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IMPROVED METHOD FOR PREPARATION OF DIBENZOCROWN-CONTAINING 4H-PYRAN-4-ONE AND SYNTHESIS OF MEROCYANINE DYESTUFFS FROM IT

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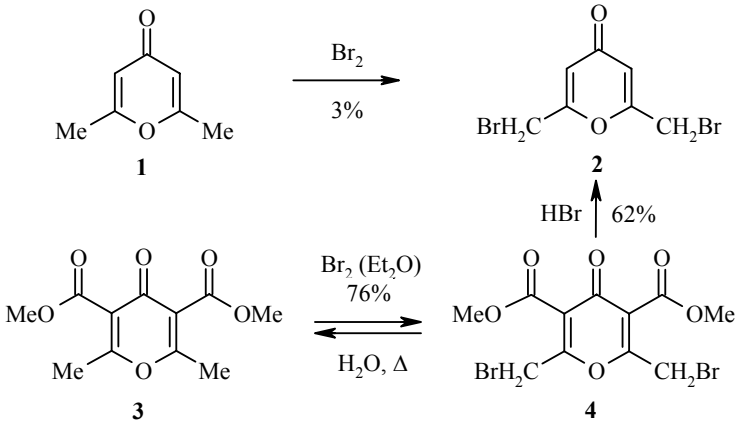
A preparative method has been developed for obtaining 2,9,12,15,22-pentaoxa[2.7]orthocyclo-[2]-2,6-pyranophan-28-one. Compounds of the merocyanine dyestuff series have been obtained from it. It was shown that complex formation with metal salts had no effect on their spectral properties.

Keywords: macrocycle, 4H-pyran-4-one, 1H-pyridin-4-one, merocyanine dyestuffs.

Macrocyclic compounds containing a heterocycle as a structural fragment, the heteroatom of which takes part in complexformation, are of significant interest in the area of "guest–host" chemistry. Among the compounds of such a type it is possible to pick out, for example, carefully studied derivatives of pyridine [1-3] and furan [4-6]. Information on similar derivatives of γ-pyrone has appeared comparatively recently [7-10]. These substances interested us primarily as starting materials for the synthesis of the corresponding pyrylocyanines.



1 **2** **3** **4**

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The key starting material 2,6-bis(bromomethyl)pyran-4-one (**2**) was initially obtained by the direct bromination of 2,6-dimethylpyran-4-one (**1**) in a yield of approximately 3% mixed with at least six products of various degrees of bromination [7]. Later a more successful synthetic pathway to pyrone **2** was found starting from chelidonic acid [8]. At approximately the same time another approach to the synthesis of compound **2** was proposed, from di(methoxycarbonyl)pyran-4-one **3** [11].

This pathway seemed to us to be the most successful. However on attempting to repeat the procedures it turned out that they were not reproduced (although the constants and spectral properties were given correctly).

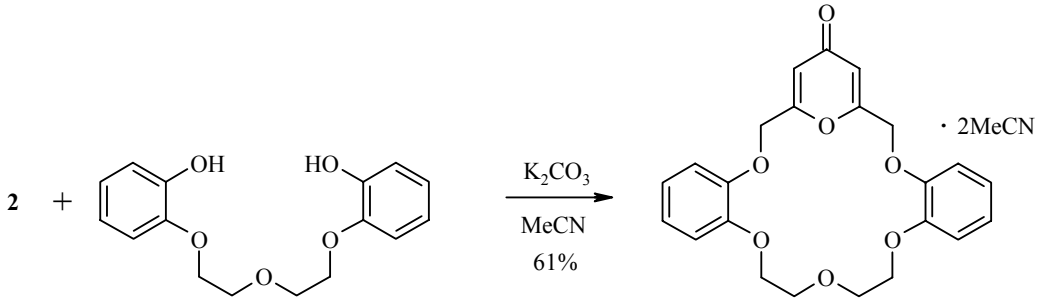
We have developed a preparative method for the synthesis of compound **2**, the yields of intermediate products were greater and the methods more convenient than claimed in [11]. Bromination of pyrone **3** was conducted best in diethyl ether (on carrying out the reaction in methylene chloride [11] a mixture of mono- and polybromo derivatives was formed). On adding bromine to an ether solution of compound **3** a reddish solid was formed, which is probably a complex of bromine with the starting material, the solution itself remained colorless. On stirring the reaction mass the solid gradually decolorized and in the end was converted into product **4**. The selectivity of the bromination reaction, in our view, is determined by the intramolecular character of the process and the efficient removal of the product from the reaction mixture due to poor solubility.

Saponification and decarboxylation of compound **4** was carried out optimally on heating in concentrated hydrobromic acid. Under these conditions 2,6-bis(bromomethyl)pyran-4-one (**2**) is formed in good yield. The use of 50% H_2SO_4 also leads to product **2**, but in lower yield, and adding acetic acid, as proposed in [11], is undoubtedly a negative factor.

Heating compound **4** in water is accompanied by the appearance in the mass (according to TLC data) of 3,5-di(methoxycarbonyl)-2,6-dimethylpyran-4-one (**3**). A process of such type, the essence of which consists of removal of hypobromous acid, is known and characterized for bromo(chloro)methyl-substituted onium salts of heterocycles [12].

Synthesis of the crown-containing pyrone **6** was described in [7] and was effected by the classical scheme for closing macrocycles under high dilution conditions with subsequent isolation by column chromatography.

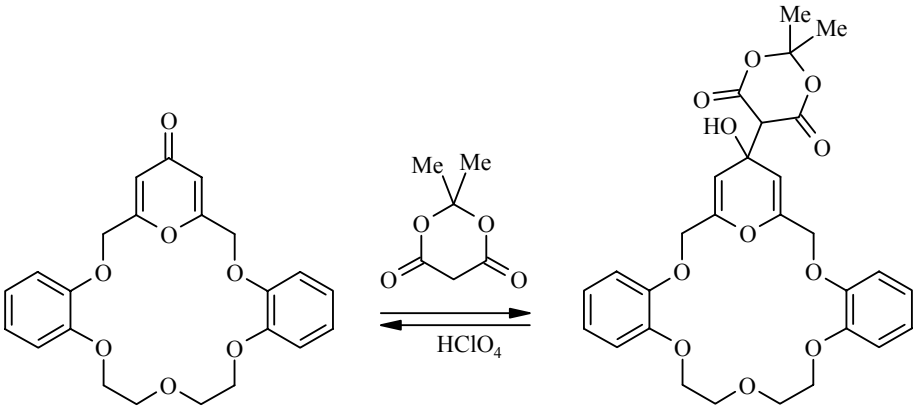
The yield in this case was 42%. We significantly improved the method of obtaining crown ether **6**. On stirring stoichiometric amounts of pyrone **2** and compound **5**, and a twofold excess of potassium carbonate in aqueous acetonitrile, reaction proceeded completely after 30 h.



5 **6**

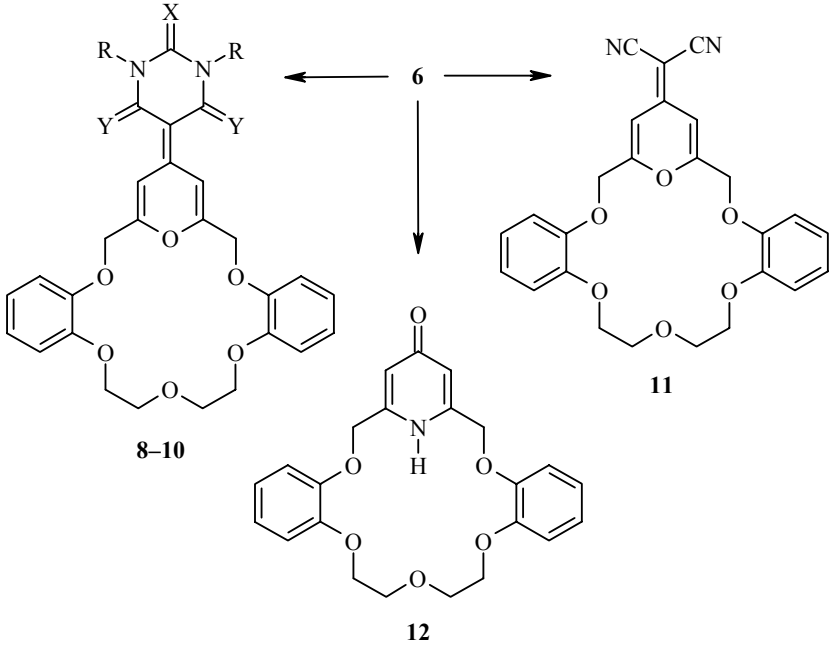
It must be recorded that pyrone **6** contains two molecules of acetonitrile in its structure which did not disappear on recrystallization from other solvents and were removed with great difficulty on prolonged drying. We suggest this is linked with a significant templating effect. The presence of acetonitrile in the reaction mixture therefore assists the clean passage of cyclization under the given conditions.

The standard method of obtaining 4-substituted pyrylium salts is the condensation of carbonyl compounds with Meldrum's acid and subsequent opening of the dioxane ring and decarboxylation. In the case of compound **6** derivative **7** was obtained on reaction with Meldrum's acid. In the presence of mineral acids dehydration and ring opening do not occur, and the initial crown ether **6** is formed (retroaldol cleavage).



6 **7**

Cyanine condensations of γ-pyrones, particularly 2,6-dimethyl-γ-pyrone, have been known for a long time [13, 14]. Merocyanines **8-11** were also obtained under such conditions, and just on heating compound **6** and appropriate methylenic components in acetic anhydride,. The spectral properties of merocyanines **8-11** proved to be close to those of their dimethyl-substituted analogs [13]. It was expected that they change on complexformation with salts of metals, primarily alkali and alkaline earth metals. In fact, such complexes (for example with potassium rhodanide) were obtained, however this had practically no effect on their absorption spectra.



8–10 **11**

12

8 R = H, X = Y = O; **9** R = Me, X = Y = O; **10** R = H, X = S, Y = O

Attempts were made to obtain cationic dyestuffs with various terminal nuclei by the interaction of pyrone **6** with quaternary salts of heterocycles with a reactive methyl group. The formation of absorption bands of the corresponding monomethinecyanine dyestuffs was observed in the reaction mixture. However derivatives of this type were completely destroyed in the process of isolation.

The instability of the cationic forms of hydroxymethyl-substituted pyrylium systems is evidently caused by the very low basicity of this nucleus, which makes it vulnerable to attack by nucleophiles.

The isocyclic oxygen atom in pyrone **6** is capable of being readily replaced by a nitrogen atom. The corresponding pyridone **12** was obtained on interaction of compound **6** with ammonia in an aqueous alcoholic medium.

A convenient preparative method has therefore been developed for obtaining crown-containing pyrone **6**. From this nucleus a series of merocyanine dyestuffs has been obtained. Attempts to obtain cationic dyestuffs proved to be unsuccessful due to their instability.

EXPERIMENTAL

The UV spectra were obtained on a Shimadzu UV-3100 in EtOH, the ^{1}H and ^{13}C NMR spectra on a Varian VXR 300 spectrometer (300 and 75 MHz respectively) in $CDCl_3$ (compounds **2-4, 6, 11**) and DMSO-d_6 (compounds **7-10, 12**), internal standard was TMS.

3,5-Di(methoxycarbonyl)-2,6-dimethyl-4H-pyran-4-one (3). The magnesium complex of acetone dicarboxylic acid dimethyl ester [11] (48 g, 100 mmol) was boiled with acetic anhydride (225 ml) for 3 h. The solvent was evaporated, and the residue was neutralized with an aqueous 15% solution of sodium bicarbonate. The mass obtained was extracted with methylene chloride, dried over $MgSO_4$, the solvent was evaporated, and an oil was obtained, which then crystallized. The product was washed with ether. Yield 26.7 g (47%); mp 97°C (lit. mp 88-90°C [11]). ^{1}H NMR spectrum, δ, ppm: 2.38 (6H, s, CH_3); 3.89 (6H, s, CH_2O). Found, %: C 55.1; H 5.0. $C_{11}H_{12}O_6$. Calculated, %: 55.0; H 5.0.

2,6-Bis(bromomethyl)-3,5-di(methoxycarbonyl)-4H-pyran-4-one (4). Bromine (12.8 g, 80 mmol) in dry methylene chloride (47 ml) was added with stirring to a boiling solution of compound **3** (9.6 g, 40 mmol) in dry ether (470 ml) during 4 h. After this the reaction mixture was maintained for 12 h at 5°C. The product was filtered off. Yield 12.3 g (75%); mp 129-130°C (lit. mp 131-133°C [11]). ^{1}H NMR spectrum, δ, ppm: 3.94 (6H, s, CH_3O); 4.39 (4H, s, CH_2Br). Found, %: C 33.4; H 2.4. $C_{11}H_{10}Br_2O_6$. Calculated, %: C 33.2; H 2.5.

2,6-Bis(bromomethyl)-4H-pyran-4-one (2). Compound **4** (19.5 g, 50 mmol) in 46% hydrobromic acid (78 ml) was heated at 65°C until disappearance of carbon dioxide gas. The reaction mixture was diluted with water, and neutralized with 15% aqueous sodium carbonate solution. The product was extracted with dichloromethane, the extract dried over $MgSO_4$, and the solvent evaporated. The crystalline mass was transferred to a filter and washed with a mixture of 2-propanol–hexane, 1:1. Yield 9.2 g (66%); mp 90-91°C (lit. mp 91°C [7, 11]). ^{1}H NMR spectrum, δ, ppm: 4.20 (4H, s, CH_2Br); 6.35 (2H, s, H-3,5). Found, %: C 29.9; H 2.2. $C_7H_6Br_2O_2$. Calculated, %: C 29.8; H 2.2.

2,9,12,15,22-Pentaoxa[2.7]orthocyclo[2]-2,6-pyranophan-28-one (6). Acetonitrile (150 ml) was added to a solution of potassium carbonate (5.5 g, 40 mmol) in water (5 ml). First compound **5** (5.8 g, 20 mmol) was added with stirring and then pyrone **2** (5.6 g, 20 mmol). The mixture was stirred for 30 h at 20°C, then diluted with water. The product was filtered off and recrystallized from acetonitrile. Yield 6.0 g (61%) (solvated with two molecules of acetonitrile); mp 82°C. ^{1}H NMR spectrum, δ, ppm: 2.00 (6H, s, $2CH_3CN$); 3.92 (4H, br. s, CH_2O); 4.18 (4H, br. s, CH_2O); 4.92 (4H, s, CH_2OAr); 6.46 (2H, s, H het.); 6.84-7.06 (8H, m, H Ar). Found, %: C 65.7; H 5.8; N 5.7. $C_{23}H_{22}O_7 \cdot 2MeCN$. Calculated, %: C 65.8; H 5.7; N 5.7.

Product free from acetonitrile was obtained after drying at 90°C in vacuum (0.1 mm Hg) for 3 h, mp 107°C (lit. mp 104°C [7]). ^{1}H NMR spectrum, δ, ppm: 3.92 (4H, br. s, CH_2O); 4.18 (4H, br. s, CH_2O); 4.92 (4H, s, CH_2OAr); 6.46 (2H, s, H het.); 6.84-7.06 (8H, m, H Ar).

28-Hydroxy-28-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2,9,12,15,22-pentaoxa[2.7]orthocyclo-[2]-2,6-pyranophane (7). Meldrum's acid (1.17 g, 8.01 mmol) was added to a solution of compound **6** (2 g, 4.07 mmol) and sodium acetate (0.37 g, 4.5 mmol) in ethanol (2 ml). The mixture was boiled for 10 min. After cooling the crystals were filtered off. Yield 1.44 g (64%); mp 210°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (6H, s, $2CH_3$); 3.24 (1H, s, CH); 3.80 (4H, br. s, CH_2O); 4.07 (4H, br. s, CH_2O); 4.92 (4H, s, CH_2O); 6.64 (2H, s, H het.); 6.86-7.02 (6H, m, H Ar); 7.08 (2H, d, *J* = 6.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 178.6, 166.1, 162.6, 147.7, 146.6, 121.8, 120.7, 116.1, 113.0, 112.3, 99.7, 68.6, 67.3, 66.4, 62.4, 25.9. Found, %: C 62.7; H 5.6. $C_{29}H_{30}O_{11}$. Calculated, %: C 62.8; H 5.5.

Merocyanines 8-11 (General Method). A mixture of pyrone **6** (1 mmol) and the appropriate methylene component (1.1 mmol) with acetic anhydride (2 ml) was boiled for 1 h. The product was filtered off after cooling to room temperature.

28-(1H,3H-2,4,6-Trioxopyrimidin-5-ylidene)-2,9,12,15,22-pentaoxa[2.7]orthocyclo[2]-2,6-pyrano-phane (8). Yield 40%, mp >300°C. UV spectrum, λ_{max}, nm: 389. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 (4H, br. s, CH_2O); 4.08 (4H, br. s, CH_2O); 5.07 (4H, s, CH_2O); 6.80-7.05 (6H, m, H Ar); 7.12 (1H, d, *J* = 7.5, H Ar); 8.99 (2H, s, H het.). Found, %: C 62.5; H 4.8; N 5.4. $C_{27}H_{24}N_2O_9$. Calculated, %: C 62.3; H 4.7; N 5.4.

28-(1H,3H-1,3-Dimethyl-2,4,6-trioxopyrimidin-2,9,12,15,22-pentaoxa[2.7]orthocyclo[2]-5-ylidene)-2,6-pyranophane (9). Yield 38%, mp 220°C. UV spectrum, λ_{max}, nm: 392. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.20 (6H, s, NCH_3); 3.79 (4H, br. s, CH_2O); 4.08 (4H, br. s, CH_2O); 5.10 (4H, s, CH_2O); 6.82-7.02 (6H, m, H Ar); 7.13 (2H, d, *J* = 7.2, H Ar); 9.00 (2H, s, H het.). Found, %: C 63.6; H 5.2; N 5.1. $C_{29}H_{28}N_2O_9$. Calculated, %: C 63.5; H 5.2; N 5.1.

28-(1H,3H-4,6-Dioxo-2-thioxopyrimidin-5-ylidene-2,9,12,15,22-pentaoxa[2.7]orthocyclo[2]-2,6-pyrano-phane (10). Yield 35%; mp >300°C. UV spectrum, λ_{max}: 409. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 (4H, br. s, $2CH_2O$); 4.07 (4H, br. s, $2CH_2O$); 5.12 (4H, s, $2CH_2O$); 6.84-7.20 (6H, m, H Ar); 7.13 (2H, d, *J* = 7.5, ArH); 9.03 (2H, s, H het.); 11.96 (2H, s, NH). Found, %: C 60.3; H 4.5; N 5.2. $C_{27}H_{24}N_2O_8S$. Calculated, %: C 60.4; H 4.5; N 5.2.

28-Dicyanomethylidene-2,9,12,15,22-pentaoxa[2,7]orthocyclo[2]-2,6-pyranophane (11). After cooling, the reaction mass was diluted with 2-propanol (20 ml), the solid was filtered off, and recrystallized from acetonitrile. Yield 0.09 g (19%); mp 197-198°C. UV spectrum λ_{max}, nm: 350. ^{1}H NMR spectrum, δ, ppm: 3.90 (4H, br. s, CH_2O); 4.17 (4H, br. s, CH_2O); 4.94 (4H, s, CH_2OAr); 6.95 (10H, m, 8H Ar + 2H het.). Found, %: C 68.0; H 4.9; N 6.2. $C_{26}H_{22}N_2O_6$. Calculated, %: C 68.1; H 4.8; N 6.1.

2,9,12,15,22-Pentaoxa[2.7]orthocyclo[2]-2,6-pyridophan-28-one (12). Compound **6** (0.2 g) was boiled for 1 h with an excess of 25% aqueous ammonia in aqueous alcohol. After cooling, the crystals were filtered off. Yield 0.12 g (72%); mp 199-200°C. ^{1}H NMR spectrum, δ, ppm: 3.78 (4H, s, $2CH_2O$); 4.04 (4H, s, $2CH_2O$); 4.41 (4H, s, $2CH_2OAr$); 6.31 (1.33H, s, H het.); 6.93 (0.66H, s, H het.); 7.09 (8H, m, H Ar); 10.94 (0.33H, s, NH); 12.03 (0.67H, s, OH); equilibrium of 67% hydroxypyridine form and 33% pyridone. Found, %: C 67.4; H 5.7; N 3.5. $C_{23}H_{23}NO_6$. Calculated, %: C 67.5; H 5.7; N 3.4.

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