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Tetrahydropyran-2,4-diones in the Synthesis of Fused N,O-Heterocycles

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Abstract—Condensation of 6-methyl(or phenyl)-tetrahydropyran-2,4-diones with 2-aminonaphthalene or 6-aminoquinoline and aromatic aldehydes in an aliphatic alcohol gave 5-aryl-2,2-dimethyl(or 2-phenyl)-1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[3,4-*c*]quinolin-4-ones and 5-aryl-2-methyl-1,2,5,6-tetrahydro-4*H*-pyrano[4,3-*a*][4,7]phenanthrolin-4-ones which are new N,O-heterocyclic systems containing fused aza- and diazaphenanthrene moieties and a 2-pyranone ring.

3,4-Dihydro-2*H*-pyran-2,4-diones and their tetrahydro analogs are polyfunctional synthons possessing enolizable β-dicarbonyl fragment which includes chemically nonequivalent lactone and ketone carbonyl groups and activated methylene group. The development of methods for preparation of substituted pyrandiones [1–3] and studies of their transformations [1, 3–6] allowed us to synthesize a natural growth regulator, Germicidin [1, 2], and a number of compounds which are precursors of prostaglandin and thromboxan analogs [4, 6].

In the previous communications [7–11] we showed that carbocylic analogs of pyrandiones, such as 1,3-cyclohexanedione, 5-methyl-1,3-cyclohexanedione, 5,5-dimethyl-1,3-cyclohexanedione, and 5,5-diphenyl-1,3-cyclohexanedione, react with 2-naphthylamine or 6-quinolylamine and aromatic aldehydes to give fused aza- and diazaphenanthrene derivatives, benzo[*a*]phenanthridines and benzo[*a*][4,7]phenanthrolines. Compounds of these series exhibit strong and versatile biological activity [12–14].

With the goal of obtaining new fused heterocycles containing azaphenanthrene and pyran moieties, we have studied for the first time reactions of tetrahydropyran-2,4-diones with 2-aminonaphthalene or 6-aminoquinoline and aromatic aldehydes. An attempt to fuse an oxygen-containing heterocycle to azaphenanthrene system was made by us previously [15]. For this purpose, 2-aminonaphthalene was brought into reaction with aromatic aldehydes and Meldrum's acid. However, the 1,3-dioxin ring in the latter decomposed during the process, and the products were oxo derivatives of tetrahydrobenzo[*f*]quinoline.

In the present work, 6-methyl-, 6,6-dimethyl-, and 6-phenyltetrahydropyran-2,4-diones **Ia**–**Ic** were involved in condensation with 2-aminonaphthalene or 6-aminoquinoline and aromatic aldehydes. The reactions were carried out by heating equimolar amounts of the reactants in boiling aliphatic alcohol (ethanol or 1-butanol). Theoretically, three-component condensation of a 1,3-dicarbonyl compound, 2-aminonaphthalene (6-aminoquinoline), and an aromatic aldehyde can take several pathways [8, 16]. Taking into account the results of our previous studies [8–10], we believe that the most probable initial reaction stage is reaction of amine **IIa** or **IIb** with aromatic aldehyde to give Schiff bases **IIIa**–**IIIf**. The subsequent condensation of the latter with tetrahydropyrandiones **Ia**–**Ic** leads to formation of fused aza- and diazaphenanthrene derivatives, 5-aryl-2,2-dimethyl- and 5-aryl-2-phenyl-1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[3,4-*c*]quinolin-4-ones **IVa** and **IVb** and 5-aryl-2-methyl-1,2,5,6-tetrahydro-4*H*-pyrano[4,3-*a*]4,7-phenanthrolin-4-ones **IVc**–**IVf** (Scheme 1).

Schiff bases **IIIa**–**IIIf** can be obtained in preparative yields from 2-aminonaphthalene or 6-amino-

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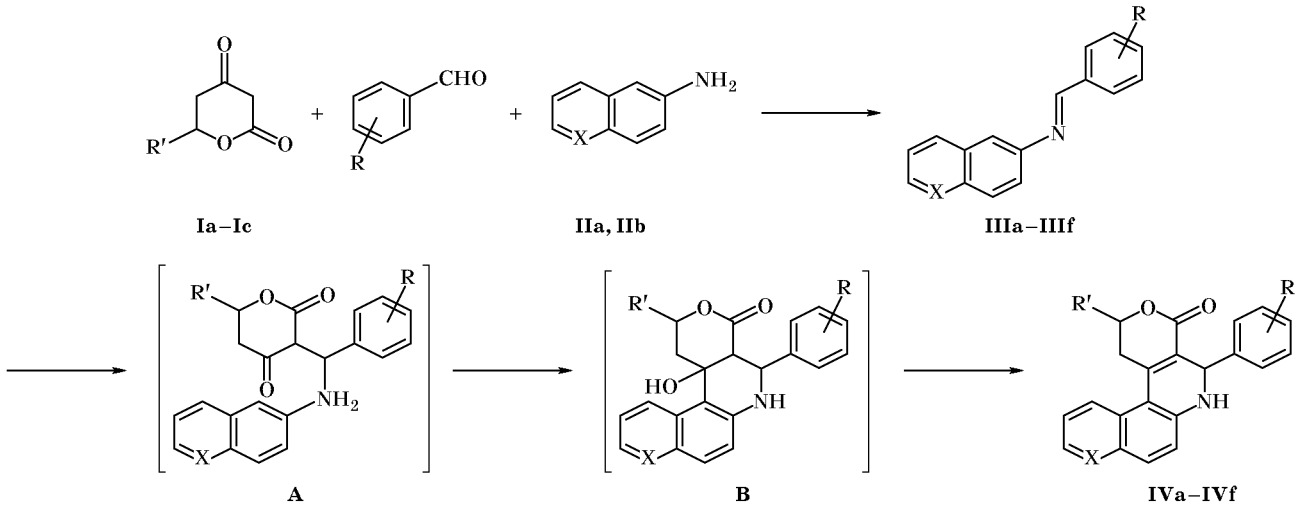
Scheme 1.



IIa, **IIIa**, **IIIb**, **IVa**, **IVb**, X = CH; **IIb**, **IIIc**–**IIIf**, **IVc**–**IVf**, X = N; **IIIa**, **IVa**, R = 4-Cl; **IIIb**, **IVb**, R = 4-EtO; **IIIc**, **IVc**, R = 4-PrO; **IIId**, **IVd**, R = 3,4-OCH_2O; **IIIe**, **IVe**, R = 2,4-Cl_2; **IIIf**, **IVf**; R = 3-HO; **Ia**, **IVc**–**IVf**, R′ = Me; **Ib**, **IVa**, R′ = Me_2; **Ic**, **IVb**, R′ = Ph.

quinoline and the corresponding aldehyde under analogous conditions. Their reaction with pyrandiones **Ia**–**Ic** results in formation of the same products as in the three-component condensation.

The mechanism of reactions of Schiff bases with CH-acids, including cyclic β-diketones, was described by us in detail in [8–10]. Due to high lability of the methylene hydrogen atom in position *3* of pyrandiones **Ia**–**Ic**, they react with Schiff bases in the absence of a catalyst. The process involves intermediate formation of 3-arylaminomethylene-6-alkyl-(aryl)-2,4-pyrandiones **A** and their cyclization products, hydroxy lactones **B**. Niether the former nor the latter were isolated. During the reaction, intermediate **A** is rapidly converted into **B**, and subsequent elimination of water yields benzopyranoquinolinones **IVa** and **IVb** or pyranophenanthrolinones **IVc**–**IVf**. The yields, melting points, and elemental analyses of compounds **IVa**–**IVf** are given in Table 1.

The structure of the initial amine and aromatic aldehyde almost does not affect the yield of the final product. The yields of 4,7-phenanthrolines **IVc**–**IVf** and benzo[*f*]quinoline **IVa** which were obtained, respectively, from methyl- and dimethyl-substituted pyrandiones **Ia** and **Ib** were relatively high, while the yield of **IVb** from phenyl-substituted derivative **Ic** was lower. Presumably, some amount of **IVb** is lost during isolation, for it is better soluble in alcohols than compounds **IVa** and **IVc**–**IVf**.

The mass spectra of benzoquinoline and 4,7-phenanthroline derivatives **IVa**–**IVf** contain the molecular ion peaks with a relative intensity of 10–15%. The most abundant ions (I_{rel} 100%) are those formed by elimination of the 5-aryl substituent from the molecular ion, $[M-C_6H_4R]^+$ ($[M-C_6H_3Cl_2]^+$ for **IVd**): *m*/*z* 278 (**IVa**), 326 (**IVb**), 265 (**IVc**–**IVf**). Fairly intense (22–26%) ion peaks with *m*/*z* 192 were present in the mass spectra of **IVa** and **IVb** and with *m*/*z* 193 for **IVc**–**IVf**; they correspond to elimination of the R′C(H)OCO fragment from $[M-C_6H_{4(3)}R]^+$. The observed fragmentation pattern is helpful in establishing the structure of **IVa**–**IVf**. In particular, it was important to determine which of the carbonyl groups of the initial pyrandione is retained in the resulting polycyclic compound and, correspondingly, which carbonyl group is involved in the condensation. In keeping with published data [17, 18], enolization of pyrandiones occurs preferentially at the ketone carbonyl with formation of 4-hydroxy structure. We believe that the cyclization of intermediate **A** also involves the ketone carbonyl and that fusion of the pyran ring occurs at C^3 and C^4 rather than at C^2 and C^3. As a result, benzo[*f*]pyrano[3,4-*c*]quinolines and pyrano[4,3-*a*][4,7]phenanthrolines are exclusively formed. Insofar as ion peaks with *m*/*z* 192 (193) were also observed in the mass spectra of carbocyclic analogs [8, 10], rearrangement of the corresponding fragment ion derived from **IVa**–**IVf** seems to be improbable. The formation of ion peaks with *m*/*z* 192 (193) is possible if the pyran methylene group is directly attached to the aza(diaza)phenanthrene system, i.e., only in the case of 3,4-fusion.

Table 1. Yields, melting points, and elemental analyses of compounds **IVa**–**IVf**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IVa[a]	87	337–338	73.84	5.19	3.47	$C_{24}H_{20}ClNO_2$	74.04	5.14	3.60
IVb	53	261–262	80.32	5.46	3.19	$C_{30}H_{25}NO_3$	80.54	5.59	3.13
IVc	84	243–244	74.11	6.04	7.02	$C_{25}H_{24}N_2O_3$	74.23	6.19	7.22
IVd	78	319–320	70.26	4.73	7.31	$C_{23}H_{18}N_2O_4$	70.59	4.81	7.49
IVe[b]	81	286–287	63.19	3.79	6.85	$C_{22}H_{16}Cl_2N_2O_2$	63.32	4.02	7.04
IVf	80	295–296	73.56	4.85	7.89	$C_{22}H_{18}N_2O_3$	73.74	5.03	7.82

[a] Found Cl: 8.69%. Calculated Cl: 9.00%.
[b] Found Cl: 17.43%. Calculated Cl: 17.58%.

A reliable proof for the above assignment was obtained from the IR spectra of **IVa**–**IVf** which contained a very strong carbonyl absorption band at 1691–1657 cm^{-1}. It appears at a considerably higher frequency than the corresponding band in the spectra of carbocyclic analogs (1630–1590 cm^{-1}) [9, 10]. Its position suggests the presence of a lactone moiety in molecules **IVa**–**IVf**. The observed low-frequency shift relative to usual position of lactone carbonyl band (1750–1735 cm^{-1}) [19] is explained by conjugation with the naphthalene (quinoline) ring and formation of intermolecular hydrogen bond with the amino group of another molecule. Stretching vibrations of the N–H group in **IVa**–**IVf** give rise to absorption in the region 3290–3180 cm^{-1}.

The aromatic part of the ^1H NMR spectra of **IVa**–**IVf** (Table 2) is identical to that typical of carbocyclic analogs [8–10]. In the aliphatic region we observed two doublets of doublets at δ 2.54–3.05 ppm, which belong to the C^1H_2 methylene group. The 2-H signal in the spectra of **IVc**–**IVf** appears as a multiplet at δ 4.10–4.72 ppm. Its downfield position (cf. [10]) is explained by deshielding effect of the neighboring oxygen atom. The signal from 2-H in compound **IVb** is located even in a weaker field, δ 5.18–5.35 ppm, due to the presence of phenyl ring on C^2. Likewise, strong deshielding by the neighboring nitrogen atom and substituted benzene ring is observed for the 5-H proton whose signal appears at δ 5.52–6.08 ppm. The 5-H signal in the spectrum of 2,2-dimethyl derivative **IVa** is a singlet, while compounds **IVb**–**IVf** display two singlets in the same region with an intensity ratio of 2:3 (**IVb** and **IVc**) and 1:2 (**IVd**–**IVf**). Analogous patterns were observed previously in the spectra of products obtained from 2-aminonaphthalene, aromatic aldehydes and monosubstituted cyclohexanediones [10, 11]. Presumably, compounds **IVb**–**IVf** are formed as mixtures of stereoisomers differing by relative arrangement of the substituents on C^2 and C^6. The same factor is responsible for the appearance of two singlets from the NH proton in the spectra of **IVb** and **IVe**, two doublets from the methyl protons in the spectra of **IVc**–**IVf**, and two doublets from the 2-H proton in the spectrum of **IVb**. The multiplet signal from 2-H in phenanthrolines **IVc**–**IVf** consists of two nearby multiplets having similar shapes; their overall intensity corresponds to one proton.

The electron absorption spectra of compounds **IVa**–**IVf** (Table 3) occupy the ultraviolet region and are characterized by a distinct vibrational structure. The positions of bands and their intensities are very similar to those observed for carbocyclic analogs [7–10]. This means that neither the pyran oxygen atom nor substituents in the pyran ring (Me, Me_2, Ph) and in the 5-phenyl ring affect electron transitions in the main chromophore (naphthalene or quinoline core). The vibrational structure of bands in the short-wave and middle part of the UV spectra of phenanrholines **IVc**–**IVf** is less pronounced, presumably due to effect of the quinoline nitrogen atom.

EXPERIMENTAL

The mass spectra (70 eV) were recorded on a Finnigan MAT Incos-50 spectrometer. The IR spectra were obtained on a Nicolet Protege-460 Fourier spectrometer. The ^1H NMR spectra were taken on a Tesla BS-567 instrument (100 MHz) in DMSO-d_6 using TMS as internal reference. The UV spectra were measured on a Specord UV-Vis spectrophotometer from solutions in ethanol ($c = 10^{-4}$ M). The melting points were determined on a Koffler device.

6-Methyltetrahydropyran-2,4-dione (Ia) was synthesized in 70% yield according to the procedure

Table 2. ^{1}H NMR spectra of 1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[3,4-*c*]quinolines **IVa** and **IVb** and 1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[4,3-*a*]4,7-phenanthrolines **IVc**–**IVf**, δ, ppm[a]

Comp. no.	1-H, d.d	2-H, m (d)	5-H, s	7-H, d	8-H, d	10-H, d	11-H, d.d	12-H, d	H_{arom}, d (m) [t]	Me, d	R	NH, s
IVa	2.62, 2.72	–	5.72	7.35–7.88 m[b]					7.20, 7.32	1.20, 1.40	–	9.80
IVb	2.80, 3.05	(5.18–5.35)	5.56, 5.80	7.20–8.00 m[b]					6.70, 7.15	–	1.24 t, 3.90 q	9.78, 9.90
IVc	2.54, 2.68	4.12–4.72	5.52, 5.69	7.48	7.87	8.69	7.30	8.30	6.68, 7.10	1.24, 1.32	0.85 t, 1.60 q, 3.78 t	9.87
IVd	2.57, 2.67	4.18–4.68	5.53, 5.71	7.50	7.88	8.67	7.32	8.28	(6.60, 6.88)	1.26, 1.35	5.96 d	9.85
IVe	2.59, 2.70	4.10–4.72	5.88, 6.08	7.49	7.90	8.70	7.28	8.30	(7.46)	1.27, 1.36	–	9.98, 10.05
IVf	2.58, 2.70	4.20–4.70	5.52, 5.70	7.51	7.90	8.71	7.36	8.24	(6.30–6.78) [6.90]	1.25, 1.34	9.20 m	9.92

[a] Coupling constants, Hz: 1-H: ^2J = 14.0, ^3J = 8.0; 2-H: ^3J = 4.5; 7-H: ^3J = 8.4; 8-H: ^3J = 8.4; 10-H: ^3J = 4.6; 11-H: ^3J = 8.2 Hz, ^4J = 2.8; 12-H: ^3J = 4.2; H_{arom}: ^3J = 8.0–8.4; Me: ^3J = 7.5–8.0.

[b] These multiplets belong to 7-H–12-H of the benzo[*f*]quinoline ring system, including the 9-H signal which is absent in the spectra of 4,7-phenanthrolines **IVc**–**IVf**.

Table 3. UV spectra of 1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[3,4-*c*]quinolines **IVa** and **IVb** and 1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[4,3-*a*]4,7-phenanthrolines **IVc**–**IVf**

Compound no.	λ_{max}, nm (log ε)
IVa	215 (4.59), 226 (4.76), 267 sh (4.10), 277 (4.23), 287 (4.33), 335 (3.89), 369 (3.88)
IVb	216 (4.59), 227 (4.73), 268 sh (4.05), 277 (4.19), 288 (4.25), 335 (3.89), 370 (3.84)
IVc	219 (4.65), 254 (4.24), 291 (4.12), 332 (3.94), 372 (3.88)
IVd	215 (4.64), 255 (4.21), 291 (4.12), 332 (3.94), 376 (3.91)
IVe	216 (4.61), 258 (4.27), 293 (4.19), 330 (3.99), 379 (3.90)
IVf	216 (4.63), 256 (4.26), 292 (4.18), 331 (3.97), 377 (3.94)

described in [20], by acylation of Meldrum's acid with diketene, reduction of the nonenolized carbonyl group in the acetoacetyl fragment of the resulting tetracarbonyl derivative with sodium tetrahydridoborate, and thermal cyclization of the reduction product. Pyrandione **Ia** was also obtained by hydrogenation of readily accessible 6-methyl-3,4-dihydro-2*H*-pyran-2,4-dione in ethanol over palladium catalyst [21]; yield 98%, mp 123–125°C; published data: mp 123–125°C [20], 123–124°C [21].

6,6-Dimethyltetrahydropyran-2,4-dione (Ib) and 6-phenyltetrahydropyran-2,4-dione (Ic) were synthesized by condensation of acetone or benzaldehyde, respectively, at the γ-position of ethyl acetoacetate dianione. The latter was prepared from ethyl acetoacetate either by successive treatment with sodium hydride and butyllithium [22] or by reaction with 2.5 equiv of lithium diisopropylamide [3]. The condensation products, δ-hydroxy-β-keto esters were subjected to cyclization by treatment with alkali and subsequent acidification. Compound **Ib**: yield 84% [3], mp 127–128°C. Compound **Ic**: yield 72% [22], 87% [3], mp 132–134°C [22].

***N*-Arylmethylene-2-aminonaphthalenes and *N*-arylmethylene-6-aminoquinolines IIIa–IIIf** were synthesized by heating of a mixture of amine **IIa** or **IIb** and the corresponding substituted benzaldehyde in boiling ethanol or 2-propanol. The procedure for preparation and properties of Schiff bases **IIIa** and **IIIc**–**IIIf** were given in [8, 23, 24].

***N*-(4-Ethoxyphenylmethylene)-2-aminonaphthalene (IIIb).** Yield 78%. mp 96–97°C. IR spectrum, ν, cm^{-1}: 1632 (C=N), 1215 (C–O–C). Mass spectrum, *m*/*z* (I_{rel}, %): 275 (M^+, 100), 230 (19). ^1H NMR spectrum, δ, ppm: 1.43 t and 4.10 q (OEt), 6.95–8.08 m (11H, H_{arom}), 8.45 s (CH=N). Found, %: C 82.68; H 6.09; N 5.11. $C_{19}H_{17}NO$. Calculated, %: C 82.91; H 6.19; N 5.09.

5-Aryl-2,2-dimethyl(or 2-phenyl)-1,2,5,6-tetrahydro-4*H*-benzo[*f*]pyrano[3,4-*c*]quinolin-4-ones IVa and IVb. *a*. A mixture of 5 mmol of 6,6-dimethyl(or 6-phenyl)tetrahydropyran-2,4-dione (**Ib** or **Ic**), 5 mmol of 2-aminonaphthalene (**IIa**), 5 mmol of *p*-chloro- or *p*-ethoxybenzaldehyde, and 20 ml of ethanol was refluxed for 1 h. The precipitate was filtered off. Crude product **IVa** was heated in boiling benzene to remove unreacted initial compounds, and benzoquinoline **IVb** was recrystallized from ethanol–benzene (1 : 2). The yields are given in Table 1.

b. A solution of 5 mmol of pyrandione **Ib** or **Ic** and 5 mmol of Schiff base **IIIa** or **IIIb** in 20 ml of ethanol was heated for 30–40 min under reflux. The products were isolated as described above in *a*. Yield 85% (**IVa**), 56% (**IVb**).

5-Aryl-2-methyl-1,2,5,6-tetrahydro-4*H*-pyrano-[4,3-*a*][4,7]phenanthrolin-4-ones IVc–IVf were synthesized following the above procedure from 6-methyltetrahydropyran-2,4-dione (**Ia**), 6-aminoquinoline (**IIb**), and the corresponding aromatic benzaldehyde (method *a*) or from pyrandione **Ia** and Schiff bases **IIIc–IIIf** (method *b*) by heating for 2 h (compounds **IVc**, **IVd**, and **IVf**) or 30 min (**IVe**) in boiling 1-butanol. Products **IVc–IVf** were purified by recrystallization from ethanol–benzene (2 : 1). Table 1 contains the yields of **IVc–IVf** according to method *a*; according to method *b*, the yields were 74–80%.

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