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Synthesis of Bis[2-methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl] Succinates

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Abstract—Reactions of succinyl chloride with 4-hydroxy-3-methoxybenzaldehyde and 3-ethoxy-4-hydroxybenzaldehyde gave the corresponding succinates which were brought into the condensation with naphthalen-2-amine to obtain Schiff bases. The latter reacted with CH acids (cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione) to form bis[2-alkoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl]-succinates which can also be obtained by three-component heterocyclization of naphthalen-2-amine with bis-(2-alkoxy-4-formylphenyl)succinates and CH acid.

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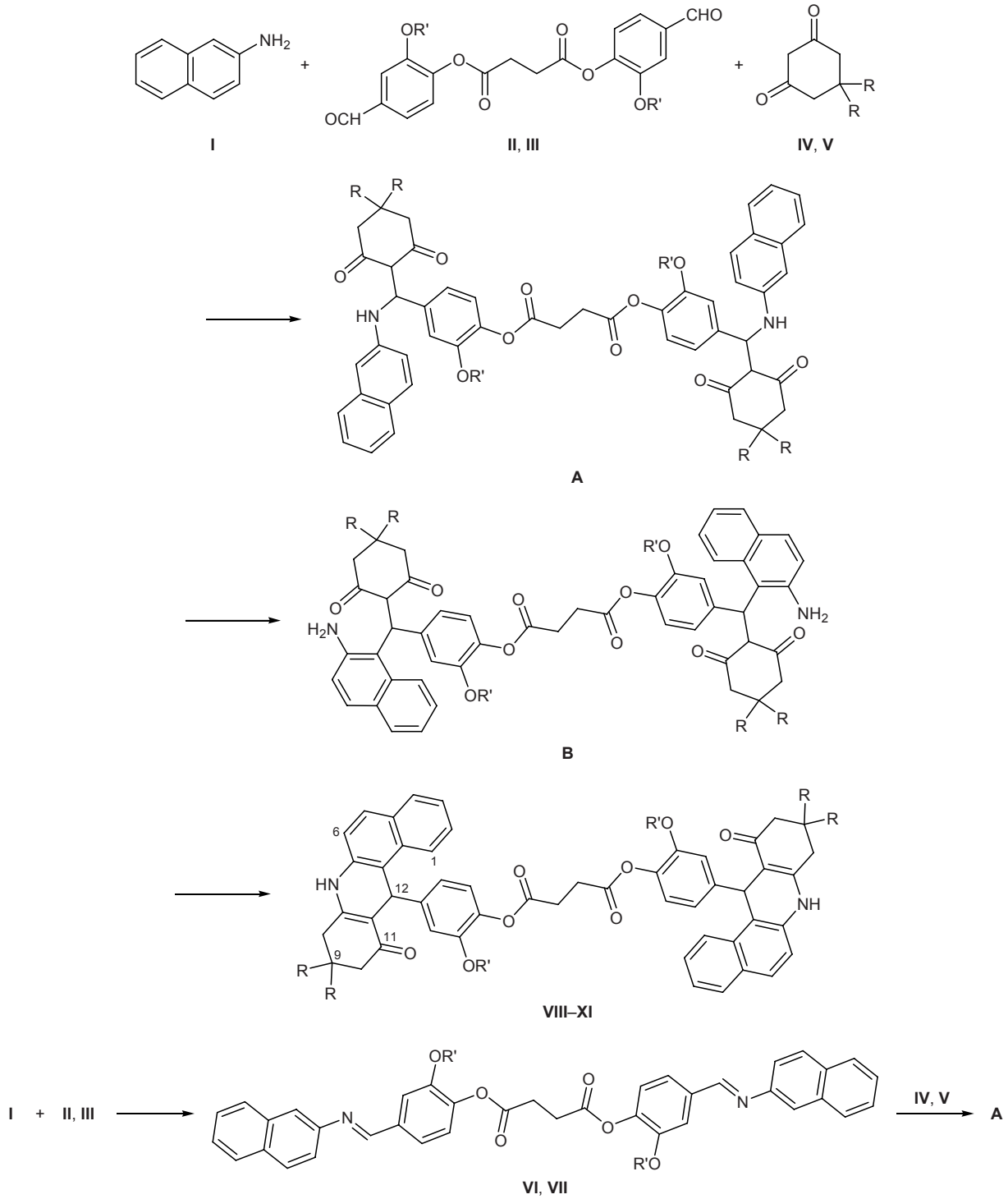
Cascade heterocyclization (cyclocondensation) of aromatic aldehydes with amines and cyclic β-diketones provides a convenient synthetic route to derivatives of benzo[*a*]acridine, 4,7-phenanthroline, and other fused nitrogen-containing heterocycles [1–3]. In particular, we studied in detail the condensation of *N*-(arylmethylidene)naphthalen-2-amines with some CH acids (1,3-diketones) [4]. On the other hand, there are no published data on condensation of bis-*N*-(arylmethylidene)naphthalen-2-amines). Kozlov and Kozlova [5] were the only to report on the synthesis of benzo[*f*]-quinoline derivatives from aryl methyl ketones and bis-Schiff base obtained from terephthalaldehyde and naphthalen-2-amine [5]. Bis-benzo[*f*]quinoline analogs obtained by such condensation and containing partially or completely hydrogenated phenanthrene or quinoline fragments are extensively studied for carcinogenic, teratogenic, and mutagenic properties intrinsic to polycyclic aromatic hydrocarbons [6, 7].

In the present work we examined reactions of 1,3-diketones **IV** and **V** with bis-Schiff bases derived from naphthalen-2-amine (**I**) and bis(2-alkoxy-4-formylphenyl) succinates **II** and **III**. Compounds **II** and **III** were selected as aldehyde components taking into account that 4-hydroxy-3-methoxybenzaldehyde (vanillin) and 3-ethoxy-4-hydroxybenzaldehyde (vanillal) are natural plant phenols which are convenient synthons for the design of biologically active compounds via introduction of pharmacophoric fragments [8–10]; furthermore, the succinate moiety can be used for the preparation of high-molecular polynuclear compounds having various functional groups [11, 12].

Schiff bases **VI** and **VII** were synthesized according to standard procedure, by heating equimolar amounts of the reactants, bis-aldehydes **II** and **III** and naphthalen-2-amine (**I**), in ethanol (Scheme 1). Their structure was unambiguously determined by IR and NMR spectroscopy. The IR spectra of **VI** and **VII** characteristically contain a strong absorption band in the region 1115–1120 cm^{-1}, which corresponds to stretching vibrations of the alkoxyphenyl C–O–C fragment, absorption band at 1690 cm^{-1} due to stretching vibrations of the C=N bonds, and carbonyl absorption bands at 1755–1760 cm^{-1}. In the ^1H NMR spectrum of **VI**, protons in the $COCH_2CH_2CO$ fragment resonated as a singlet at δ 3.11 ppm, methoxy protons gave a singlet at δ 3.95 ppm, aromatic proton signals appeared in the region δ 7.24–7.84 ppm, and the CH=N proton signal was located at δ 8.54 ppm. In the spectrum of **VII**, protons in the ethoxy group gave rise to a triplet at δ 1.45 ppm (CH_3) and a quartet at δ 4.20 ppm (CH_2O).

Schiff bases **VI** and **VII** were brought into condensation with such CH acids as cyclohexane-1,3-dione (**IV**) and 5,5-dimethylcyclohexane-1,3-dione (**V**, dimedone) on heating for 10–15 min. As a result, we

Scheme 1.



II, **VI**, **VIII**, **X**, R′ = Me; **III**, **VII**, **IX**, **XI**, R′ = Et; **IV**, **VIII**, **IX**, R = H; **V**, **X**, **XI**, R = Me.

obtained the corresponding bis[2-alkoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl) phenyl] and bis[2-alkoxy-9.9-dimethyl-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)-phenyl] succinates **VIII**–**XI** in 49 to 75% yield (calculated on the initial aldehyde). Cyclization products **VIII**–**XI** were also formed under milder conditions: they separated from the reaction mixture in 1 h after

mixing warm alcoholic solutions of the reactants. Presumably, the heterocyclization is favored by facile enolization of diketones **IV** and **V**.

It is known that cyclic 1,3-diketones in anhydrous benzene exist mainly in the diketone form [13]; therefore, the reaction rate was expected to change in going to benzene as solvent. In fact, hexahydrobenzo[*a*]acridine derivatives in benzene were formed only after heating for 1.5 h under reflux. Compounds **VI** and **VII** are soluble neither in alcohol nor in benzene, so that the reaction onset can readily be monitored: the product crystallized from the hot solution. These findings indicate that the degree of enolization of initial 1,3-diketones affects the cyclization process.

With a view to improve the yield of **VIII**–**XI** and simplify the experimental procedure, we tried to perform three-component condensation of naphthalen-2-amine with succinates **II** and **III** and diketones **IV** and **V**. The reactions were carried out by heating the reactants in boiling butanol. The use of 2 equiv of naphthalen-2-amine and 1,3-diketone ensured selective formation of compounds **VIII**–**XI** (Scheme 1). The reactions were complete in 5–10 min, and the yields of **VIII**–**XI** were 57 to 85%. Thus the three-component condensation ensures better yields of bis[2-alkoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)-phenyl] succinates than does the synthesis from preliminarily prepared Schiff bases **VI** and **VII**. Hexahydrobenzo[*a*]acridines **VIII**–**XI** were isolated as colored crystalline substances with sharp melting points.

A probable mechanism of the three-component cyclocondensation was repeatedly discussed previously [14]. Presumably, the reaction involves formation of Mannich base **A** which undergoes rearrangement to give intermediate **B**. Cyclization of the latter yields compounds **VIII**–**XI**.

The structure of compounds **VIII**–**XI** was determined by IR and ^{1}H NMR spectroscopy. Unlike initial Schiff bases **VI** and **VII**, the IR spectra of **VIII**–**XI** lacked C=N absorption band, but several bands appeared in the region 3070–3350 cm^{-1} due to stretching vibrations of the NH groups; in addition, a couple of bands at ~1580/1600 cm^{-1} was present, which is typical of conjugated ketoenamine fragment (vinylogous amide). Compounds **VIII**–**XI** displayed in the ^{1}H NMR spectra signals from protons on the C^{12} and nitrogen atoms as singlets at δ 5.8 and 9.8 ppm, respectively. The succinate fragment gave a singlet at δ 3.35 ppm. In the spectra of **VIII** and **X**, protons in the methoxy groups resonated at δ 3.6 ppm (s), and signals from aromatic protons were located in the region δ 6.6–8.0 ppm. Hexahydrobenzo[*a*]acridines **IX** and **XI** showed signals from the ethoxy protons at δ 1.1 (t, CH_3) and 3.8 ppm (q, CH_2).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^{1}H NMR spectra were recorded on Bruker AC-500 (500 MHz) and Tesla BS-567 (100 MHz) instruments using DMSO-d_6 and chloroform-*d* as solvents and tetramethylsilane as internal reference. The melting points were determined on a Kofler hot stage.

Bis(2-alkoxy-4-formylphenyl) succinates **II** and **III** were synthesized according to the procedure reported in [15]. Bis[2-alkoxy-4-(naphthalen-2-yliminomethyl)-phenyl] succinates **VI** and **VII** were prepared as described in [16].

Bis[2-methoxy-4-(naphthalen-2-yliminomethyl)-phenyl] succinate (VI). Yield 98%, mp 201–202°C. ^{1}H NMR spectrum, δ, ppm: 3.11 s (4H, CH_2), 3.95 s (6H, OCH_3), 7.24–7.84 m (20H, H_{arom}), 8.54 s (2H, CH=N). Found, %: C 75.69; H 5.19; N 4.14. $C_{40}H_{32}N_2O_6$. Calculated, %: C 75.46; H 5.07; N 4.40.

Bis[2-ethoxy-4-(naphthalen-2-yliminomethyl)-phenyl] succinate (VII). Yield 89%, mp 145–146°C. ^{1}H NMR spectrum, δ, ppm: 1.44 t (6H, $CH_2C\mathbf{H}_3$), 3.11 s (4H, CH_2CH_2), 4.21 q (4H, OCH_2), 7.24–7.93 m (20H, H_{arom}), 8.53 s (2H, CH=N). Found, %: C 76.04; H 5.65; N 4.06. $C_{42}H_{36}N_2O_6$. Calculated, %: C 75.89; H 5.46; N 4.21.

Succinates VIII–XI (*general procedure***).** *a*. A solution of 0.25 mmol of Schiff base **IV** or **V** and 0.5 mmol of 1,3-diketone **VI** or **VII** in 20 ml of butan-1-ol was heated under reflux until a solid separated (~10–15 min). The precipitate was filtered off, washed with hot benzene, and dried.

b. A mixture of 0.35 mmol of naphthalen-2-amine (**I**) and 0.17 mmol of the corresponding bis-aldehyde **II** or **III** in 20 ml of butan-1-ol was heated for 10 min under reflux. The mixture was cooled, 0.35 mmol of cyclohexane-1,3-dione (**IV**) or dimedone (**V**) was added, and the mixture was heated under reflux until a solid separated (~ 5 min). The precipitate was filtered off, washed with hot benzene, and dried.

Bis[2-methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl] succinate (VIII). Yield 50 (*a*), 59% (*b*); mp 205–207°C. ^{1}H NMR spec-

trum, δ, ppm: 1.8 m (4H, CH_2), 2.25 m (4H, CH_2), 2.8 m (4H, CH_2), 3.32 s (4H, OCH_2CH_2O), 3.57 s (6H, OCH_3), 5.8 s (2H, 12-H), 6.60–8.0 m (18H, H_{arom}), 9.8 s (2H, NH). Found, %: C 75.71; H 5.38; N 3.39. $C_{52}H_{44}N_2O_8$. Calculated, %: C 75.82; H 5.29; N 3.44.

Bis[4-(9,9-dimethyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)-2-methoxyphenyl] succinate (IX). Yield 75 (*a*), 84% (*b*); mp 282–284°C. ^{1}H NMR spectrum, δ, ppm: 0.87 s (6H, CH_3), 1.03 s (6H, CH_3), 2.15 m (4H, CH_2), 2.75 m (4H, CH_2), 3.32 s (4H, OCH_2CH_2O), 3.57 s (6H, OCH_3), 5.8 s (2H, 12-H), 6.60–8.0 m (18H, H_{arom}), 9.8 s (2H, NH). Found, %: C 76.34; H 5.95; N 3.18. $C_{56}H_{52}N_2O_8$. Calculated, %: C 75.82; H 5.29; N 3.44.

Bis[2-ethoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl] succinate (X). Yield 52 (*a*), 57% (*b*); mp 262–264°C. ^{1}H NMR spectrum, δ, ppm: 1.12 t (6H, $CH_2C\mathbf{H}_3$), 1.8 m (4H, CH_2), 2.25 m (4H, CH_2), 2.8 m (4H, CH_2), 3.32 s (4H, OCH_2CH_2O), 3.85 q (4H, $C\mathbf{H}_2CH_3$), 5.8 s (2H, 12-H), 6.60–8.0 m (18H, H_{arom}), 9.8 s (2H, NH). Found, %: C 76.04; H 5.67; N 3.28. $C_{54}H_{48}N_2O_8$. Calculated, %: C 75.96; H 5.61; N 3.34.

Bis[4-(9,9-dimethyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)-2-ethoxyphenyl] succinate (XI). Yield 49 (*a*), 57% (*b*); mp 300–302°C. ^{1}H NMR spectrum, δ, ppm: 0.87 s (6H, CH_3), 1.03 s (6H, CH_3), 1.12 t (6H, $CH_2C\mathbf{H}_3$), 2.15 m (4H, CH_2), 2.75 m (4H, CH_2), 3.32 s (4H, OCH_2CH_2O), 3.85 q (4H, $C\mathbf{H}_2CH_3$), 5.8 s (2H, 12-H), 6.60–8.0 m (18H, H_{arom}), 9.8 s (2H, NH). Found, %: C 76.63; H 6.21; N 3.08. $C_{58}H_{56}N_2O_8$. Calculated, %: C 76.76; H 6.35; N 3.24.

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