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REACTION OF LONG-CHAIN VANILLYL ESTERS WITH CH-ACIDS AND 2-NAPHTHYLAMINE

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The previously unknown 4-(alkyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[a]acridin-12-yl)- and 4-(alkyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)-2-methoxyphenyl esters of aliphatic (C_5-C_7, C_{12}) carboxylic acids were synthesized via cascade heterocyclization of cyclohexane-1,3-dione and dimedone with 2-naphthylamine and long-chain vanillyl esters.

Key words: heterocyclization, esters, synthesis, esterification, alkylcarboxylic acid derivatives.

Vanillin is an interesting structural motif for the synthesis of condensed N-containing heterocycles in our studies of the condensation of aromatic aldehydes with 2-naphthylamine and CH-acids [1-3]. By supplying a methoxyphenyl substituent and a methine group to the structure of the azaheterocycles, vanillin plays an exclusive role in the synthesis of biologically active compounds that are analogs of cardioprotectors, enzyme inhibitors, analgesics, preparations with antitumor activity [4-7], and acridone plant alkaloids [8-10].

However, the resulting heterocycles are unreactive owing to their complex structures and low solubility in organic solvents. Therefore, their further modification is difficult. Introducing into the heterocycle an alkylphenoxycarboxylate with a long alkyl radical (from C_5 to C_{12}) changes the hydrophilic—lipophilic properties of the compounds and increases their biological activity.

We esterified the hydroxyl of the starting vanillin using chlorides of long-chain aliphatic acids. The vanillyl esters were subsequently used in the reaction of 2-naphthylamine and CH-acids as synthons in the targeted synthesis of previously unknown benzo[*a*]acridine and xanthene alkylcarboxylates.

We studied the reaction of cyclohexane-1,3-dione (**1a**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone, **1b**) with 2-naphthylamine (**2**) and vanillyl esters (**3a-d**). The reaction was performed by boiling the starting materials in ethanol. The pure derivatives 2-methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl carboxylates (**4a-c**) were synthesized from equimolar mixtures using cyclohexane-1,3-dione; 2-methoxy-4-(9,9-dimethyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl carboxylates (**5a-d**), using dimedone.

Two pathways are preferred in the three-component reagent mixture (**1a** or **1b**, **2**, **3a-d**), each of which can react with two others. These are (**1a** or **1b**) + **2** = A and (**1a** or **1b**) + (**3a-d**) = B. The reactions of the enamine (A) with aldehydes **3a-d** and of the dione (B) with **2** lead to an intermediate (C), dehydration of which gives benzo[*a*]acridin-11-ones (**4a-c** and **5a-d**). The reaction occurs with formation of a 1,4-dihydropyridine ring, probably with an axial aryl substituent that is out of the plane of the main ring.

The synthesized annelated benzo[*a*]acridines (**4a-c** and **5a-d**) are white or light yellow crystalline compounds.

The benzo[*a*]acridin-11-ones (**4a-c** and **5a-d**) are accompanied in the reaction by arylmethylenebisdiketones (D), dehydration of which produces 4-(1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)- (**6a** and **c**) or 4-(3,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)- (**7**) 2-methoxyphenyl esters of carboxylic acids. Reaction of these with 2-naphthylamine gives **4a-c** and **5a-d**. The octahydro-1H-xanthen-9-yl derivatives (**6a**, **c**, **7**) were obtained both as side products of the reaction and by boiling in ethanol a two-fold excess of the diketone (**1a** and **b**) with aldehydes (**3a** and **c**).

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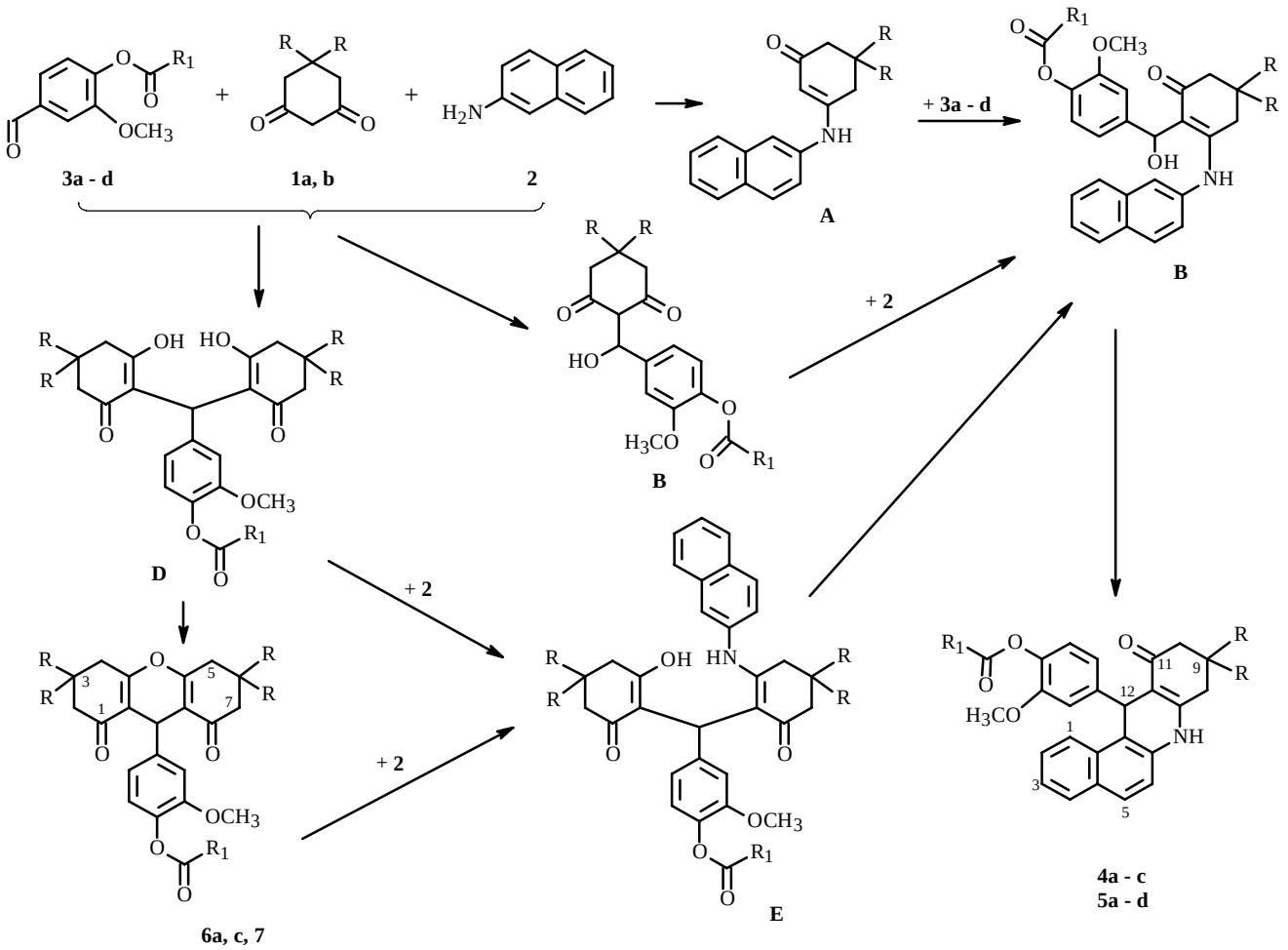

R = H (**1a**), CH_3 (**1b**) R_1 = C_5H_{11} (**3a**), C_6H_{13} (**3b**), C_7H_{15} (**3c**), $C_{12}H_{25}$ (**3d**)
R = H, R_1 = C_5H_{11} (**4a, 6a**), C_6H_{13} (**4c**), C_7H_{15} (**4c**, **6c**)
R = CH_3 , R_1 = C_5H_{11} (**5a, 7**), C_6H_{13} (**5b**), C_7H_{15} (**5c**), $C_{12}H_{25}$ (**5d**)

PMR spectra of **4a-c** and **5a-d** are consistent with the position and multiplicity of the aromatic protons in benzo[*a*]acridines [11]. The methine proton (H^{12}) of the dihydropyridine gives a singlet at 5.88-5.94 ppm. The weak-field shift of this signal compared with the usual position for signals of methine protons in cyclic compounds [12] is due to the anisotropic effect of the neighboring aromatic ring. PMR spectra of octahydro-1H-xanthen-9-yl compounds (**6a**, **c**, **7**) confirm completely the structures of these compounds.

IR spectra of **4a-c** and **5a-d** have characteristic stretching and deformation bands for NH at 3310-3300 and 1655-1650 cm^{-1}, respectively. Stretching vibrations of the ketone conjugated to the enamine in **4a-c**; **5a-d**; and **6a**, **c**, and **7** appear at 1615-1610 cm^{-1}. The ester carbonyl gives a strong absorption at 1640-1630 cm^{-1}. The shift of this band to low frequencies is apparently due to the formation of intermolecular H-bonds involving the ester, amino group, and an enolized ketone carbonyl. The C–O–C group gives bands at 1240-1220 cm^{-1}. Stretchings of alkyl and cycloaliphatic CH bonds appear at 2960-2840 cm^{-1}; of aromatic CH, at 3130-3030 cm^{-1}.

Mass spectra of **4a-c**; **5a-d**; and **6a**, **c**, and **7** have peaks for molecular ions $[M]^+$ (**1**, 11-18%). The base peaks (100%) correspond with $[M - MeO - R'COOC_6H_3]^+$ ions. The spectra of all benzo[*a*]acridines (**4a-c** and **5a-d**) contain a peak with *m*/*z* 193 (15-38%) that corresponds to elimination from the base peak of CH_2CH_2CO for **4a-c** and $(CH_3)_2CHCH_2CO$ from **5a-d**. Such peaks do not appear in mass spectra of **6a**, **c**, and **7**.

EXPERIMENTAL

Mass spectra were measured on a Finnigan MAT INCOS 50 instrument with 70-eV ionizing electrons. IR spectra were recorded on a Nicolet Protege-460 Fourier spectrometer. PMR spectra were recorded on AC-500 (500 MHz, Bruker) and Tesla

BS-567 (100 MHz) spectrometers in DMSO-d_6 with TMS internal standard. Melting points were determined on a Kofler block. Elemental analyses of all compounds agreed with those calculated.

Vanillyl Alkanoates (3a-d). A solution of vanillin (0.2 mole) in absolute CH_2Cl_2 (500 mL) was treated with absolute pyridine (0.25 mol) and the appropriate acid chloride (0.2 mol) in small portions while shaking the contents of the flask. The acid chlorides were prepared by boiling for 6 h a mixture of carboxylic acid (1 mol), $SOCl_2$ (1.3 mol), and absolute benzene (500 mL) with subsequent distillation of benzene and the solid (in vacuum for dodecanoyl chloride). The reaction mixture was boiled for 1 h. CH_2Cl_2 was removed by heating on a water bath. The solid was dissolved in benzene (500 mL), washed three times each with water and aqueous $NaHCO_3$ (5%), and dried over $CaCl_2$. The solvent was distilled. The solid was sublimed in vacuum or recrystallized from benzene:hexane (1:1).

3a, $C_{14}H_{18}O_4$, yield 85%, bp 155-156°C (0.5 mm Hg), n_D^{20} 1.5068. PMR spectrum (δ, ppm): 0.90 (3H, t, Me), 1.12-1.90 (6H, m, CH_2), 2.58 (2H, m, CH_2), 3.88 (3H, s, OMe), 7.13 (d, arom. H), 7.44 (m, arom. H), 9.95 (1H, s, CH).

3b, $C_{15}H_{20}O_4$, yield 82%, bp 163-164°C (0.5 mm Hg), n_D^{20} 1.5092. PMR spectrum (δ, ppm): 0.96 (3H, t, Me), 1.15-1.88 (8H, m, CH_2), 2.51 (2H, m, CH_2), 3.86 (3H, s, OMe), 7.12 (d, arom. H), 7.45 (m, arom. H), 9.91 (1H, s, CH).

3c, $C_{16}H_{22}O_4$, yield 77%, bp 170-171°C (0.5 mm Hg), n_D^{20} 1.5079. PMR spectrum (δ, ppm): 0.92 (3H, t, Me), 1.32 (8H, m, CH_2), 1.79 (2H, m, CH_2), 2.60 (2H, m, CH_2), 3.88 (3H, s, OMe), 7.14 (d, ArH), 7.47 (3H, m, ArH), 9.90 (1H, s, CH).

3d, $C_{21}H_{32}O_4$, yield 75%, oil. PMR spectrum (δ, ppm): 0.89 (3H, t, Me), 1.30 (18H, m, CH_2), 1.75 (2H, m, CH_2), 2.59 (2H, m, CH_2), 3.87 (3H, s, OMe), 7.16 (d, arom. H), 7.41 (m, arom. H), 9.91 (1H, s, CH).

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl Caproylate (4a). 2-Naphthylamine (**2**, 0.01 mol) was dissolved in ethanol (50 mL), treated with **3a** (0.01 mol) and **1a** (0.01 mol), boiled for 2 h, and cooled. The resulting crystalline precipitate was separated, washed with hot methanol, and recrystallized from benzene to afford **4a**, 0.9 g (60%), $C_{30}H_{31}NO_4$, mp 250-252°C. PMR spectrum (δ, ppm, J/Hz): 0.9 (3H, t, Me), 1.35 (4H, m, CH_2), 1.65 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 1.90, 2.20, 2.60 (m, cycloaliphatic H), 3.69 (3H, s, OMe), 5.88 (1H, s, CH), 6.55 (d, J = 8.0, arom. H), 6.73 (d, J = 8.2, arom. H), 7.13 (s, arom. H), 7.30 (m, arom. H), 7.43 (t, arom. H), 7.75 (m, arom. H), 7.95 (d, J = 7.6, arom. H), 9.70 (s, NH).

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl esters of C_6 and C_7 aliphatic carboxylic acids (4b and c) were prepared analogously.

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl Enanthate (4b). $C_{31}H_{33}NO_4$, yield 60%, mp 230-232°C. PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, t, Me), 1.35 (6H, m, CH_2), 1.75 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 1.90, 2.20, 2.58 (m, cycloaliphatic H), 3.72 (3H, s, OMe), 5.90 (1H, s, CH), 6.49 (d, J = 7.8, arom. H), 6.62 (d, J = 8.0, arom. H), 7.08 (s, arom. H), 7.30 (m, arom. H), 7.38 (t, arom. H), 7.68 (d, J = 8.8, arom. H), 7.79 (d, J = 7.0, arom. H), 9.50 (s, NH).

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl Caprylate (4c). $C_{32}H_{35}NO_4$, yield 48%, mp 201°C. PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, t, Me), 1.30 (8H, m, CH_2), 1.65 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 1.90, 2.20, 2.50 (m, cycloaliphatic H), 3.75 (3H, s, OMe), 5.90 (1H, s, CH), 6.48 (d, J = 8.0, arom. H), 6.65 (d, J = 8.7, arom. H), 7.14 (s, arom. H), 7.30 (m, arom. H), 7.40 (m, arom. H), 7.68 (d, J = 6.8, arom. H), 7.73 (d, J = 7.2, arom. H), 7.95 (d, J = 7.5, arom. H), 9.48 (s, NH).

4-(9,9-Dimethyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)-2-methoxyphenyl Caproylate (5a). $C_{32}H_{35}NO_4$. 2-Naphthylamine (**2**, 0.01 mol) was dissolved in ethanol (50 mL), treated with the appropriate vanillyl hexanoate (**3a**, 0.01 mol) and dimedone (**1b**, 0.01 mol), boiled for 4 h, and cooled. The resulting crystalline precipitate was separated, washed with hot methanol, and recrystallized from benzene to afford **5a**, 1.09 g (73%), mp 210°C. PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, t, Me), 1.35 (4H, m, CH_2), 1.75 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 2.15, 2.30 (m, cycloaliphatic H), 3.74 (3H, s, OMe), 5.87 (1H, s, CH), 0.95 (s, 3H, Me), 1.10 (s, 3H, Me), 6.80 (d, J = 8.4, arom. H), 7.12 (d, J = 8.3, arom H), 7.18 (s, arom H), 7.34 (m, arom. H), 7.40 (t, arom. H), 7.60 (d, J = 7.8, arom. H), 7.90 (d, J = 7.9, arom. H), 9.37 (s, NH).

4-(9,9-Dimethyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)-2-methoxyphenyl esters of C_6, C_7, and C_{12} aliphatic acids (5b-d) were prepared analogously.

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl Enanthate (5b). $C_{33}H_{37}NO_4$, yield 60%, mp 184-186°C. PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, t, Me), 1.35 (6H, m, CH_2), 1.65 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 2.15, 2.40 (m, cycloaliphatic H), 3.70 (3H, s, OMe), 5.89 (1H, s, CH), 0.95 (s, 3H, Me), 1.10 (s, 3H, Me), 7.00 (d, J = 7.9, arom. H), 7.14 (d, J = 7.3, arom. H), 7.10 (s, arom. H), 7.35 (m, arom. H), 7.37 (t, arom. H), 7.68 (d, J = 6.7, arom. H), 7.75 (d, J = 7.4, arom. H), 7.95 (d, J = 6.9, arom. H), 9.37 (s, NH).

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl Caproylate (5c). Yield 52%, mp 210-212°C. PMR spectrum (δ, ppm, J/Hz): 0.85 (3H, t, Me), 1.30 (8H, m, CH_2), 1.65 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 2.10, 2.25 (m, cycloaliphatic H), 3.76 (3H, s, OMe), 5.88 (1H, s, CH), 0.98 (s, 3H, Me), 1.10 (s, 3H, Me), 6.60, 7.10, 7.60, 8.00 (m, arom. H), 9.37 (s, NH). Found (%): C 77.73, H 7.45, N 2.70. $C_{34}H_{39}NO_4$. Cald. (%): C 77.71, H 7.42, N 2.67.

2-Methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl Tridecanoate (5d). $C_{39}H_{49}NO_4$, yield 40%, mp 138-140°C. PMR spectrum (δ, ppm, J/Hz): 0.85 (3H, t, Me), 1.30 (18H, m, CH_2), 1.60 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 2.09, 2.13 (m, cycloaliphatic H), 3.69 (3H, s, OMe), 5.82 (1H, s, CH), 0.90 (s, 3H, Me), 1.10 (s, 3H, Me), 6.55 (d, J = 8.1, arom. H), 6.60 (d, J = 7.3, arom. H), 7.10 (s, arom. H), 7.30, 7.45, 7.58 (m, arom. H), 7.90 (d, J = 6.8, arom. H), 9.57 (s, NH).

4-(1,8-Dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)-2-methoxyphenyl Caproylate (6a). Vanillyl hexanoate (**3a**, 0.01 mol) was dissolved in ethanol (50 mL), treated with cyclohexane-1,3-dione (**1a**, 0.02 mol), and boiled for 2 h. The resulting crystalline precipitate was separated, washed with ether, dried, and recrystallized from ethanol to afford **6a**, yield 41%, $C_{26}H_{30}O_6$, mp 176-178°C. PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, t, Me), 1.35 (4H, m, CH_2), 1.70 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 1.90, 2.24, 2.40 (m, cycloaliphatic H), 3.80 (3H, s, OMe), 4.65 (1H, s, CH), 6.85 (d, J = 8.9, arom. H), 6.75 (d, J = 8.0, arom. H), 7.00 (s, arom. H), 7.30.

4-(1,8-Dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)-2-methoxyphenyl Caproylate (6c) was prepared analogously. $C_{28}H_{34}O_6$, yield 43%, mp 116-118°C. PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, t, Me), 1.30 (8H, m, CH_2), 1.75 (2H, m, CH_2), 2.45 (2H, m, $COCH_2$), 1.95, 2.26, 2.65 (m, cycloaliphatic H), 3.75 (3H, s, OMe), 4.63 (1H, s, CH), 6.67 (d, J = 8.6, arom. H), 6.78 (d, J = 8.0, arom. H), 6.69 (s, arom. H).

4-(3,6-Tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)-2-methoxyphenyl Caproylate (7). Vanillyl hexanoate (**3a**, 0.01 mol) was dissolved in ethanol (50 mL), treated with dimedone (**1b**, 0.02 mol), and boiled for 3 h. The resulting crystalline precipitate was separated, washed with ether, dried, and recrystallized from methanol to afford **7**, 0.43 g (22%), $C_{30}H_{38}O_6$, mp 133°C. PMR spectrum (δ, ppm, J/Hz): 0.95 (3H, t, Me), 1.40 (4H, m, CH_2), 1.70 (2H, m, CH_2), 2.40 (2H, m, $COCH_2$), 2.10, 2.35 (m, cycloaliphatic H), 3.76 (3H, s, OMe), 4.70 (1H, s, CH), 0.90 (s, 6H, 2Me), 1.10 (s, 6H, 2Me), 6.80 (d, J = 9.3, arom. H), 6.85 (s, arom. H), 7.15 (d, J = 7.9, arom. H).

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