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Bromination of 9-dimedonyltetrahydroxanthenone as a route to a new type of substituted hydrochromeno[2,3,4-*kl*]xanthenones

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Bromination of 9-dimedonyl-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one was carried out to provide a route to a new series of substituted hydrochromeno[2,3,4-*kl*]xanthenones, which may find application for the synthesis of poorly accessible compounds including the heteroanalogs. A dependence of transformations of dimedonyltetrahydroxanthenone on the nature of the solvent was elucidated: bromination at the α-methylene groups of the dimedonyl substituent is accompanied by heterocyclization involving 1- and 5-oxo groups. Quantum chemical HF/6-311(d,p) *ab initio* calculations for the proposed mechanism of hemiacetalization and halogenation were carried out.

Key words: oxo compounds, bromination, heterocyclization, enolization, hydrochromenoxanthenones, quantum chemical calculations, HF/6-311(d, p) method.

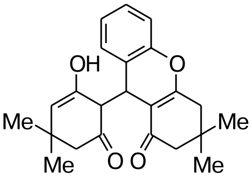
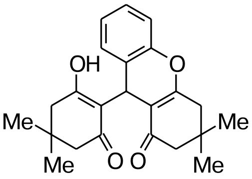
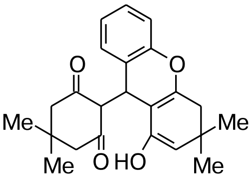
The continuous interest in the chemistry of diketones is caused by the set of unique properties they possess owing to the presence of oxo groups with different positions and types (conjugated or nonconjugated), the methylene unit, and the ability to undergo heterocyclization, which make them valuable substrates for investigations and for practical purposes.

As a continuation of the systematic research of the properties of oxo compounds,[1,2] we studied for the first time electrophilic reactions with acids and bromination of 3,3-dimethyl-9-(4,4-dimethyl-2,6-dioxocyclohexan-1-yl)-1,2,3,4-tetrahydro-9*H*-xanthen-1-one (**1**) and elucidated the dependence of its transformations on the nature of the solvent. Triketone **1** occupies a special place among oxo-1,5-diketones. Apart from the presence of conjugated and nonconjugated 1,3- and 1,5-carbonyl groups, it is distinguished by the presence of a tetrahydroxanthene fragment, which affects the reactivity, for example, toward nucleophilic reactions with amines.[3]

Since the molecule of triketone **1** has several reaction centers, we carried out quantum chemical prediction of the most likely site of electrophilic addition of bromine taking into account the first step of bromination, *i.e.*, enolization of one of the carbonyl functions.[4,5]

According to quantum chemical calculations, the formation of enol **1B** is thermodynamically most favorable (Table 1). For enol **1A**, the energy barrier to the reaction is much higher. Indeed, enolization of triketone **1** with participation of carbonyl groups of the dimedonyl substituent was confirmed by ^{1}H NMR data in particular, by

Table 1. Total energies of the enol forms of oxo compound **1** according to RHF/6-311G(d,p) calculations

Form	E_{tot}	ΔE_{tot}
	kcal mol^{-1}	
 **1A**	−99184.76	4.30
 **1B**	−99186.43	2.63
 **1C**	−99183.08	5.98

Note. ΔE_{tot} was calculated as the difference between the total energies of the enol and ketone forms of triketone **1** on the basis of E_{tot} of the ketone form (−99189.06 kcal mol^{-1}).

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a broad low-field signal for the OH proton (δ 10.42) and a signal for the tertiary proton at δ 5.06.

The alternative addition of the bromine atom at the multiple bond of the xanthene fragment of substrate **1** also cannot be ruled out.

In acetic acid medium, the predominant route is enolization of the dimedonyl carbonyl (enol **1B**), giving rise to 9-(2-bromo-4,4-dimethyl-2,6-dioxocyclohexan-1-yl)-3,3-dimethyl-1,2,3,4-tetrahydro-9*H*-xanthen-1-one (**2**), involving the tertiary hydrogen atom as the most mobile in oxo compound **1** (Scheme 1). Preferred bromination along this route in acetic acid was also noted for related bisdimedonylmethane.[6]

Compound **2** is the only product that can be isolated from the reaction mixture. In the ^{1}H NMR spectrum of this compound, the signal for the tertiary proton shifts downfield (δ 6.41). No signals are present for the hydroxyl group protons of the enol form of **1**. The spectral pattern of the heterocyclic fragment is generally retained. The signals for the methylene protons of the dimedonyl substituent change positions. The presence of bromine in the β-position removes the degeneracy of the signals of axial and equatorial protons and gives rise to one more signal at δ 2.12.

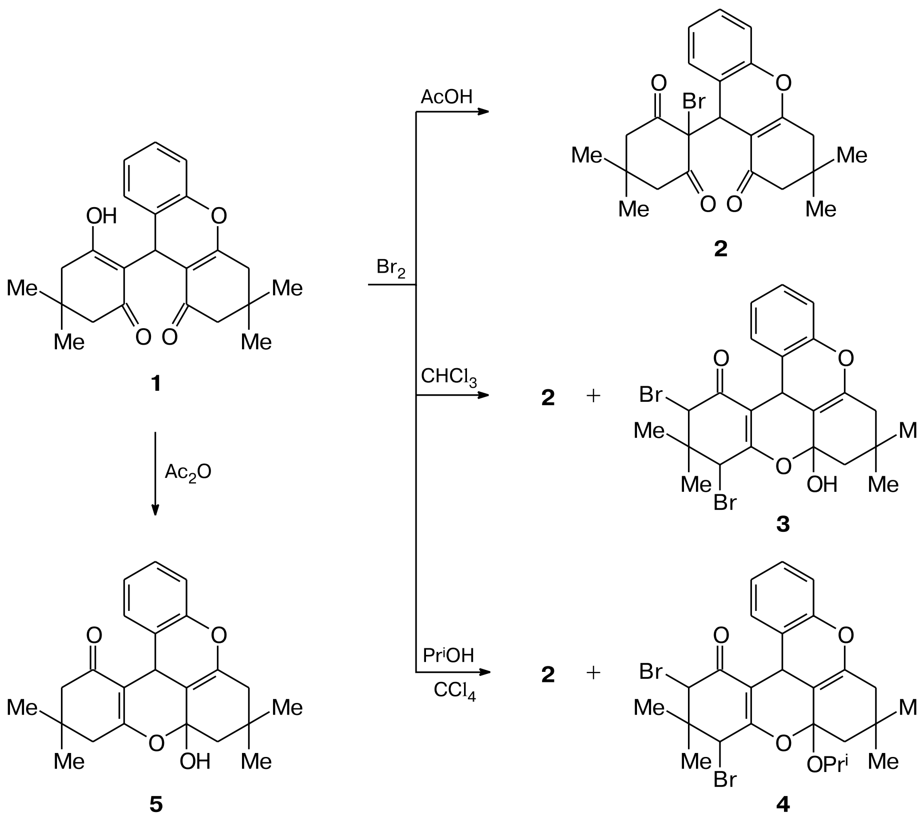
In chloroform or in a propan-2-ol and carbon tetrachloride mixture, the solubility of triketone **1** increases, which promotes heterocyclization involving 1,5-dioxo groups and bromination of the hemiacetal thus formed. Propan-2-ol acts simultaneously as a reagent, resulting in the formation of 2,4-dibromo-5a-isopropoxy-3,3,7,7-tetramethyl-2,3,4,5a,6,7,8,13b-octahydro-1*H*-chromeno[2,3,4-*kl*]xanthen-1-one (**4**). According to TLC data, brominated triketone **2** is also present among the reaction products.

Bromination of triketone **1** implies two transformation routes for the substrate under these conditions.

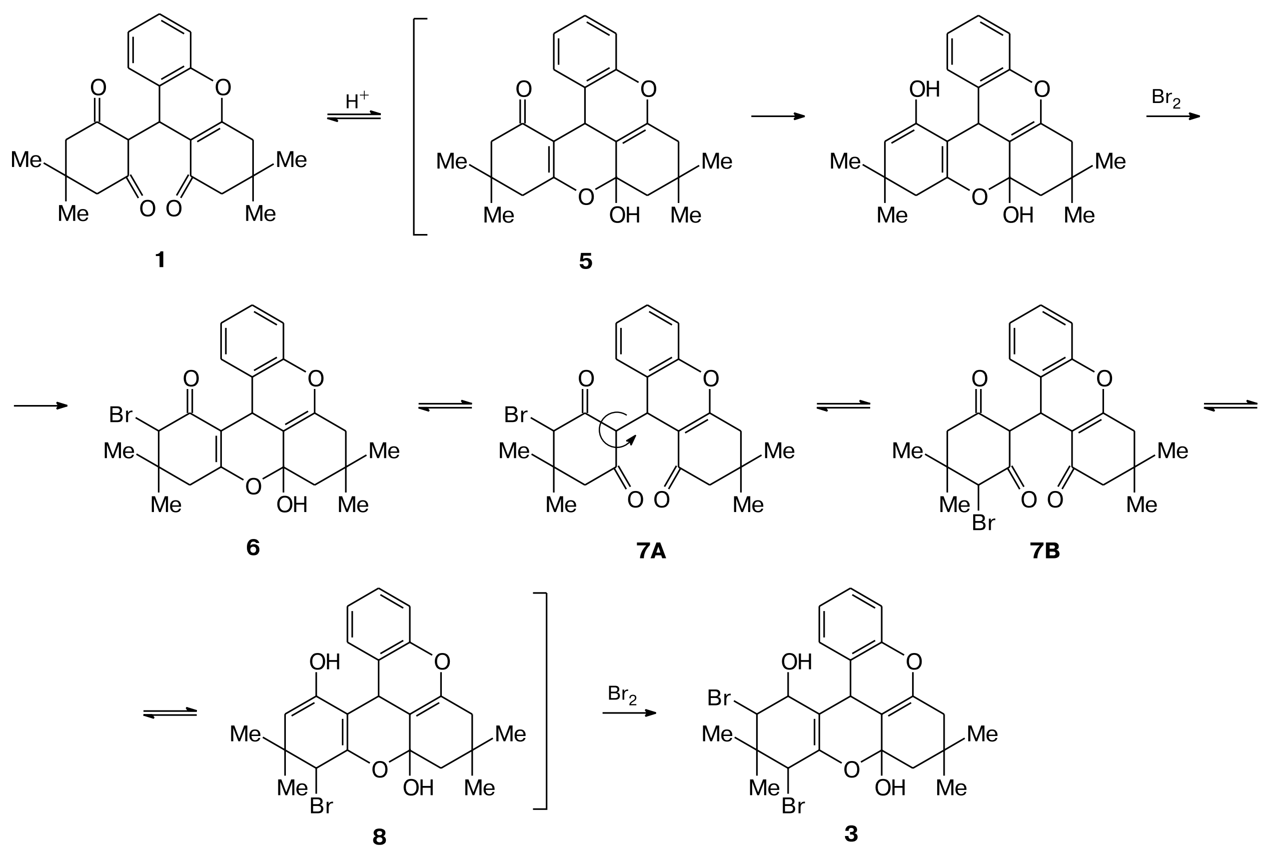
The first route includes the initial hemiacetalization and bromination at the α′-position of the aliphatic ring fused to the hemiacetalized heterofragment. The subsequent transformations can take place after opening of the heterocycle in monobrominated hemiacetal **6** followed by probable rotation of the dimedonyl fragment at C(9) around the single bond[7] (**7A** $\rightleftharpoons$ **7B**), heterocyclization, and repeated bromination of the resulting compound **8** at the unsubstituted methylene unit of the dimedonyl aliphatic ring capable of enolization (Scheme 2).

The calculation of the total energies of tautomers **6**, **7A** and **7B**, and **8** showed that the thermodynamic effect of the ring-chain tautomerism of monobrominated substrate does not exceed 8.4 kcal mol^{-1} (Fig. 1). This energy barrier is most often lower when the reaction is carried

Scheme 1



Scheme 2



out in a solvent;[8] thus, the proposed bromination mechanism is feasible under the chosen conditions.

The alternative route includes the initial enolization and, as shown above, bromination of the dimedonyl fragment of triketone **1** at the tertiary carbon atom, which precludes hemiacetalization.

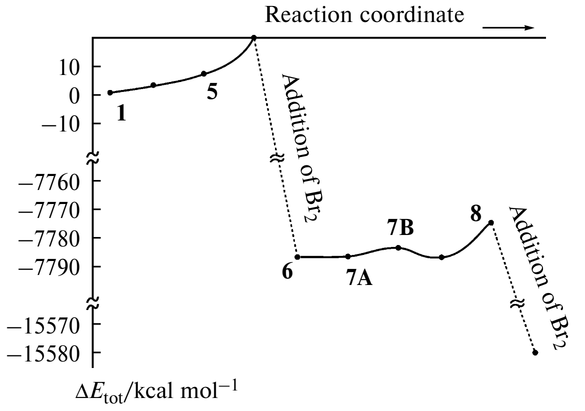


Fig. 1. Relative total energy (ΔE_{tot}) *vs.* the reaction coordinate for bromination of triketone **1** in chloroform (ΔE_{tot} calculated as the difference between the total energy of the molecule and the energy equal to −99190 kcal mol^{-1}).

The possibility of hemiacetalization of triketone **1** was confirmed by a special experiment, namely, on refluxing in acetic acid in the presence of acetic anhydride, it was converted into 5a-hydroxy-3,3,7,7-tetramethyl-2,3,4,5a,6,7,8,13b-octahydro-1*H*-chromeno[2,3,4-*kl*]-xanthen-1-one (**5**) (see Scheme 1).

The signals of the methylene protons of the xanthene fragments in the ^{1}H NMR spectra of compounds **3**—**5** retain their positions, while the signals of the dimedonyl fragment in products **3**, **4** disappear. The downfield shift of the tertiary proton is insignificant. The appearance of two new signals in the spectra of dibrominated products **3**, **4** at δ 5.02, 5.03 and 5.37, 5.39, respectively, indicates that bromination involves the methylene units of the dimedonyl substituent.

Experimental and calculation procedure

The structures of all molecules participating in the bromination reactions were determined by *ab initio* RHF/6-311G(d,p) calculations[9,10] with full geometry optimization in the gas phase using the PC GAMESS program package.[11]

The melting points were determined on a Koefler hot stage. IR spectra were measured on Specord M-80 spectrometer in mineral oil and hexachlorobutadiene (thin film). The ^{1}H and

^{13}C NMR spectra were measured on a Varian Unity Inova instrument (600 (^{1}H) and 150 MHz (^{13}C)) in $CDCl_3$ and DMSO-d_6 using Me_4Si as the internal standard. The reactions were monitored and the purity of compounds was checked by TLC on Silufol UV-254 plates using a hexane—ether—acetone mixture (3 : 1 : 1) as the eluent and iodine vapor and UV irradiation for visualization.

The initial 9-dimedonyl-3,3-dimethyl-1,2,3,4-tetrahydro-9*H*-xanthen-1-one (**1**) was prepared by condensation of dimedone with salicylic aldehyde by a known procedure.^{3} ^{1}H NMR, δ: 0.89, 0.98, 1.05 (all s, 12 H, Me); 2.00, 2.21, 2.37 (all m, 8 H, CH_2); 5.06 (s, 1 H, CH); 6.96, 7.10 (both m, 4 H, H arom.).

Bromination of 9-(4,4-dimethyl-2,6-dioxocyclohexan-1-yl)-3,3-dimethyl-1,2,3,4-tetrahydro-9*H*-xanthen-1-one (1) (general procedure). Triketone **1** (3 g, 8 mmol) was dissolved in 50 mL of a solvent. Bromine (1.4 g, 8.8 mmol) was added dropwise with continuous stirring.

9-(2-Bromo-4,4-dimethyl-2,6-dioxocyclohexan-1-yl)-3,3-dimethyl-1,2,3,4-tetrahydro-9*H*-xanthen-1-one (2). Acetic acid was used as the solvent. The reaction mixture was heated with stirring for 12 h at 70 °C and treated with water (100 mL). The product was isolated by column chromatography (silica gel 100/400, elution with hexane—AcOEt, 20 : 1). Yield 1.53 g (42%), red-colored crystals, m.p. 129—130 °C. Found (%): C, 61.97; H, 5.45; Br, 17.80. $C_{23}H_{25}BrO_4$. Calculated (%): C, 62.03; H, 5.66; Br, 17.94. IR, ν/cm^{-1}: 3065 (C—H arom.); 2968—2872 (C—H aliphatic); 1763 (C=O); 1676 (C=O, C=C); 1583, 750 (Ar); 716, 675 (C—Br). ^{1}H NMR, δ: 1.21, 1.28, 1.39 (all s, 12 H, Me); 2.02, 2.12, 2.29, 2.41 (all m, 8 H, CH_2); 6.41 (s, 1 H, CH); 6.96—7.67 (m, 4 H, H arom.). MS, *m*/*z* ($I_{\rm rel}$ (%)): 444 $[M - H]^+$ (18), 364 $[M - HBr]^+$ (100).

2,4-Dibromo-5a-hydroxy-3,3,7,7-tetramethyl-2,3,4,5a,6,7,8,13b-octahydro-1*H*-chromeno[2,3,4-*kl*]xanthen-1-one (3). Chloroform was used as the solvent. The reaction was carried out at ~20 °C. The solvent was evaporated under reduced pressure. The resulting oil was crystallized by treatment with hexane, and washed with ethyl acetate and with acetone. The presence of product **2** in the filtrate was established by chromatography. The yield of compound **3** was 0.77 g (18%), colorless crystals, m.p. 181—182 °C. Found (%): C, 52.52; H, 4.72; Br, 30.81. $C_{23}H_{24}Br_2O_4$. Calculated (%): C, 52.69; H, 4.61; Br, 30.48. IR, ν/cm^{-1}: 2584 (OH); 1676 (C=C—CO); 1583, 750 (Ar); 1273, 1028 (=C—O—C); 716, 675 (C—Br). ^{1}H NMR, δ: 0.89, 1.17, 1.32 (all s, 12 H, Me); 1.95, 2.40 (both m, 4 H, CH_2); 5.03, 5.37 (s, 2 H, CH—Br); 5.12 (s, 1 H, CH); 7.01—7.24 (m, 4 H, H arom.); 9.29 (s, 1 H, OH).

2,4-Dibromo-5a-isopropoxy-3,3,7,7-tetramethyl-2,3,4,5a,6,7,8,13b-octahydro-1*H*-chromeno[2,3,4-*kl*]xanthen-1-one (4). A propan-2-ol—CCl_4 mixture (2 : 1) was used as the solvent. The reaction mixture was heated with stirring for 16 h at 76.5 °C and treated with water (80 mL). The precipitated crystals were filtered off and recrystallized from ethyl acetate. The presence of product **2** in the filtrate was established by chromatography. The yield of compound **4** was 1.85 g (40%), colorless crystals, m.p. 174—175 °C. Found (%): C, 55.05; H, 5.06; Br, 27.91. $C_{26}H_{30}Br_2O_4$. Calculated (%): C, 55.14; H, 5.34; Br, 28.22. IR, ν/cm^{-1}: 1666 (C=C—CO); 1583, 750 (Ar); 1255, 1030 (=C—O—C); 1074 (C—O—C); 716, 675 (C—Br). ^{1}H NMR, δ: 0.89, 1.03, 1.17, 1.32 (all s, 18 H, Me); 1.92, 2.40 (both m, 4 H, CH_2); 4.82 (s, 1 H, $\underline{C}\underline{H}(CH_3)_2$); 5.02, 5.39 (both s, 2 H, CH—Br); 5.11 (s, 1 H, CH); 7.06—7.19 (m, 4 H, H arom.). ^{13}C NMR, δ: 20.4, 27.6, 28.6, 28.8, 31.7 (Me); 38.6; 40.6; 41.1; 56.4 (C(4)); 64.4 (C(2)); 70.2 ($\underline{C}H(CH_3)_2$); 115.5; 115.6; 115.7; 115.8; 124.5; 125.3; 127.4; 127.7; 128.0; 128.3; 149.5; 159.6; 159.7; 186.8 (C(1)).

5a-Hydroxy-3,3,7,7-tetramethyl-2,3,4,5a,6,7,8,13b-octahydro-1*H*-chromeno[2,3,4-*kl*]xanthen-1-one (5). Triketone **1** (2 g, 5.5 mmol) was dissolved in a mixture of acetic anhydride (50 mL) and glacial acetic acid (10 mL) and refluxed for 5 h. The crystals that precipitated after cooling were washed with diisopropyl ether and recrystallized from diethyl ether. Yield 1.09 g (54.5%), colorless crystals, m.p. 193—194 °C. Found (%): C, 75.22; H, 7.23. $C_{23}H_{26}O_4$. Calculated (%): C, 75.38; H, 7.15. IR, ν/cm^{-1}: 3650 (OH); 2885—2975 (C—H aliph.); 1650 (C=O, C=C); 1560 (Ar); 1250 (=C—O—C); 1150 (C—O—C). ^{1}H NMR, δ: 0.99—1.08 (m, 12 H, Me); 2.07—2.44 (m, 8 H, CH_2); 5.18 (s, 1 H, CH); 6.92—7.10 (m, 4 H, H arom.); 9.60 (s, 1 H, OH). MS, *m*/*z* ($I_{\rm rel}$ (%)): 366 $[M]^+$ (28), 364 $[M - (CH_3)_2CH_2CO]^+$ (100), 364 $[M - C_8H_{10}O_2]^+$ (52).

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