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Acetylation of 2-(1-Piperazinyl)- and 2-Morpholino-1,4-dihydroxyanthraquinones

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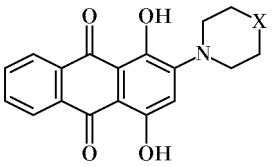
Abstract—Successive acetylation of 2-(1-pipepazinyl)- and 2-morpholino-1,4-dihydroxyanthraquinones with acetic anhydride was accomplished.

Hydroxyanthraquinone derivatives are pharmacologically active substances [1–6]. In particular, acyl- (or alkyl)oxyanthraquinones exhibit antitumor [1, 2], immunotropic [3], and antiviral [4] activity.



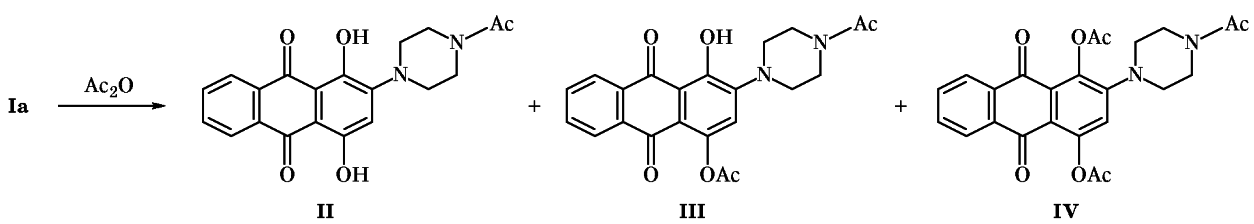
Ia–Ig

X = NH (**a**), NMe (**b**), NEt (**c**), NPh (**d**), $NCHPh_2$ (**e**), O (**f**), S (**g**).

With the goal of searching for new biologically active compounds in the hydroxyanthraquinone series we have studied acetylation of 2-amino-substituted 1,4-dihydroxyanthraquinones (quinizarins) **Ia**–**Ig** having piperazinyl and morpholino groups. It is known that the presence of these groups enhances biological activity [7, 8]. Fokin *et al.* [9] described the reaction of 1,4-dihydroxy-2-piperidinoanthraquinone with acetic anhydride in pyridine at 100°C, which resulted in acetylation of the two hydroxy groups. We have found that acetylation of compounds **Ia**–**Ig** under milder conditions gives not only exhaustive but also partial acetylation products. Treatment of 1,4-dihydroxy-2-(1-piperazinyl)anthraquinone with acetic anhydride at 20–25°C resulted in acetylation of only the NH group, and the corresponding 2-(4-acetyl-1-piperazinyl) derivative **II** was obtained in 55% yield (Scheme 1).

It is known that esterification of α-hydroxyanthraquinones requires the presence of an acid or base, for the α-hydroxy group in the substrate is involved in intramolecular hydrogen bond with the carbonyl oxygen atom [6]. Correspondingly, treatment of compound **Ia** with acetic anhydride at 20–25°C in the presence of a catalytic amount of sulfuric acid leads to acetylation not only of the NH group but also of the hydroxy groups. Here, the 4-hydroxy group, which is more distant from the 2-substituent, is acetylated first. The isolation of individual compounds from mixtures of *N*,*O*-diacetyl and *N*,*O*,*O'*-triacetyl derivatives **III** and **IV** was complicated by the sensitivity of the *O*-acetyl derivatives to hydrolysis, as well as by more or less considerable tarring (depending on the reaction time). The best conditions for the preparation of product **III** were treatment of *N*-acetyl derivative

Scheme 1.



II **III** **IV**

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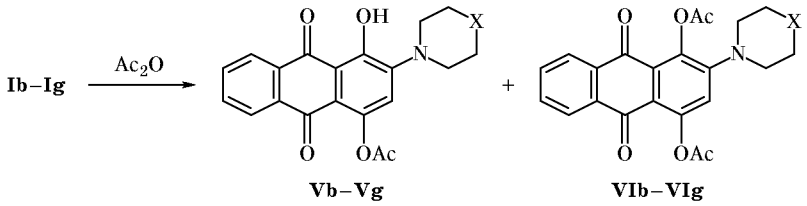
Scheme 2.



V, **VI**, X = NMe (**b**), NEt (**c**), NPh (**d**), $NCHPh_2$ (**e**), O (**f**), S (**g**).

II with acetic anhydride in the presence of H_2SO_4 for a short time; and the best results in the preparation of compound **IV** were obtained by acetylation of anthraquinone **Ia** in pyridine on heating.

Substituted anthraquinones **Ib**–**Ig** reacted with acetic anhydride at 20–25°C, following a similar scheme. Under conditions of acid catalysis, mono-*O*-acetyl derivatives **Vd**–**Vg** were obtained in a good yield (50–70%). However, the acetylation of more basic *N*-alkylpipepazinyl compounds was less smooth. Monoacetate **Vb** was isolated from the reaction mixture in a fairly poor yield (26%), while compound **Vc** was obtained with an acceptable yield only when the reaction was carried out under conditions of base catalysis (in pyridine). Analogous conditions (heating in pyridine) were applied to synthesize diacetates **VId** and **VIf** from aminoanthraquinones **Id** and **If**. Diacetates **VIe** and **VIg** are less sensitive to hydrolysis, and they can be obtained by acetylation in the presence of H_2SO_4 of monoacetate **Ve** and thiomorpholinoanthraquinone **Ig**, respectively. It should be noted that we failed to isolate analytically pure *O*,*O*′-diacetates derived from *N*-alkylpipepazinyl derivatives **Ib** and **Ic**, for these products turned out to be insufficiently stable.

Compounds **I**–**VI** are crystalline substances which are soluble in most organic solvents. The color of 2-amino derivatives is deeper than that of quinizarin. Esterification of the hydroxy groups is accompanied by a considerable blue shift of the long-wave absorption maximum. In going from piperazinyl derivative **Ia** to *N*-acetyl derivatives **II**, the position of the long-wave absorption maximum changes insignificantly (by 4 nm), while the corresponding shifts for *N*,*O*-diacetyl and *N*,*O*,*O*′-triacetyl derivatives **III** and **IV** are 43 and 106 nm, respectively.

The structure of the products was established on the basis of their analytical and spectral data (Tables 1, 2). In the ^1H NMR spectra of dihydroxyanthraquinones **I** and **II**, signals from the hydroxy protons appear as singlets at δ 14.3 (1-OH) and 13.5 ppm (4-OH). The substituent in position *2* exerts a stronger deshielding effect on the proton of the neighboring hydroxy group in position *1*, as compared to the more distant 4-hydroxy group [10]. In keeping with the above stated, the spectra of 4-acetoxy derivatives **III** and **V** contain only one downfield signal at δ ~14.3 ppm, which belongs to the hydroxy proton in position *1*. The spectra of 1,4-diacetates **IV** and **VI** lack signals in that spectral region. The IR spectra of compounds **I**–**VI** are characterized by the presence of carbonyl absorption bands at 1650–1670 (C=O, quinone), 1614–1640 (C=O, quinone, involved in hydrogen bond with the hydroxy group), ~1650 (*N*-acetyl group), and 1750–1770 cm^{-1} (*O*-acetyl group).

The main fragmentation pathway of acetylated compounds **II**–**IV** under electron impact is elimination of the acetyl groups and subsequent cleavage of the heteroring, leading to the quinizarin molecular ion with *m*/*z* 240). For example, triacetyl derivative **IV** successively loses *O*-acetyl groups with expulsion of two ketene molecules (*m*/*z* 42) and formation of rearranged ions $\mathbf{F}_1$ and $\mathbf{F}_2$, which is consistent with the lower stability of acetates. Ion $\mathbf{F}_2$ loses *N*-acetyl group (*m*/*z* 43) to give ion $\mathbf{F}_3$. Cleavage of the heteroring involves successive elimination of CH_2N and

Scheme 3.

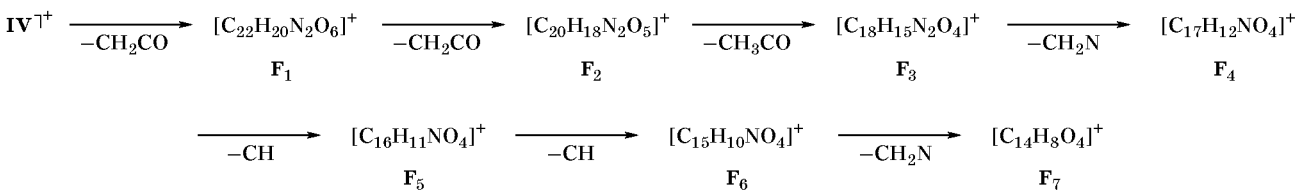


Table 1. Yields, melting points, elemental analyses, and molecular weights of compounds **I**–**VI**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calcd.
Ia	50	206–208 (EtOH)	66.76	4.99	8.20	$C_{18}H_{16}N_2O_4$	66.66	4.93	8.64	324.1107	324.1110
Ib	27	219–222 ($CHCl_3$–MeOH)	67.13	5.47	7.92	$C_{19}H_{18}N_2O_4$	67.45	5.32	8.28		
Ic	29	191–192.5 ($CHCl_3$–MeOH)			7.93	$C_{20}H_{20}N_2O_4$			7.95		
Id	40	240–241.5 ($CHCl_3$)	72.30	4.95	6.95	$C_{24}H_{20}N_2O_4$	72.00	5.00	7.00	400.1415	400.1423
Ie	50	216–218 (C_6H_6–EtOH)	76.83	5.53	5.71	$C_{31}H_{26}N_2O_4$	75.92	5.31	5.71		
Ig	66	259–261 ($CHCl_3$–MeOH)			4.26	$C_{18}H_{15}NO_4S$[a]			4.10		
II	55	226–229 ($CHCl_3$–MeOH)	65.47	4.95	7.77	$C_{20}H_{18}N_2O_5$	65.57	4.91	7.65	366.1221	366.1216
III	61	176–179 (MeOH)	64.00	4.88	6.95	$C_{22}H_{20}N_2O_6$	64.70	4.90	6.86	408.1316	408.1321
IV	36	166–169 (CH_2Cl_2–Et_2O)	64.22	4.88	5.84	$C_{24}H_{22}N_2O_7$	64.00	4.89	6.22	450.1414	450.1427
Vb	26	196–199 (CH_2Cl_2–Et_2O)	66.70	5.11	7.67	$C_{21}H_{20}N_2O_5$	66.31	5.26	7.36		
Vc	59	188–190 (MeOH)	66.40	5.61	6.90	$C_{22}H_{22}N_2O_5$	67.00	5.58	7.10	394.1538	394.1529
Vd	71	207–210 (CH_2Cl_2–MeOH)	70.15	5.04	6.10	$C_{26}H_{22}N_2O_5$	70.58	4.97	6.33		
Ve	46	219–222 (CH_2Cl_2–MeOH)	73.69	5.74	4.83	$C_{33}H_{28}N_2O_5$	74.44	5.26	5.26	532.1999	532.1998
Vf	69	203–208 (C_6H_6)	65.26	4.51	3.55	$C_{20}H_{17}NO_6$	65.39	4.63	3.81	367.1051	367.1056
Vg	66	206–208 ($CHCl_3$–MeOH)	62.47	4.35	3.21	$C_{20}H_{17}NO_5S$	62.66	4.44	3.65		
VId	59	175–177 (CH_2Cl_2–MeOH)	69.11	4.82	5.59	$C_{28}H_{24}N_2O_6$	69.42	4.96	5.78		
VIe	58	198–202 (CH_2Cl_2–MeOH)	73.55	5.40	4.79	$C_{35}H_{30}N_2O_6$	73.17	5.23	4.88		
VIf	62	214–217 (CH_2Cl_2–MeOH)	64.21	4.74	3.35	$C_{22}H_{19}NO_7$	64.55	4.64	3.42		
VIg	29	186–189 (CH_2Cl_2–MeOH)	61.56	4.51	2.88	$C_{22}H_{19}NO_6S$[b]	62.12	4.47	3.29	425.0891	425.0933

[a] Found, %: S 9.50. Calculated, %: S 9.38.
[b] Found, %: S 6.96. Calculated, %: S 7.53.

CH fragments (which is typical of saturated nitrogen-containing heterocycles). This pathway is confirmed by the presence of peaks from ions $\mathbf{F}_4$–$\mathbf{F}_7$ in the high-resolution mass spectrum (Scheme 3). The fragmentation of monoacetates **Vc**, **Ve**, and **Vf** and diacetate **VIg** follows a similar pattern. Previously unknown 2-amino-1,4-dihydroxyanthraquinones **Ia**–**Ie** and **Ig** were synthesized by known method, amination of

Table 2. IR and ^{1}H NMR spectra of compounds **I**–**VI**

Comp. no.	^{1}H NMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}	
		C=O	C=C
Ia	3.05 m, 3.40 m (8H, 4CH_2), 6.53 s (1H, 3-H), 7.75 m (2H, 6-H, 7-H), 8.28 m (2H, 5-H, 8-H)[a]	1640, 1617	1584
Ib	2.35 s (3H, CH_3), 2.60 m, 3.43 m (8H, 4CH_2), 6.54 s (1H, 3-H), 7.75 m (2H, 6-H, 7-H), 8.28 m (2H, 5-H, 8-H), 13.52 s (1H, 4-OH), 14.32 s (1H, 1-OH)	1635 sh, 1614	1582
Ic	1.12 t, 2.49 q (5H, CH_3CH_2), 2.65 m, 3.45 m (8H, 4CH_2), 6.55 s (1H, 3-H), 7.75 m (2H, 6-H, 7-H), 8.29 (2H, 5-H, 8-H), 13.54 s (1H, 4-OH), 14.34 s (1H, 1-OH)	1636, 1614	1586
Id	3.39 m, 3.56 m (8H, 4CH_2), 6.63 s (1H, 3-H), 6.97 m, 7.29 m (5H, H_{arom}), 7.78 m (2H, 6-H, 7-H), 8.32 m (2H, 5-H, 8-H), 13.55 s (1H, 4-OH), 14.35 s (1H, 1-OH)	1634, 1614	1583
Ie	2.62 m, 3.43 m (8H, 4CH_2), 4.29 s (1H, CH), 6.53 s (1H, 3-H), 7.15 m, 7.44 m (10H, H_{arom}), 7.75 m (2H, 6-H, 7-H), 8.30 m (2H, 5-H, 8-H), 13.58 s (1H, 4-OH), 14.32 s (1H, 1-OH)	1629 sh, 1616	1585
If	3.39 m, 3.90 m (8H, 4CH_2), 6.57 s (1H, 3-H), 7.78 m (2H, 6-H, 7-H), 8.31 m (2H, 5-H, 8-H), 13.50 s (1H, 4-OH), 14.29 s (1H, 1-OH)	1633 sh, 1618	1587
Ig	2.82 m, 3.68 m (8H, 4CH_2), 6.57 s (1H, 3-H), 7.77 m (2H, 6-H, 7-H), 8.32 m (2H, 5-H, 8-H), 13.50 s (1H, 4-OH), 14.26 s (1H, 1-OH)	1626 sh, 1615	1583
II	2.14 s (3H, $COCH_3$), 3.33 m, 3.40 m, 3.66 m, 3.80 m (8H, 4CH_2), 6.51 s (1H, 3-H), 7.76 m (2H, 6-H, 7-H), 8.26 m (2H, 5-H, 8-H), 13.40 s (1H, 4-OH), 14.20 s (1H, 1-OH)	1652, 1634, 1615	1584
III	2.14 s, 2.45 s, (6H, 2$COCH_3$), 3.28 m, 3.37 m, 3.66 m, 3.82 m (8H, 4CH_2), 6.70 s (1H, 3-H), 7.75 m (2H, 6-H, 7-H), 8.25 m (2H, 5-H, 8-H), 14.23 s (1H, 1-OH)	1768, 1656, 1629	1591
IV	2.13 s, 2.48 s (9H, 3$COCH_3$), 3.24 br.m, 3.60 m, 3.75 m (8H, 4CH_2), 6.90 (1H, 3-H), 7.70 m (2H, 6-H, 7-H), 8.12 m (2H, 5-H, 8-H)	1775, 1673, 1650	1590
Vb	2.35 s (3H, CH_3), 2.44 s (3H, $COCH_3$), 2.61 m, 3.38 m (8H, 4CH_2), 6.69 s (1H, 3-H), 7.73 m (2H, 6-H, 7-H), 8.22 m (2H, 5-H, 8-H), 14.27 s (1H, 1-OH)	1760, 1660, 1624	1592
Vc	1.12 t, 2.49 q (5H, CH_3CH_2), 2.45 s (3H, $COCH_3$), 2.64 m, 3.42 m (8H, 4CH_2), 6,69 s (3-H), 7.74 m (2H, 6-H, 7-H), 8.24 m (2H, 5-H, 8-H), 14.28 s (1H, 1-OH)	1761, 1660, 1623	1585
Vd	2.46 s (3H, $COCH_3$), 3.38 m, 3.53 m (8H, 4CH_2), 6.75 s (1H, 3-H), 6.95 m, 7.28 m (5H, H_{arom}), 7.75 m (2H, 6-H, 7-H), 8.25 m (2H, 5-H, 8-H), 14.28 s (1H, 1-OH)	1759, 1660, 1625	1592
Ve	2.45 s (3H, $COCH_3$), 2.60 m, 3.39 m (8H, 4CH_2), 4.30 s (1H, CH), 7.24 m, 7.44 m (10H, H_{arom}), 7.74 m (2H, 6-H, 7-H), 8.22 m (2H, 5-H, 8-H), 14.24 s (1H, 1-OH)	1769, 1656, 1640	1585
Vf	2.45 s (3H, $COCH_3$), 3.34 m, 3.89 m (8H, 4CH_2), 6.69 s (1H, 3-H), 7.73 m (2H, 6-H, 7-H), 8.23 m (2H, 5-H, 8-H), 14.24 s (1H, 1-OH)	1757, 1656, 1623	1589
Vg	2.46 s (3H, $COCH_3$), 2.83 m, 3.59 m (8H, 4CH_2), 6.71 s (1H, 3-H), 7.74 m (2H, 6-H, 7-H), 8.24 m (2H, 5-H, 8-H), 14.20 s (1H, 1-OH)	1755, 1656, 1627	1590
VId	2.46 s, 2.48 s (6H, 2$COCH_3$), 3.32 m, 3.45 m (8H, 4CH_2), 6.94 m, 7.24 m (6H, H_{arom}, 3-H), 7.69 m (2H, 6-H, 7-H), 8.13 m (2H, 5-H, 8-H)	1774, 1671	1592

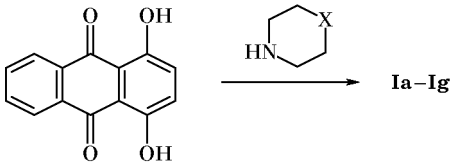
Table 2. (Contd.)

Comp. no.	^{1}H NMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}	
		C=O	C=C
VIe	2.41 s, 2.47 s (6H, 2COCH$_3$), 2.53 m, 3.25 m (8H, 4CH$_2$), 4.26 s (1H, CH), 6.87 s (1H, 3-H), 7.23 m, 7.36 m (10H, H$_{arom}$), 7.68 m (2H, 6-H, 7-H), 8.11 m (2H, 5-H, 8-H)	1772, 1674, 1659	1581
VIf	2.46 s, 2.47 s (6H, 2COCH$_3$), 3.21 br.m, 3.82 m (8H, 4CH$_2$), 6.90 s (1H, 3-H), 7.69 m (2H, 6-H, 7-H), 8.12 m (2H, 5-H, 8-H)	1770, 1672	1590
VIg	2.47 s, 2.48 s (6H, 2COCH$_3$), 2.76 m, 3.44 m (8H, 4CH$_2$), 6.91 s (1H, 3-H), 7.70 m (2H, 6-H, 7-H), 8.10 m (2H, 5-H, 8-H)	1777, 1670, 1651	1591

[a] Signals from the OH and NH protons are not observed in the spectrum due to exchange.

quinizarin in pyridine at 50–60°C in the presence of boric acid [6, 9] (Scheme 4).

Scheme 4.



EXPERIMENTAL

The IR spectra were recorded on a Vector 22 spectrometer in KBr. The electron absorption spectra were measured on a Hewlett–Packard 8453 instrument in chloroform. The ^{1}H NMR spectra were obtained on a Bruker WP-200SY spectrometer in $CDCl_3$ using the residual proton signal of the solvent as reference. The mass spectra were run on a Finnigan MAT-8200 mass spectrometer; the molecular weights and elemental compositions were determined from the precise *m*/*z* values. The progress of reactions was monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates using chloroform–acetone (10 : 1) as eluent.

2-(1-Pipepazinyl)-1,4-dihydroxyanthraquinone (Ia). A mixture of 1.2 g of quinizarin, 0.4 g of boric acid, and 1.3 g of piperazine in 15 ml of pyridine was stirred for 3 h at 50–60°C. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 0.8 g. Electron absorption spectrum, λ_{max}, nm (ε): 247 (17852), 271 (22130), 317 (7508), 510 (10880).

Compounds **Ib**–**Ig** were synthesized in a similar way. Compound **If**: yield 40%, mp 249–252°C; published data [9]: mp 251–252°C.

2-(4-Acetyl-1-piperazinyl)-1,4-dihydroxyanthraquinone (II). A mixture of 0.32 g of compound **Ia** and 5 ml of acetic anhydride was kept for 96 h at 20–25°C. The red precipitate was filtered off, washed with diethyl ether, and recrystallized from chloroform–methanol. Yield 0.2 g. Electron absorption spectrum, λ_{max}, nm (ε): 268 (27710), 313 (8200), 506 (12135).

4-Acetoxy-2-(4-acetyl-1-piperazinyl)-1-hydroxyanthraquinone (III). A mixture of 0.12 g of compound **II**, 5 ml of acetic anhydride, and 0.03 ml of concentrated sulfuric acid was stirred for 3 h at 20–25°C. Ice was then added, and the red precipitate was filtered off and recrystallized from methanol. Yield 0.08 g. Electron absorption spectrum, λ_{max}, nm (ε): 260 (29114), 309 (8862), 467 (6724).

Acetates **Vb**, **Vd**–**Vg**, and **VIg** were synthesized in a similar way from anthraquinones **Ib** and **Id**–**Ig**, respectively, and diacetate **VIe**, from monoacetoxy derivative **Ve**. Diacetate **VIg** was isolated from the mother liquor by column chromatography on silica gel using benzene as eluent.

1,4-Diacetoxy-2-(4-acetyl-1-piperazinyl)anthraquinone (IV). *a.* A mixture of 0.48 g of compound **Ia**, 8 ml of acetic anhydride, and 0.06 ml of concentrated sulfuric acid was kept for 25 days at 20–25°C. The black tar-like precipitate was filtered off and washed with methanol. The filtrate was poured into ice water, and the yellow–brown precipitate was separated and recrystallized from methylene chloride–diethyl ether. Yield 0.08 g (12%). Electron absorption spectrum, λ_{max}, nm (ε): 250 (24800), 297 (17884), 404 (5492).

b. A mixture of 0.16 g of compound **Ia**, 1 ml of pyridine, and 0.5 ml of acetic anhydride was heated for 2 h at 50–60°C. It was then poured into ice water,

and the precipitate was filtered off, recrystallized from methylene chloride–methanol, and washed with diethyl ether. Yield 0.08 g.

Compounds **Vc**, **VId**, and **VIf** were synthesized in a similar way from aminoanthraquinones **Ic**, **Id**, and **If**, respectively.

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