the reaction of dimedone with arylideneanilines [5]. We report this effect for arylidene-2-naphthylamines for the first time; it occurs only in the presence of an ortho hydroxy substituted azomethine. If the molecule also contains an electron acceptor nitro group or bromine atom in the phenyl ring, activating the azomethine through their –I effect (compounds Ia, d), this reaction does not occur and benzo[a]phenanthridin-4-ones IIIa, d are smoothly formed.

Belorussian Institute of Physicoorganic Chemistry, Minsk 220603. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 34-39, January, 1996. Original article submitted July 22, 1995.



I, III, IV a R = C_6H_5; b R = p-FC_6H_4; c R = o-OH—m-$NO_2C_6H_3$; d R = o-OH—m-BrC_6H_3; e R = o-OHC_6H_4; f R = p-OHC_6H_4; g R = m,p-$(OH)_2C_6H_3$; h R = m-OCH_3-p-OHC_6H_3; i R = 2-x*l*-2-quindyl; j R = 3-pyridyl ; k R = m,p-$CH_2O_2C_6H_3$; *l* R = p-$COOCH_3C_6H_4$; m R = p-BrC_6H_4; n R = o,p-$(OH)_2C_6H_3$; o R = 1-(2-hydroxy)naphthyl

The 2,2-dimethyl-5-R-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-4-ones IIIa-m are high melting, white or pale yellow crystalline substances. We noted that melting point determination occurred with decomposition hence we carried out a determination of the thermal stability of IIIa, b, f by derivatography [9]. Analysis of the derivatograms showed that the compounds began to lose mass at 320-330°C which corresponded to their melting temperature. Compounds IIIa, b, f decomposed with a clearly marked exotherm in the temperature range 320-428°C showing maximum decomposition at 412°C and mass loss of 53-67%. Evidently there is an initial fission of the C−R bond and cycloaliphatic part of the molecule (27-48%) followed by a more fundamental degradation tied to the formation of N-oxide type oxidation products and the elimination of nitrogen as oxides [10].

The mass spectra of IIIa-m show molecular ion peaks (M^+, 18-25%) with relatively few peaks for fragmentation ions. The highest intensity peak is shown for $[M-R]^+$ at *m/z* 276. The spectra of IIIc-h also show ion peaks for $[M-NO_2]^+$, $[M-OH]^+$, and $[M-OCH_3]^+$. All of the compounds show a characteristic peak at *m/z* 182 (10-15%) associated with fission of the fragment $CH_2-C(CH_3)_2-CH_2$ from the $[M-R]^+$ ion.

The IR spectra of IIIa-m show typical absorption stretching vibrations for CO and NH at 1620-1590 and 3280-3200 cm^{-1} respectively. Shift of this absorption band to lower frequency is evidently due to the presence of an intermolecular hydrogen bond (in agreement with literature data [11]) and, in the case of the carbonyl group, also by its conjugation with the naphthalene ring. When taken in chloroform solution, the spectra of IIIa-m show a shift of ν_{NH} to 3420-3400 cm^{-1}. The stretching vibrations for CH_2 and CH_3 appear at 2940-2870 cm^{-1} and for the aromatic ring CH at 3100-3030 cm^{-1}. Bands for C−O−C appear in the spectra of IIIh, k, *l* at 1260-1245 cm^{-1} and an ester ν_{CO} is seen at 1730 cm^{-1} in III*l*.

Electronic spectral absorption bands for IIIa-m are seen in the ultraviolet region and have a clearly defined vibrational structure (Table 2). In the IIIa-m molecules the unshared electrons of the phenanthridine ring nitrogen atom are excluded from the overall conjugation network and the basic contribution to the $\pi-\pi^*$ electron transitions derives from the naphthalene ring conjugated to the carbonyl group. This causes three absorption maxima to appear in the regions 203-234, 270-294, and 323-376 nm corresponding to a bathochromic shift of the three bands in the spectrum of 2-naphthylamine [12]. The resolution of the vibrational structure of each band and the increase in long wave maximum intensity in IIIa-m is evidently due to the effect of the carbonyl group on the π-electron system. The substituent in the phenyl ring has almost no effect on the overall spectrum. A small bathochromic shift of the long wave band is observed for IIIe, h containing the electron donor OH and OCH_3 groups. Changing the phenyl ring for quinoline (IIIi) causes an increased intensity of the second maximum (288 nm) and the absorption

TABLE 1. Parameters for 2,2-Dimethyl-5-R-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-4-ones IIIa-m

Compound	Found, %			Empirical formula	Calculated, %			mp, °C	Yield, %
	C	H	N		C	H	N		
IIIa	85,02	6,35	4,17	$C_{25}H_{23}NO$	84,94	6,57	3,96	324...326	60
IIIb	—	—	3,69	$C_{25}H_{22}FNO$	—	—	3,77	319...320	73
IIIc	72,28	5,44	7,01	$C_{25}H_{22}N_2O_4$	72,45	5,35	6,76	302...304	63
IIId†	66,64	4,72	3,61	$C_{25}H_{22}BrNO_2$	66,97	4,96	3,12	290...292	30
IIIe	80,96	6,31	3,44	$C_{25}H_{23}NO_2$	81,26	6,29	3,79	304...306	19
IIIf	81,11	6,04	4,02	$C_{25}H_{23}NO_2$	81,26	6,29	3,79	317...318	53
IIIg	77,68	5,80	3,62	$C_{25}H_{23}NO_3$	77,89	6,03	3,63	250...252	52
IIIh	78,04	6,68	3,17	$C_{26}H_{25}NO_3$	78,16	6,32	3,51	303...304	38
IIIi	82,89	6,20	6,48	$C_{28}H_{24}N_2O$	83,13	5,99	6,92	292...293	31
IIIj	81,18	5,94	8,11	$C_{24}H_{22}N_2O$	81,31	6,27	7,90	279...280	95
IIIk	78,20	5,92	3,14	$C_{26}H_{23}NO_3$	78,56	5,84	3,52	307...309	62
III*l*	78,94	6,10	3,18	$C_{27}H_{25}NO_3$	78,80	6,14	3,40	282...284	75
IIIm‡	69,43	5,08	2,97	$C_{25}H_{22}BrNO$	69,44	5,14	3,24	310...312	68

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*According to data in [5] mp = 324-326°C.

†Found, % Br = 17.94; calculated = 17.82.

‡Found, % Br = 18.36; calculated = 18.48.

TABLE 2. UV Spectra of 2,2-Dimethyl-5-R-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-4-ones IIIa-m

Compound	λ_{max}, nm (log ε)
IIIa	217 (4,60); 233 (4,71); 270 (4,12); 281 (4,34); 292 (4,39); 324 (3,83); 340 (4,02); 372 (4,06)
IIIb	204 (4,50), 217 (4,54), 233 (4,65), 270 (4,04), 280 (4,24), 294 (4,31), 323 (3,77), 339 (3,93), 370 (3,95)
IIIc	204 (4,53), 216 (4,57), 236 (4,67), 270 (4,01), 282 (4,31), 294 (4,35), 323 (4,04), 339 (4,01), 372 (4,01)
IIId	204 (4,52), 217 (4,55), 231 (4,56), 270 (3,98), 282 (4,19), 294 (4,23), 325 (3,57), 340 (3,71), 374 (3,95)
IIIe	204 (4,49), 217 (4,60), 229 (4,56), 235 (4,60), 273 (4,06), 283 (4,26), 296 (4,30), 326 (3,58), 342 (3,85), 377 (4,01)
IIIf	203 (4,48), 218 (4,63), 230 (4,65), 270 (4,12), 283 (4,25), 293 (4,28), 324 (3,80), 340 (3,95), 371 (4,04)
IIIg	204 (4,42), 217 (4,59), 233 (4,60), 271 (4,06), 282 (4,19), 293 (4,21), 324 (3,76), 340 (3,92), 371 (4,00)
IIIh	204 (4,67), 217 (4,61), 234 (4,56), 271 (3,99), 283 (4,17), 297 (4,21), 326 (3,61), 342 (3,78), 376 (3,94)
IIIi	210 (4,91), 235 (4,91), 288 (4,48), 308 (4,24), 321 (4,24), 340 (3,87), 369 (4,00)
IIIj	216 (4,51), 234 (4,70), 269 (4,15), 281 (4,28), 292 (4,32), 324 (3,86), 341 (3,90), 373 (3,98)
IIIk	203 (4,83), 217 (4,72), 232 (4,82), 282 (4,43), 293 (4,50), 323 (4,03), 340 (4,09), 370 (4,14)
III*l*	217 (4,68), 235 (4,80), 273 (4,25), 283 (4,38), 294 (4,40), 326 (3,81), 340 (3,91), 373 (4,00)
IIIm	217 (4,59), 234 (4,71), 270 (4,09), 281 (4,25), 293 (4,31), 325 (3,77), 340 (3,91), 372 (3,99)

at 321 nm and also the appearance of a fairly intense absorption at 308 nm due to an $n-\pi^*$ band transition of the quinoline nitrogen atom [12].

The PMR spectra of IIIa-m (Table 3) show two singlets for the methyl group protons at 0.87-1.05 and 1.05-1.18 ppm. The signals for the protons at C_1 appear as a pair of doublets at 2.20-2.48 ppm with a geminal spin–spin coupling of about 16 Hz and a clearly defined "roof effect"; those at C_3 give a multiplet at 2.6-2.8 ppm. The singlet signal for the methine proton

TABLE 3. PMR Spectra of IIIa-m

Compound	Chemical shift, δ, ppm						
	1-H(2H, dd)	3-H(2H, m)	5-H (1H, s)	H_{arom} (m)	NH (1H, s)	gem-CH_3	
						(3H, s)	(3H, s)
IIIa	2,20	2,60	5,88	7,06...8,10 (11H)	9,80	0,95	1,15
IIIb	2,21	2,60	5,95	6,95...8,06 (10H)	9,80	0,95	1,10
IIIc	2,40	2,70	6,00	7,02...8,00 (9H)	9,50	0,95	1,10
IIId	2,48	2,82	6,10	6,80...8,10 (9H)	9,40	1,05	1,10
IIIe	2,32	2,60	5,99	6,65...7,95 (10H)	10,18	0,95	1,10
IIIf	2,20	2,60	5,80	6,58...8,08 (10H)	9,70	1,00	1,18
IIIg	2,20	2,60	5,75	6,58...8,10 (9H)	9,70	0,98	1,10
IIIh*	2,32	2,60	5,95	6,22...7,98 (9H)	9,84	0,96	1,08
IIIi	2,24	2,60	6,22	7,61...8,60 (12H)	9,90	1,00	1,15
IIIj	2,22	2,60	5,92	7,18...8,64 (9H)	9,88	0,92	1,16
IIIk†	2,22	2,60	5,81	6,64...8,10 (9H)	9,78	0,96	1,16
IIIl‡	2,25	2,40	6,10	7,05...7,98 (10H)	9,92	0,87	1,05
IIIm	2,30	2,70	6,10	7,42...8,15 (10H)	8,90	1,00	1,20

*3.85 (3H, s, OCH_3).

†3.90 (3H, s, $COOCH_3$).

‡5.92 (2H, m, $O-CH_2-O$).

of the hydrogenated pyridine ring (5-H) is found at 5.88-6.22 ppm. The shift of this signal to low field of the usual position of methine protons in cyclic compounds [13] is evidently due to an anisotropic effect of the neighboring nitrogen atom and the aromatic ring. A small shift of 5-H (6.22 ppm) is found for the quinolyl derivative IIIi. The aromatic protons of the naphthalene ring and substituent R appear as a multiplet at 6.22-8.60 ppm and the amino group as a broadened singlet at 8.90-10.18 ppm.

EXPERIMENTAL

IR Spectra were recorded on a UR-20 instrument for KBr tablets and solutions in chloroform (concentration $1 \cdot 10^{-3}$ molar). Mass spectra were taken on an MX-1320 instrument. UV Spectra were recorded on a Specord UV-vis for solutions in ethanol ($1 \cdot 10^{-4}$ molar). PMR Spectra were recorded on a Tesla 567-A instrument (100 MHz) for solutions in $CDCl_3$ (III*l*), $(CD_3)_2SO$ (IIIa, b, e-k and IVe, n, o), or $(CD_3)_2CO$ (IIIc, d, m). The internal standard was TMS. Thermal studies were carried out on a Paulik–Paulik–Erdey derivatogram in air with a linear temperature increase of 7°C/min. The weight of compound was 100 mg, DTG 1/10, DTA 1/10.

2,2-Dimethyl-5-R-1,2,3,4,5,6-hexahydrobenzo[a]phenanthridin-4-ones (IIIa-m). A solution of the azomethine Ia-m (0.01 mole) and dimedone (0.0125 mole) in a mixture of ethanol and benzene (1:1, 20-30 ml) was heated on a water bath (50-100°C). The precipitate was filtered and crystallized from a mixture of nitrobenzene and toluene (1:1).

3,3,6,6-Tetramethyl-9(-(hydroxy)phenyl or α-(β-Hydroxy)naphthyl)-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-diones (IVe, n, o). Compound IVe was obtained by evaporation of the mother liquor after separation of IIIe (see above) using a mixture of ethanol and toluene (1:1). Compound IVn, o were prepared from dimedone and azomethines In, o as described for IIIa-m and recrystallized.

Compound IVe. Yield 36%, mp 205-206°C. Found, %: C 75.0, H 7.1. $C_{23}H_{26}O_4$. Calculated, %: C 75.4, H 7.1. Mass spectrum, *m/z* (I_{rel}, %): 366 (M^+, 58), 281 (100), 227 (80). IR Spectrum: 1620 (C=O), 1255 (C–O–C), 2960-2870 (CH_3, CH_2), 3200 cm^{-1} (OH). PMR Spectrum: 0.96 (6H, s, CH_3), 1.08 (3H, s, CH_3), 1.14 (3H, s, CH_3), 2.18-2.60 (8H, m, CH_2), 5.08 (1H, s, CH), 7.00-7.20 ppm (4H, m, H_{arom}).

Compound IVn. Yield 66%, mp 242-244°C. Found, %: C 72.0, H 6.9. $C_{23}H_{26}O_5$. Calculated, %: C 72.3, H 6.8. Mass spectrum, *m/z* (I_{rel}, %): 382 (M^+, 20), 298 (25), 242 (50), 227 (100). IR Spectrum: 1630 (C=O), 1240 (C–O–C), 2970-2890 (CH_3, CH_2), 3200 cm^{-1} (OH). PMR Spectrum: 0.98 (6H, s, CH_3), 1.08 (3H, s, CH_3), 1.16 (3H, s, CH_3), 2.20-2.62 (8H, m, CH_2), 5.00 (1H, s, CH), 6.38-6.88 (3H, m, H_{arom}).

Compound IVo. Yield 48%, mp 244-245°C. Found, %: C 77.4, H 6.5. $C_{27}H_{28}O_4$. Calculated, %: C 77.9, H 6.7. Mass spectrum, *m/z* (I_{rel}, %): 416 (M^+, 50), 332 (45), 277 (100). IR Spectrum: 1650 (C=O), 1240 (C–O–C), 2950-2820 (CH_3, CH_2), 3200 cm^{-1} (OH). PMR Spectrum: 0.90 (6H, s, CH_3), 1.08 (3H, s, CH_3), 1.18 (3H, s, CH_3), 2.10-2.68 (8H, m, CH_2), 5.62 (1H, s, CH), 7.20-8.35 (6H, m, H_{arom}).

According to their melting points and spectroscopic parameters, IVe, n, o are identical to materials made by condensation of dimedone with the corresponding aldehydes (ratio of reagents 2:1) in ethanol or propanol.

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