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REACTIONS OF METHOXYBENZYLIDENE DERIVATIVES OF 2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE AND THEIR SATURATED ANALOGS WITH CERTAIN NUCLEOPHILIC REAGENTS

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The reactions of the methoxybenzylidene derivatives of 2,2-dimethyl-1,3-dioxane-4,6-dione and their saturated analogs with potassium hydroxide in methanol, ammonia, and hydrazine hydrate were realized. The 1,2-bis(methoxybenzylidene)hydrazines, amides, and hydrazides of methoxybenzylidene-malonic acid, suitable for use as structural blocks in the synthesis of various structures based on them, were prepared and characterized.

Keywords: amides, benzylidene derivatives, hydrazides, 2,2-dimethyl-1,3-dioxane-4,6-dione, methoxybenzaldehydes.

The methoxyphenyl substituent is a structural fragment of a large number of pharmaceutical preparations, the best known of which are drugs with a stimulating action on the cardiovascular system [1, 2] and neurotropic activity [3].

As starting materials containing the above-mentioned fragment for the synthesis of new compounds, unknown in the literature, we chose the methoxybenzylidene derivatives of 2,2-dimethyl-1,3-dioxane-4,6-dione **3** and their saturated analogs **4**. Compounds **3** are the products from the condensation of methoxy-substituted benzaldehydes **1** with 2,2-dimethyl-1,3-dioxane-4,6-dione (isopropylidenemalonate, Meldrum's acid) (**2**).

Methods for the production of the 2,5- (**3a**), 2,4- (**3b**), and 3,4,5- (**3c**) methoxybenzylidene derivatives are known in the literature [4], and the 2,3,4- (**3c**) and 3,4,5- (**3d**) methoxy derivatives were obtained by an analogous procedure.

The hydrogenation of compounds **3** was conducted with sodium borohydride in methanol at room temperature.

In view of the fact that the 1,3-dioxane ring in isopropylidenemalonates readily undergoes decomposition with ring opening in reactions with nucleophilic reagents [5-7] we realized the reactions of compounds **3** and **4** with potassium hydroxide in methanol, ammonia (donors of ammonia: ammonium hydroxide and hexamethyldisilazane), and hydrazine hydrate.

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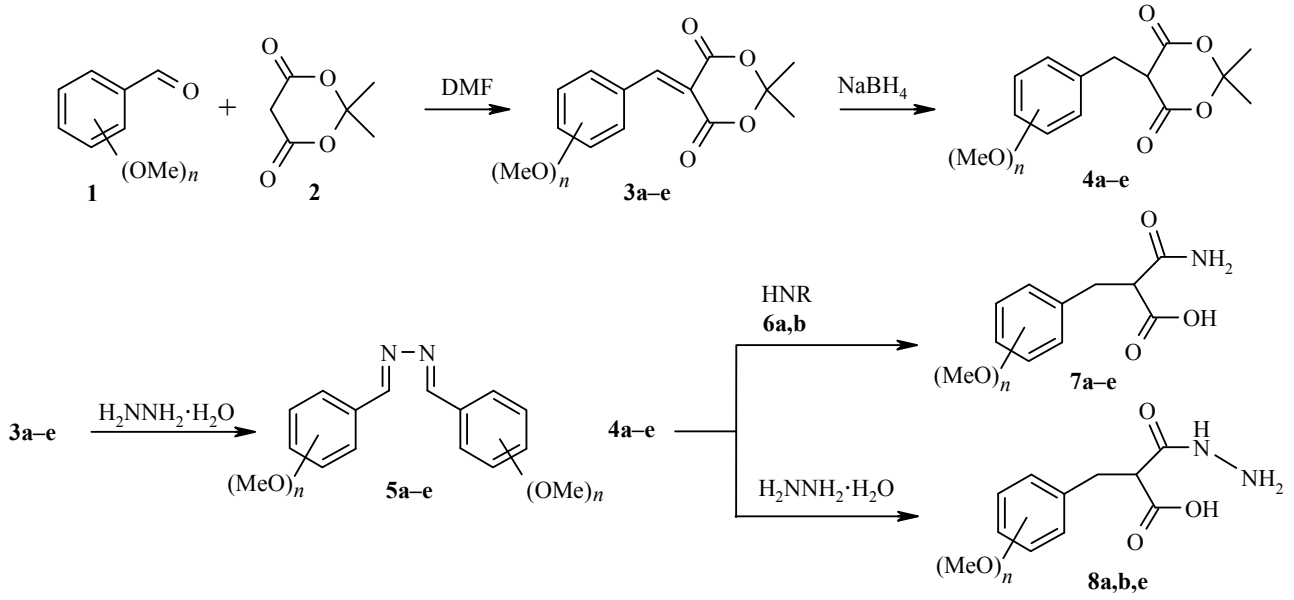
The experiments showed that compounds **3** and **4** were isolated unchanged during the reactions with potassium hydroxide even after boiling the reaction components in methanol for 15 h. The initial compounds **3** were also isolated during the reaction of the methoxybenzylidene derivatives with ammonia. The saturated compounds **4** react both with an aqueous solution of ammonia **6a** and with hexamethyldisilazane **6b**. The best yields here were obtained with hexamethyldisilazane **6b**, while a few side products were obtained in addition to the desired products **7** during the reaction with ammonium hydroxide.



3-8 a 2,5-OMe, **b** 2,4-OMe; **3–7 c** 2,3,4-OMe, **d** 3,4,5-OMe; **3-8 e** 2,4,5-OMe;
3–8 a,**b** n = 2; **e** n = 3, **3–7 c**,**d** n = 3; **6 a** R = H, **b** R = Me_3Si.

With hydrazine hydrate compounds **3** and **4** form different products. With hydrazine hydrate the unsaturated compounds **3** form derivatives of bis-benzylidenehydrazines **5**. It can be supposed that on account of the donating effect of the methoxy groups situated in the benzene ring the reaction takes place by a retro-aza-Claisen mechanism.

With hydrazine hydrate under analogous conditions the saturated compounds **4a**,**b** and **4e** form the corresponding methoxyphenyl-2-hydrazinocarbonylpropionic acids **8a**,**b** and **8e**, while compounds **4c** and **4d** do not react under these conditions.

All the obtained compounds are of interest not only as potential biologically active substances but also as active building blocks for the creation of more complex structures based on them.

The composition of the synthesized compounds was confirmed by the results of elemental analysis, and the structure was confirmed by the ^{1}H NMR spectra, in which the signals for the protons of all the fragments of the molecules resonate in the characteristic regions.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker 300 instrument (300 MHz) in $CDCl_3$ (compounds **4a-e** and **5a-e**) and DMSO-d_6 (compounds **7a-e** and **8a**,**b**,**e**) with TMS as internal standard.

The individuality of the synthesized compounds was verified by TLC on Merck silica gel 60 F_{254} plates in the solvent systems: chloroform–methanol–glacial acetic acid 95:5:3 (for **4a-e**, **7a-e**, and **8a**,**b**,**e**) and ethyl acetate–ethanol–glacial acetic acid 9:1:1 (for **5a-e**).

5-(2,3,4-Trimethoxy)-2,2-dimethyl- (3c) and 5-(3,4,5-Trimethoxy)-2,2-dimethylbenzylidene-1,3-dioxane- 4,6-diones (3d). These compounds were obtained by the method in [4].

Compound 3c. The yield 89%; mp 138-139°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.65 (6H, s, $2CH_3$); 5.35 (9H, s, $3OCH_3$); 6.49 (1H, s, arom); 7.49 (1H, s, arom); 8.62 (1H, s, =CH).

Compound 3d. The yield 86%; mp 114-115°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.65 (6H, s, $2CH_3$); 5.35 (9H, s, $3OCH_3$); 6.28 (1H, s, arom); 6.55 (1H, s, arom); 8.62 (1H, s, =CH).

5-Mthoxybenzyl-2,2-dimethyl-1,3-dioxane-4,6-diones 4a-e. To a suspension of the compound **3a-e** (0.01 mol) in methanol (30 ml) we added with stirring sodium borohydride (0.018 mol). A few minutes after all the sodium borohydride had been added the reaction solution became colorless. The mixture was stirred for a further 1 h and acidified to pH ~2-3 with dilute (1:1) hydrochloric acid. The precipitate was filtered off and recrystallized from ethanol.

1,2-Bis(*p*-methoxybenzylidene)hydrazines 5a-e. A mixture of the compound **3a-e** (0.01 mol), hydrazine hydrate (8 ml), and dioxane (30 ml) was stirred at room temperature for 12 h. The dioxane was distilled, and the residue was dissolved in water and acidified to pH ~3-4 with dilute hydrochloric acid (1:1). The precipitate was filtered off and recrystallized from ethanol (**5a**,**c-e**) or diluted ethanol (1:1) (**5b**).

TABLE 1. Characteristics of the Synthesized Compounds **4a-e**, **5a-e**, **7a-e**, and **8a**,**b**,**e**

Compound	Empirical Formula	Found, % / Calculated, %			mp,°C	Yield, %
		C	H	N		
4a	$C_{15}H_{18}O_6$	61.13 / 61.22	6.09 / 6.16	—	99–100	92
4b	$C_{15}H_{18}O_6$	61.41 / 61.22	6.18 / 6.16	—	113–115	85
4c	$C_{16}H_{20}O_7$	59.23 / 59.25	6.15 / 6.22	—	89-90	78
4d	$C_{16}H_{20}O_7$	59.28 / 59.25	6.40 / 6.22	—	106-108	90
4e	$C_{16}H_{20}O_7$	59.35 / 59.25	6.18 / 6.22	—	128-130	85
5a	$C_{18}H_{20}N_2O_4$	65.79 / 65.84	6.09 / 6.14	8.50 / 8.53	163-165	43
5b	$C_{18}H_{20}N_2O_4$	65.44 / 65.84	6.10 / 6.14	8.55 / 8.53	237-238	50
5c	$C_{20}H_{24}N_2O_6$	61.58 / 61.84	6.27 / 6.23	7.22 / 7.21	210-212	48
5d	$C_{20}H_{24}N_2O_6$	61.62 / 61.84	6.27 / 6.23	7.24 / 7.21	194-195	44
5e	$C_{20}H_{24}N_2O_6$	61.80 / 61.84	6.20 / 6.23	7.20 / 7.21	222-224	46
7a	$C_{12}H_{15}NO_5$	56.87 / 56.91	5.89 / 5.97	5.31 / 5.53	150-151	89
7b	$C_{12}H_{15}NO_5$	56.87 / 56.91	5.91 / 5.97	5.43 / 5.53	170-171	61
7c	$C_{13}H_{17}NO_6$	55.15 / 55.12	6.12 / 6.01	5.16 / 4.94	123-125	64
7d	$C_{13}H_{17}NO_6$	54.62 / 55.12	5.97 / 6.01	5.14 / 4.94	158-160	65
7e	$C_{13}H_{17}NO_6$	55.23 / 55.12	6.02 / 6.05	4.83 / 4.94	167-168	72
8a	$C_{12}H_{16}N_2O_5$	53.69 / 53.73	5.94 / 6.01	10.25 / 10.44	154-156	93
8b	$C_{12}H_{16}N_2O_5$	53.43 / 53.73	5.89 / 6.01	10.44 / 10.44	156-158	86
8e	$C_{13}H_{18}N_2O_6$	52.02 / 52.34	5.96 / 6.08	9.26 / 9.39	158-160	83

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **4a-e**, **5a-e**, **7a-e**, **8a**,**b**,**e**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
4a	1.75 (3H, s, CH_3); 1.79 (3H, s, CH_3); 3.38 (2H, d, *J* = 5.84, CH_2); 3.78 (6H, d, *J* = 3.39, $2OCH_3$); 4.05 (1H, t, *J* = 5.84, CH); 6.80 (2H, s, arom); 7.28 (1H, s, arom)
4b	1.71 (3H, s, CH_3); 1.76 (3H, s, CH_3); 3.33 (2H, d, *J* = 5.86, CH_2); 3.81 (6H, d, *J* = 3.52, $2OCH_3$); 3.94 (1H, t, *J* = 5.86, CH); 6.52 (2H, s, arom); 7.25 (1H, s, arom)
4c	1.73 (3H, s, CH_3); 1.78 (3H, s, CH_3); 3.34 (2H, d, *J* = 5.47, CH_2); 3.84 (9H, d, *J* = 6.4, $3OCH_3$); 3.98 (1H, t, *J* = 5.47, CH); 6.61 (1H, s, arom); 7.03 (1H, s, arom)
4d	1.50 (3H, s, CH_3); 1.73 (3H, s, CH_3); 3.44 (2H, d, *J* = 4.69, CH_2); 3.72 (1H, t, *J* = 4.69, CH); 3.80 (3H, br. s, OCH_3); 3.83 (6H, br. s, $2OCH_3$); 6.56 (2H, s, arom)
4e	1.71 (3H, s, CH_3); 1.76 (3H, s, CH_3); 3.33 (2H, d, *J* = 5.47, CH_2); 3.80 (3H, d, *J* = 3.52, OCH_3); 3.85 (6H, t, *J* = 5.81, $2OCH_3$); 3.93 (1H, t, *J* = 5.48, CH); 6.49 (1H, s, arom); 6.92 (1H, s, arom)
5a	3.87 (6H, s, $2OCH_3$); 3.88 (6H, s, $2OCH_3$); 6.91 (2H, d, *J* = 9.0, arom); 7.00 (2H, dd, *J* = 9.0, *J* = 3.2, arom); 7.68 (2H, d, *J* = 3.2, arom); 9.10 (2H, s, 2CH=)
5b	3.87 (12H, br. s, 4 OCH_3); 6.46 (2H, d, *J* = 2.3, arom); 6.58 (2H, d, *J* = 8.2, arom); 8.10 (2H, br. s, arom); 9.06 (2H, s, 2CH=)
5c	3.89 (6H, br. s, $2OCH_3$); 3.93 (6H, s, $2OCH_3$); 3.98 (6H, s, $2OCH_3$); 6.77 (2H, d, *J* = 8.9, arom); 7.93 (2H, br. s, arom); 9.00 (2H, s, 2CH=)
5d	3.91 (6H, s, $2OCH_3$); 3.94 (12H, s, $4OCH_3$); 7.09 (4H, s, arom); 8.57 (2H, s, 2CH=)
5e	3.88 (6H, s, $2OCH_3$); 3.94 (6H, s, $2OCH_3$); 3.95 (6H, s, $2OCH_3$); 6.51 (4H, s, arom); 9.04 (2H, s, 2CH=)
7a	2.87 (1H, dd, *J* = 14.01, *J* = 8.6, CH); 2.97 (1H, dd, *J* = 14.01, *J* = 6.2, CH); 3.48 (1H, dd, *J* = 8.6, *J* = 6.2, CH); 3.66 (3H, s, OCH_3); 3.73 (3H, s, OCH_3); 6.67 (1H, d, *J* = 3.1, arom); 6.73 (1H, dd, *J* = 8.9, *J* = 3.2, arom); 6.84 (1H, s, NH); 6.86 (1H, d, *J* = 8.9, arom); 7.41 (1H, s, NH); 12.45 (1H, s, COOH)
7b	2.79 (1H, dd, *J* = 14.0, *J* = 8.5, CH); 2.92 (1H, dd, *J* = 14.0, *J* = 6.4, CH); 3.43 (1H, dd, *J* = 8.50, *J* = 6.40, CH); 3.73 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 6.39 (1H, dd, *J* = 8.1, *J* = 2.1, arom); 6.49 (1H, d, arom); 6.95 (1H, d, *J* = 8.1, arom); 6.96 (1H, br. s, NH); 7.37 (1H, br. s, NH); 12.4 (1H, br. s, COOH)
7c	2.85 (1H, dd, *J* = 14.01, *J* = 8.5, CH); 2.95 (1H, dd, *J* = 14.1, *J* = 6.4, CH); 3.43 (1H, dd, *J* = 8.60, *J* = 6.4, CH); 3.73 (3H, s, OCH_3); 3.79 (6H, s, $2OCH_3$); 6.67 (1H, d, *J* = 8.6, arom); 6.81 (1H, d, *J* = 8.6, arom); 6.98 (1H, s, NH); 7.43 (1H, s, NH); 12.43 (1H, s, COOH)
7d	2.91 (1H, dd, *J* = 14.1, *J* = 8.2, CH); 2.96 (1H, dd, *J* = 14.1, *J* = 6.60, CH); 3.49 (1H, dd, *J* = 8.30, *J* = 6.6, CH); 3.61 (3H, s, OCH_3); 3.73 (6H, s, $2OCH_3$); 6.51 (2H, br. s, arom); 7.05 (1H, s, NH); 7.46 (1H, s, NH); 12.48 (1H, s, COOH)
7e	2.83 (1H, dd, *J* = 13.7, *J* = 8.6, CH); 2.93 (1H, dd, *J* = 13.70, *J* = 6.2, CH); 3.43 (1H, dd, *J* = 8.6, *J* = 6.6, CH); 3.64 (3H, s, OCH_3); 3.75 (6H, s, $2OCH_3$); 6.63 (1H, s, arom); 6.71 (1H, s, arom); 6.98 (1H, s, NH); 7.37 (1H, s, NH); 12.41 (1H, s, COOH)
8a	2.84 (1H, dd, *J* = 13.9, *J* = 8.6, CH); 3.02 (1H, dd, *J* = 13.9, *J* = 6.2, CH); 3.28-3.40 (2H, m, NH_2); 3.43 (1H, dd, *J* = 8.60, *J* = 6.20, CH); 3.65 (3H, s, OCH_3); 3.72 (3H, s, OCH_3); 6.64 (1H, d, *J* = 3.0, arom); 6.71 (1H, d, *J* = 3.0, arom); 6.83 (1H, d, *J* = 3.0, arom); 6.86 (1H, br. s, NH); 9.22 (1H, s, COOH)
8b	2.79 (1H, dd, *J* = 13.7, *J* = 8.6, CH); 2.97 (1H, dd, *J* = 13.7, *J* = 6.2, CH); 3.20-3.30 (2H, m, NH_2); 3.38 (1H, dd, *J* = 8.6, *J* = 6.2, CH); 3.72 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 6.37 (1H, d, *J* = 2.3, arom); 6.39 (1H, d, *J* = 2.3, arom); 6.49 (1H, d, *J* = 2.3, arom); 6.93 (1H, s, NH); 9.1 (1H, br. s, COOH)
8e	2.80 (1H, dd, *J* = 13.7, *J* = 8.6, CH); 2.96 (1H, dd, *J* = 13.7, *J* = 6.2, CH); 3.08-3.22 (2H, m, NH_2); 3.37 (1H, dd, *J* = 8.6, *J* = 6.2, CH); 3.64 (3H, s, OCH_3); 3.75 (6H, s, $2OCH_3$); 6.62 (1H, s, arom); 6.66 (1H, s, arom); 6.89 (1H, s, NH); 9.11 (1H, s, COOH)

Amides of 2-(*p*-Methoxybenzyl)malonic acid 7a-e. A mixture of the compound **4a-e** (0.01 mol), hexamethyldisilazane (0.03 mol), and methylene chloride (40 ml) was boiled with stirring for 3 h. The solvent was distilled, and the residue was dissolved in 30 ml of 2-propanol and stirred until a precipitate formed (~2 h). The precipitate was filtered off, dissolved in water, and acidified to pH ~2-3 with dilute hydrochloric acid (1:1).

The product was filtered off and recrystallized from ethanol (**7a**,**b** and **7d**,**e)** or a mixture of ethyl acetate and hexane (1:0.5) (**7c**).

Hydrazides of 2-(*p*-Methoxybenzyl)malonic Acid 8a,b,e. A mixture of the compound **4a**,**b**,**e** (0.01 mol), hydrazine hydrate (8 ml), and dioxane (30 ml) was stirred at room temperature for 12 h. The reaction products were isolated under conditions similar to the conditions for the production of the bis products **5a**-**e**. They were recrystallized from ethanol.

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