

4-Aryl-2,4-dioxobutanoic Acids and Their Derivatives in Reactions with Diazoalkanes

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Abstract—By treating 4-aryl-2,4-dioxobutanoic acids or their alkyl esters with diazomethane alkyl 4-aryl-2-methoxy-4-oxo-2-butenates and 1-R-3-aryl-4-methoxy-4-methoxycarbonyl-4,5-dihydropyrazoles were prepared. O-Alkyl derivatives and substituted pyrazoles were also obtained by reaction of 4-aryl-2,4-oxobutanoic acids aryl amides with diazomethane and diazoethane.

4-Aryl-2,4-dioxobutanoic acids, their alkyl esters and arylamides were formerly established to exist both in crystalline state and in solutions in an enol form with an internal hydrogen bond (IHB) of H-chelate type with the proton of the H-chelate ring localized at the oxygen C², i.e., as Z-isomers, 4-aryl-2-hydroxy-4-oxo-(Z)-2-butenic acids, their alkyl esters, and amides [1-3]. An example of reaction of diazomethane with alkyl 4-aryl-2,4-dioxobutanoates resulting in α -O-methyl derivatives of the initial esters was described [4]. Diphenyldiazomethane with 4-aryl-2,4-dioxobutanoic acids affords benzhydryl esters of the acids, and with alkyl esters thereof arise products of α -O-alkylation and β -C-alkylation [5]. Products of 1,3-dipolar cycloaddition of diphenyldiazomethane to the multiple C²=C³ bond of the esters were mentioned in [6]. Arylamides of the acids with diphenyldiazomethane furnished products of β -C-alkylation [7]. Since the reactivity of diazo compounds is very high, and in the carbonyl substrate exist several reactive centers the nearly total lack of heterocyclic compounds among the products suggests that not all possible directions of reactions between 4-aryl-2,4-dioxobutanoic acids and their derivatives with diazo compounds are revealed.

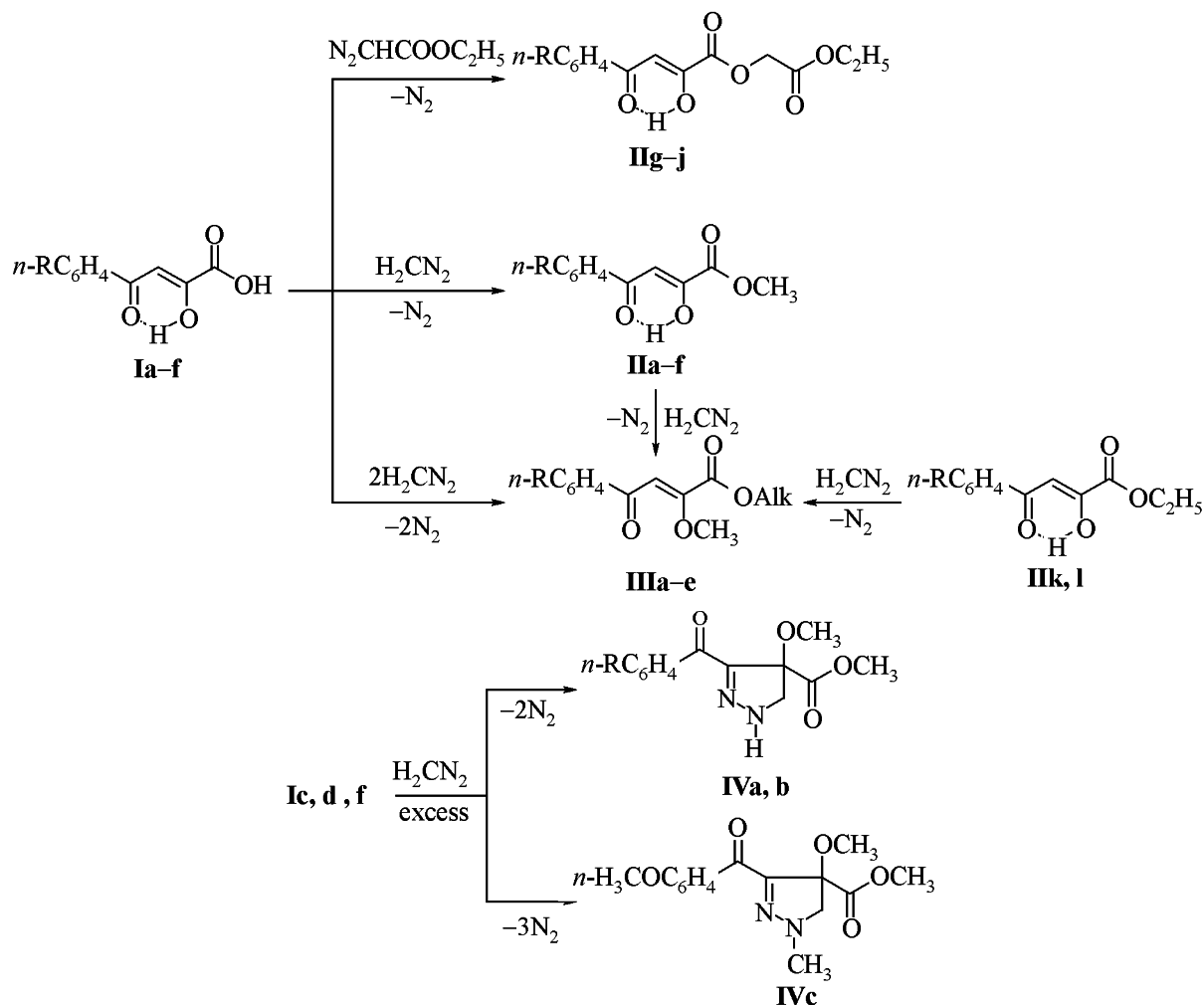
We established that diazomethane vigorously reacted with 4-aryl-2-hydroxy-4-oxo-(Z)-2-butenic acids (**I**) affording a mixture of products. The composition of the mixture depended on the reaction conditions and reagents ratio. For instance, at equimolar amounts of acids **Ia-f** and diazomethane the final products were methyl 4-aryl-2-hydroxy-4-oxo-(Z)-2-butenates (**Ila-f**) that had been previously obtained

by the other methods [8]. As testified by TLC, the reaction was not selective, and in the reaction mixture were present from two to three impurity compounds. Unlike diazomethane the less reactive ethyl diazoacetate selectively reacted with acids **Ia-e** furnishing a sole product, ethoxycarbonylmethyl 4-aryl-2-hydroxy-4-oxo-(Z)-2-butenate (**Ilg-j**) (Tables 1, 2, Scheme 1). Further reaction of acids **Ia-e** with ethyl diazoacetate did not occur even at heating. At the ratio diazomethane to acid **I** 2:1 the reaction gave rise to several products, methyl 4-aryl-2-methoxy-4-oxo-(Z)-2-butenates (**IIla-e**) prevailing. From acids **Ia, c, d** with diazomethane were obtained esters **IIla-c**. Esters **IIla-c**, and also ethyl 4-aryl-2-methoxy-4-oxo-(Z)-2-butenates (**IIId, e**) were obtained by treating with diazomethane respectively esters **Ila, c, e**, and ethyl 4-aryl-2-hydroxy-4-oxo-(Z)-2-butenates (**IIk, l**) at the reagents ratio 1:1.

The IR spectra of compounds **IIa-l** contain one (for compounds **IIa-f, k, l**) [3] or two (for compounds **Ilg-j**) absorption bands of ester carbonyl in the region 1750-1762, 1730-1735 cm⁻¹. The absorption band of the ketone carbonyl C⁴=O involved into the intramolecular hydrogen bond is observed at 1605-1610 cm⁻¹. In contrast to compounds **II** in the IR spectra of compounds **IIla-e** lacking intramolecular hydrogen bond the absorption band of the C⁴=O group shifts to higher frequencies (1640-1660 cm⁻¹), and the ester carbonyl absorbs in the region 1712-1732 cm⁻¹.

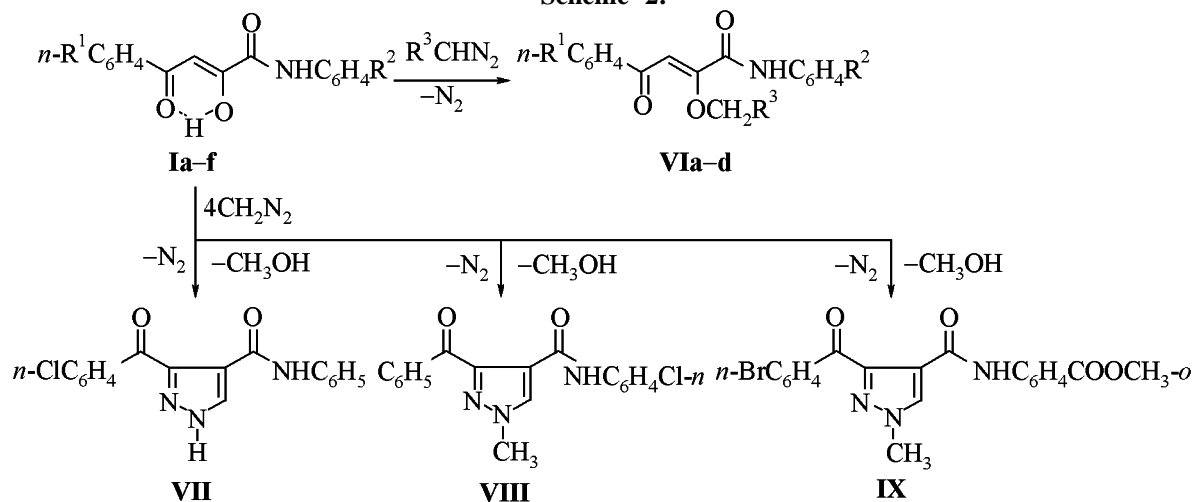
In the UV spectra of acids **Ia-f** appears an absorption maximum in the longwave region at λ_{\max} 311-328 nm (log ϵ 3.17-3.26). The position and intensity

Scheme 1.



I, II, R = H (**a, g**), CH_3 (**b**), CH_3O (**c, h, k**), Cl (**d, i**), Br (**e, j, l**), $\text{C}_2\text{H}_5\text{O}$ (**f**); **III**, Alk = CH_3 : R = H (**a**), CH_3O (**b**), Cl (**c**); Alk = C_2H_5 , R = CH_3O (**d**), Br (**e**); **IV**, R = Cl (**a**), $\text{C}_2\text{H}_5\text{O}$ (**b**).

Scheme 2.



V, $\text{R}^2 = \text{H}$: $\text{R}^1 = \text{H}$ (**a**), Cl (**b**); $\text{R}^1 = \text{H}$, $\text{R}^2 = p\text{-Cl}$ (**c**); $\text{R}^1 = \text{Br}$, $\text{R}^2 = o\text{-CH}_3\text{OCO}$ (**d**); **VI**, $\text{R}^1 = \text{R}^2 = \text{H}$: $\text{R}^3 = \text{H}$ (**a**), CH_3 (**b**); $\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{R}^3 = \text{H}$ (**c**); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Cl}$, $\text{R}^3 = \text{CH}_3$ (**d**).

Table 1. Yields, melting points, IR and ¹H NMR spectra of compounds **IIg-j**, **IIIa-e**, **IVa-c**, **VIa-d**, **VII-IX**

Compd. no.	Yield, %	mp, °C	IR spectrum, ν , cm^{-1}	¹ H NMR spectrum, δ , ppm
IIg	84	80–82	1752, 1730 (COO), 1610 ($\text{C}^{\text{d}}=\text{O}$, C=C)	1.26 t (3H, CH ₃), 4.22 q (2H, CH ₂), 4.90 s (2H, CH ₂), 7.15 s (1H, CH), 7.70 s (5H, C ₆ H ₅), (CH ₃) ₂ SO- <i>d</i> ₆
IIh	91	78–80	1762 br (COO), 1605 ($\text{C}^{\text{d}}=\text{O}$, C=C)	
IIi	88	93–95	1750, 1730 (COO), 1605 ($\text{C}^{\text{d}}=\text{O}$, C=C)	1.22 t (3H, CH ₃), 4.20 q (2H, CH ₂), 4.88 s (2H, CH ₂), 7.15 s (1H, CH), 7.80 s (4H, C ₆ H ₄), (CH ₃) ₂ SO- <i>d</i> ₆
IIj	90	94–96	1755, 1735 (COO), 1610 ($\text{C}^{\text{d}}=\text{O}$, C=C)	1.25 t (3H, CH ₃), 4.20 q (2H, CH ₂), 4.90 s (2H, CH ₂), 7.14 s (1H, CH), 7.90 s (4H, C ₆ H ₄), (CH ₃) ₂ SO- <i>d</i> ₆
IIIa	45	Oily substance	1732 (COO), 1660 ($\text{C}^{\text{d}}=\text{O}$, C=C)	3.78 s (6H, 2CH ₃), 6.21 s (1H, CH), 7.38 s (5H, C ₆ H ₅), CCl ₄
IIIb	81	38–39	1730 (COO), 1656 ($\text{C}^{\text{d}}=\text{O}$, C=C)	3.60 s (3H, CH ₃ OC ₆ H ₄), 3.74 s (6H, 2CH ₃), 6.75 s (1H, CH), 7.63 q (4H, C ₆ H ₄), CHCl ₃ - <i>d</i>
IIIc	69	66–67	1726 (COO), 1651 ($\text{C}^{\text{d}}=\text{O}$, C=C)	3.85 s (6H, 2CH ₃), 6.90 s (1H, CH), 7.63 q (4H, C ₆ H ₄), CHCl ₃ - <i>d</i>
IIId	84	46–48	1712 (COO), 1640 ($\text{C}^{\text{d}}=\text{O}$, C=C)	1.38 t (3H, CH ₃), 3.75 s (6H, 2CH ₃), 4.32 q (2H, CH ₂), 6.05 s (1H, CH), 7.65 q (4H, C ₆ H ₄), CHCl ₃ - <i>d</i>
IIIe	78	81–83	1721 (COO), 1653 ($\text{C}^{\text{d}}=\text{O}$, C=C)	1.40 t (3H, CH ₃), 3.81 s (6H, 2CH ₃), 4.35 q (2H, CH ₂), 6.25 s (1H, CH), 7.58 q (4H, C ₆ H ₄), CHCl ₃ - <i>d</i>
IVa	60	169–171	3375 (NH), 1753 (COOCH ₃), 1665 ($\text{C}^{\text{d}}=\text{O}$), 1619 (C=N)	3.11 s (3H, CH ₃ O), 3.61 s (3H, CH ₃ OCO), 3.91 s (2H, CH ₂), 7.68 q (4H, C ₆ H ₄), 9.83 s (1H, NH), CHCl ₃ - <i>d</i>
IVb	71	156–157	3310 (NH), 1741 (COOCH ₃), 1658 ($\text{C}^{\text{d}}=\text{O}$), 1613 (C=N)	1.28 t (3H, CH ₃), 3.11 s (3H, CH ₃ O), 3.61 s (3H, CH ₃ OCO), 3.88 q (2H, CH ₂), 4.00 d (2H, CH ₂), 7.35 q (4H, C ₆ H ₄), 9.55 s (1H, NH), CHCl ₃ - <i>d</i>
IVc	65	176–177	1735 (COOCH ₃), 1660 ($\text{C}^{\text{d}}=\text{O}$), 1610 (C=N)	1.78 s (3H, CH ₃ N), 3.15 s (3H, CH ₃ O), 3.55 s (3H, CH ₃ OCO), 3.75 s (3H, CH ₃ OC ₆ H ₄), 4.01 d (2H, CH ₂), 7.51 q (4H, C ₆ H ₄), (CH ₃) ₂ SO- <i>d</i> ₆
VIa	38	146–147	3320 (NH), 1698 (CONH), 1660 ($\text{C}^{\text{d}}=\text{O}$)	3.68 s (3H, CH ₃ O), 5.98 s (1H, CH), 7.25 s (11H, 2C ₆ H ₅ +NH), (CH ₃) ₂ SO- <i>d</i> ₆
VIb	18	86–88	3300 (NH), 1685 (CONH), 1670 ($\text{C}^{\text{d}}=\text{O}$)	1.28 t (3H, CH ₃), 3.45 q (2H, CH ₂), 7.38 s (11H, 2C ₆ H ₅ +CH), 9.15 s (1H, NH), CHCl ₃ - <i>d</i>
VIc	15	80–83	3336 (NH), 1684 (CONH), 1664 ($\text{C}^{\text{d}}=\text{O}$)	
VIId	27	76–78	3311 (NH), 1685 (CONH), 1675 ($\text{C}^{\text{d}}=\text{O}$)	
VII	41	205–207 (decomp.)	3315 (NH), 1660 br (C=O), 1615 (C=N, C=C)	6.30 s (1H, CH), 7.26 s (9H, C ₆ H ₅ +C ₆ H ₄), 10.78 s (1H, NHCO), 12.13 s (1H, NH), (CH ₃) ₂ SO- <i>d</i> ₆
VIII	51	216–218	3308 (NH), 1692, 1684 (C=O), 1628, 1616 (C=N, C=C)	3.93 s (3H, CH ₃), 7.60 s (10H, C ₆ H ₅ +C ₆ H ₄ +CH), 10.91 s (1H, NH), (CH ₃) ₂ SO- <i>d</i> ₆
IX	48	181–183	3204 br (NH), 1708 (COOCH ₃), 1692, 1674 (C=O), 1603 (C=N, C=C)	3.82 s (3H, CH ₃ O), 3.95 s (3H, CH ₃ N), 6.75 s (1H, CH), 7.58 s (8H, 2C ₆ H ₄), 12.12 s (1H, NH), (CH ₃) ₂ SO- <i>d</i> ₆

of the maximum are retained on going to methyl esters **IIa-f**: λ_{max} 313–339 nm ($\log \epsilon$ 3.15–3.40), and also to ethoxycarbonylmethyl esters **IIg-j**: λ_{max} 316–338 nm ($\log \epsilon$ 4.18–4.24).

Compounds **IIIa-e** were obtained in 45–84% yield, but the yields notably decreased in reactions of acids **I** or esters **II** with excess diazomethane. For

instance, on treating acids **Id**, **f** with excess diazomethane 3-aryoyl-4-methoxy-4-methoxycarbonyl-4,5-dihydropyrazoles (**IVa**, **b**) were obtained, and with acid **Ic** the diazomethane afforded 1-methyl-4-methoxy-3-(4-methoxybenzoyl)-4-methoxycarbonyl-4,5-dihydropyrazole (**IVc**). The latter product resulted from N-methylation of the intermediately arising 4-meth-

Table 2. Elemental analyses of compounds **IIg-j**, **IIIa-e**, **IVa-c**, **VIa-d**, **VII-IX**

Compd. no.	Found, %				Formula	Calculated, %			
	C	H	Hlg	N		C	H	Hlg	N
IIg	60.46	5.03			C ₁₄ H ₁₄ O ₆	60.43	5.07		
IIh	58.50	5.21			C ₁₅ H ₁₆ O ₇	58.44	5.23		
IIi	53.69	4.13	11.41		C ₁₇ H ₁₃ ClO ₃	53.77	4.19	11.34	
IIj	46.92	3.60	22.51		C ₁₇ H ₁₃ BrO ₃	47.08	3.67	22.37	
IIIa	65.56	5.40			C ₁₂ H ₁₂ O ₄	65.45	5.49		
IIIb	62.37	5.68			C ₁₃ H ₁₄ O ₅	62.39	5.64		
IIIc	56.58	4.19	14.07		C ₁₂ H ₁₁ ClO ₄	56.60	4.35	13.92	
IIId	63.71	6.03			C ₁₄ H ₁₆ O ₅	63.63	6.10		
IIIe	49.94	4.03	25.64		C ₁₃ H ₁₃ BrO ₄	49.86	4.18	25.52	
IVa	52.77	4.32	12.22	9.32	C ₁₃ H ₁₃ ClN ₂ O ₄	52.62	4.42	11.95	9.44
IVb	58.96	5.84		9.03	C ₁₅ H ₁₈ N ₂ O ₅	58.82	5.92		9.15
IVc	58.89	5.88		9.07	C ₁₅ H ₁₈ N ₂ O ₅	58.82	5.92		9.15
VIa	72.75	5.24		4.76	C ₁₇ H ₁₅ NO ₃	72.58	5.37		4.98
VIb	73.32	5.71		4.82	C ₁₈ H ₁₇ NO ₃	73.20	5.80		4.74
VIc	64.55	4.34	11.39	4.34	C ₁₇ H ₁₄ ClNO ₃	64.67	4.47	11.23	4.44
VIId	65.43	4.85	10.97	4.07	C ₁₈ H ₁₆ ClNO ₃	65.56	4.89	10.75	4.25
VII	62.76	3.58	11.06	12.73	C ₁₇ H ₁₂ ClN ₃ O ₂	62.68	3.71	10.88	12.90
VIII	63.75	4.02	10.52	12.14	C ₁₈ H ₁₄ ClN ₃ O ₂	63.63	4.15	10.43	12.37
IX	54.14	3.54	18.31	9.37	C ₂₀ H ₁₆ BrN ₃ O ₄	54.31	3.65	18.07	9.50

oxy-3-(4-methoxybenzoyl)-4-methoxycarbonyl-4,5-dihydropyrazole that we failed to isolate under the reaction conditions used. All pyrazole derivatives obtained are products of 1,3-dipolar cycloaddition of diazomethane across the C²=C³ bond with obligatory attack of the nucleophilic carbon atom of diazomethane on C² atom of substrate. No isomeric products of the obtained 4-aryl-5-methoxy-5-methoxycarbonyl-4,5-dihydropyrazoles were detected. Note that with excess diazomethane arose complicated mixtures of products (up to 6 substances as showed TLC) that we often were unable to separate.

Similarly to acids **I** and esters **II** reacted with diazoalkanes also 4-aryl-2-hydroxy-4-oxo-(Z)-2-butenic acids arylamides (**V**). For instance, among the products obtained from arylamides **Va-c** and diazomethane and diazoethane at the equimolar amounts of reagents were 2-alkoxy-4-aryl-4-oxo-2-butenic acids aryl amides (**VIa-d**) (Tables 1, 2, Scheme 2).

At excess diazomethane amides **Vb-d** gave a mixture of compounds from which were isolated respectively 4-phenylcarbamoyl-3-(4-chlorobenzoyl)pyrazole (**VII**), 3-benzoyl-1-methyl-4-(4-chlorophenylcarbamoyl)pyrazole (**VIII**), and 3-(4-bromobenzoyl)-1-methyl-4-(2-methoxycarbonylphenylcarbamoyl)pyr-

azole (**IX**). Pyrazoles **VII-IX** arise apparently from methanol elimination during workup from primary products, 4-methoxy-4,5-dihydropyrazole derivatives.

EXPERIMENTAL

IR spectra were recorded on spectrometers UR-20 or Specord M80 from mulls in mineral oil. ¹H NMR spectra were registered on instruments RYa-2310 (60 MHz) and Bruker WR-80-SY (80 MHz), internal reference HMDS, as solvents were used CDCl₃ and DMSO-*d*₆. UV spectra were taken on SF-46 device from solutions in ethanol of 10⁻⁴ M concentration. The reaction progress was monitored and the homogeneity of compounds obtained was checked by TLC on Silufol UV-254 plates in the solvents system ether-benzene-acetone (10:9:1).

Ethoxycarbonylmethyl 4-aryl-2-hydroxy-4-oxo-Z-2-butenates (IIg-j). A mixture of 0.01 mol of acid **Ia-e** and 0.011 mol of ethyl diazoacetate in 20 ml of ethanol was boiled for 2 h. The reaction mixture was then maintained for 3 h at -5-0°C. The precipitate was filtered off and recrystallized from ethanol.

Alkyl 4-aryl-2-methoxy-4-oxo-Z-2-butenates (IIIa-e). To a solution of 0.01 mol of ester

IIa, c, e, k, l in 30 ml of chloroform at $-5-0^{\circ}\text{C}$ was added while stirring a solution of 0.01 mol of diazomethane in 15 ml of ether. After standing for 24 h the solution was evaporated, the residue was recrystallized from hexane.

1-R-3-Aroyl-4-methoxy-4-methoxycarbonyl-4,5-dihydropyrazoles (IVa-c). To a solution of 0.01 mol of compound **Ic, d, f** in 30 ml of chloroform was added at stirring a solution of 0.06 mol of diazomethane in 90 ml of ether. After standing for 24 h the solution was evaporated, the residue was recrystallized from toluene (compounds **IVa, b**) or ethanol (compound **IVc**).

2-Alkoxy-4-aryl-4-oxo-2-butenic acids arylamides VIa-d. To a solution of 0.01 mol of compound **Va-c** in 50 ml of dioxane at $5-10^{\circ}\text{C}$ while stirring was added 0.01 mol of diazomethane (diazomethane) in 15 ml of ether. After standing for 24 h the solution was evaporated, the residue was recrystallized from tetrachloromethane (compound **VIa**) or hexane.

4-Phenylcarbamoyl-3-(4-chlorobenzoyl)pyrazole (VII), 3-benzoyl-1-methyl-4-(4-chlorophenylcarbamoyl)pyrazole (VIII), and 3-(4-bromobenzoyl)-1-methyl-4-(2-methoxycarbonylphenylcarbamoyl)pyrazole (IX). To a solution of 0.01 mol of compound **Vb-d** in 40 ml of dioxane at $5-10^{\circ}\text{C}$ while stirring was added 0.04 mol of diazomethane in 60 ml of

ether. After standing for 24 h the solution was evaporated, the residue was recrystallized from chloroform (compound **VII**), acetone (compound **VIII**), or ethanol (compound **IX**).

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