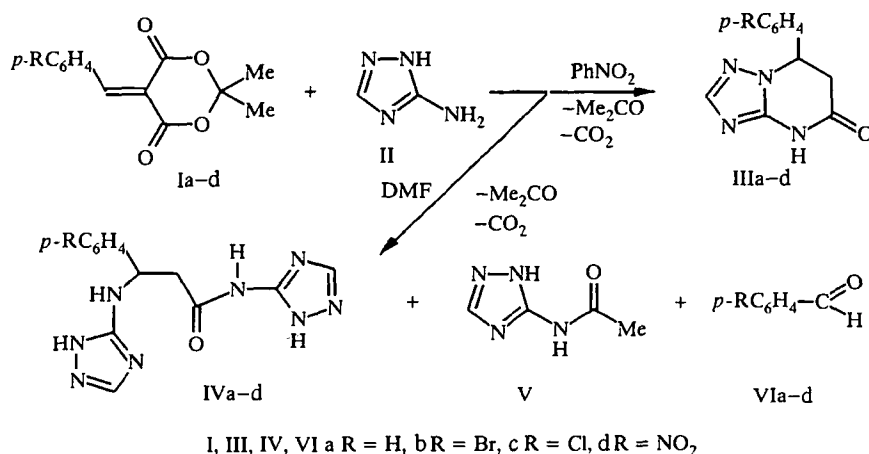


**REACTION OF ARYLIDENE
DERIVATIVES OF MELDRUM'S
ACID WITH 3-AMINO-1,2,4-TRIAZOLE**

V. V. Lipson, V. D. Orlov, S. M. Desenko,
T. M. Karnozhitskaya, and M. G. Shirobokova

The condensation of arylidene derivatives of Meldrum's acid with 3-amino-1,2,4-triazole in nitrobenzene leads to 4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-5-ones. In DMF the reaction proceeds with the formation of arylsubstituted N-(2H-1,2,4-triazol-3-yl)-3-(2H-1,2,4-triazol-3-ylamino)propionamides.

Arylidene derivatives of Meldrum's acid are convenient synthons of various heterocyclic systems [1-4]. While attempting to include these derivatives in the range of reagents used in the synthesis of partially hydrogenated azolopyrimidines we investigated the condensation of compounds Ia-d with 3-amino-1,2,4-triazole (II) under various conditions.



It turned out that on boiling solutions of equimolar quantities of these compounds in nitrobenzene the corresponding 4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-5-ones IIIa-d were formed. Their structure was confirmed by data of elemental analysis and by spectral methods. There were bands characteristic of amide groups at 3184-3200 (ν_{NH}) and 1700-1720 cm^{-1} ($\nu_{\text{C=O}}$) in the IR spectra of compounds IIIa-d (see Table 1). Signals for the protons of the ABX system of the pyrimidine ring, the triazole ring, and the NH group were present in the ¹H NMR spectra (Table 2). The position of the latter signal was typical of an amide group, which indicates unequivocally the formation in the condensation of 5- and not 7-oxoisomers. The products IIIa-d therefore were formed by reaction of the β -carbon atom of the biselectrophile with the endocyclic nitrogen atom of the aminoazole.

Ukrainian Research Institute for the Pharmacotherapy of Endocrine Diseases, Kharkov 310002. Kharkov State University, Kharkov 310077, Ukraine; e-mail: desenko@orgchem.univer.kharkov.ua. Translated from Khimiya Geterotsiklicheskih Soedinenii, No. 5, pp. 664-668, May, 1999. Original article submitted March 12, 1998; revision submitted April 17, 1998.

TABLE 1. Characteristics of Compounds IIIa-d, IVa-d, and V

Compound	Empirical formula	Found, %		mp, °C	IR spectrum (KBr), ν, cm ⁻¹	$\frac{[M+H]}{[M-H]}$	Yield, %
		Calculated, %	N				
IIIa	C ₁₁ H ₁₀ N ₄ O	$\frac{26.3}{26.2}$		215...217	1548, 1704, 3192	—	66
IIIb	C ₁₁ H ₉ N ₄ BrO	$\frac{19.4}{19.1}$		219...221	1568, 1700, 3184	—	71
IIIc	C ₁₁ H ₉ N ₄ ClO	$\frac{22.3}{22.5}$		225...227	1548, 1704, 3200	—	62
IIId	C ₁₁ H ₉ N ₅ O ₃	$\frac{27.1}{27.0}$		227...229	1532, 1720, 3200	—	47
IVa	C ₁₃ H ₁₄ N ₈ O	$\frac{37.8}{37.6}$		304...307	1560, 1676, 3284	—	20 (42)
IVb	C ₁₃ H ₁₃ N ₈ BrO	$\frac{29.8}{29.7}$		265...266	1560, 1676, 3280	$\frac{378}{376}$	20 (38)
IVc	C ₁₃ H ₁₃ N ₈ ClO	$\frac{33.9}{33.6}$		258...259	1560, 1672, 3280	$\frac{334}{332}$	22 (43)
IVd	C ₁₃ H ₁₃ N ₉ O ₃	$\frac{36.9}{36.7}$		237...238	1560, 1672, 3280	$\frac{344}{342}$	24 (45)
V	C ₄ H ₆ N ₄ O	$\frac{44.6}{44.4}$		287...289	1560, 1688, 3284	—	13

* Yield of products obtained by method A, those in parentheses – by method B.

Amides IVa-d were formed on carrying out the reaction between equimolar amounts of compounds Ia-d and 3-amino-1,2,4-triazole II in DMF. In addition, the amide V and the known aldehydes VIa-d were present in the reaction mixture. The structure of products IVa-d and V were confirmed by data of elemental analysis and by spectral methods (Tables 1,2). Aldehydes VIa-d were identified by TLC using 2,4-dinitrophenylhydrazine as visualizing agent. The formation of condensed pyrimidine systems was not recorded under these conditions.

It is known [1] that compounds of type I undergo readily nucleophilic addition at a double bond with the formation of β-adducts. Structure of the reaction products shows the endocyclic imino group of compound II participates in this process in nitrobenzene, but when a carboxyl group is liberated as a result of thermolysis it reacts with the amino group. The direction of the process is changed in the highly basic but substantially lower boiling DMF: β-adducts are formed due to the amino group of compound II. The carboxyl group, formed in the course of pyrolysis of the dioxan ring (or upon hydrolysis catalyzed by amine), also reacts with the amino group of a second molecule of II. Under these conditions a recondensation of the arylidene derivatives of Meldrum's acid occurs, which explains the appearance of compounds V and VIa-d in the reaction mixture.

The nontrivial results obtained stimulated us to investigate in detail the interaction of reactants I and II in DMF. Under the action of water in the DMF compounds of type I are capable of hydrolysis with the formation of the corresponding aldehyde and Meldrum's acid [1,5]. It was shown by us that benzaldehyde VIa and the Michael adduct VII were formed on boiling compound Ia in DMF.

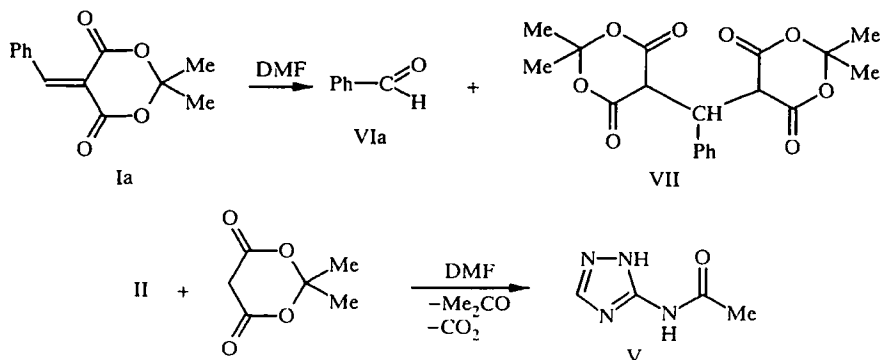
The presence of benzaldehyde was confirmed by the formation of the corresponding dinitrophenylhydrazone after removal of adduct VII from the reaction mixture. The adduct VII was identified by comparison of its characteristics with literature data [5]. On boiling amine II with Meldrum's acid in DMF the main product was amide (V).

Condensation of equimolar quantities of the appropriate benzaldehyde VIa-d, Meldrum's acid, and amine II also leads to the formation of compounds IVa-d. In addition, the yield of amides IVa-d doubled uniformly at a ratio of the appropriate benzaldehyde:acid:amine of 1:1:2. Under these conditions the formation of amide V was noted only by TLC and products of type VII were not present in the mixture.

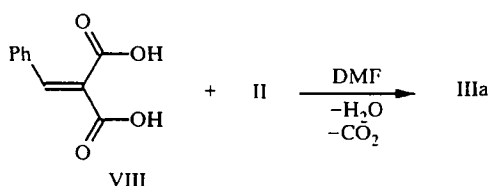
TABLE 2. ¹H NMR Spectral Characteristics for Compounds IIIa-d, IVa-d, and V, δ , ppm, and Coupling Constants (J , Hz)

Compound	NH (1H, br. s)	CH= (1H, s)	ArH (m)	CH _X	CH _A H _B
IIIa	11,65	7,78	7,05...7,40 (5H)	5,73 (1H, dd, $J_{AX} = 4,6$; $J_{BX} = 7,1$)	3,42 (1H, dd, $J_{AB} = -16,4$); 2,92 (1H, dd)
IIIb	11,70	7,78	7,10...7,60 (4H)	5,73 (1H, dd, $J_{AX} = 5,8$; $J_{BX} = 6,9$)	3,36 (1H, dd, $J_{AB} = -16,4$); 2,92 (1H, dd)
IIIc	11,60	7,75	7,10...7,30 (4H)	5,74 (1H, dd, $J_{AX} = 5,4$; $J_{BX} = 6,9$)	3,41 (1H, dd, $J_{AB} = -16,6$); 2,90 (1H, dd)
III d	11,74	7,82	7,40...8,25 (4H)	5,91 (1H, dd, $J_{AX} = 5,6$; $J_{BX} = 6,2$)	3,42 (1H, dd, $J_{AB} = -16,2$); 2,92 (1H, dd)
IVa	13,33; 12,26; 12,10; 11,41	7,74*	7,20...7,38 (6H)	5,11 (1H, dd, $J_{AX} = 2,9$; $J_{BX} = 7,8$)	2,89 (1H, dd, $J_{AB} = -15,6$); 2,92 (1H, dd)
IVb	13,32; 12,66; 12,12; 11,44	7,71*	7,38...7,49 (5H)	5,07 (1H, dd, $J_{AX} = 2,9$; $J_{BX} = 7,8$)	2,87 (1H, dd, $J_{AB} = -15,6$); 2,92 (1H, dd)
IVc	13,38; 12,77; 12,19; 11,56	7,68 7,99	7,20...7,50 (4H)	5,09 (1H, br. s)	2,73 (2H, br. s)
IVd	13,34; 12,73; 12,22; 11,50	7,70	7,67...8,18 (5H)	5,25 (1H, br. s)	2,93 (2H, br. s)
V	13,29; 11,45	7,69	—	—	2,09 (3H, s, CH ₃)

* The second signal is overlapped by the multiplet of the aromatic protons (ArH).



An arylidenemalonic acid may be a possible intermediate in the reaction being studied, however on carrying out the condensation of benzylidene-malonic acid VIII with amine II in DMF the sole reaction product was compound IIIa. In this case the endocyclic nitrogen atom and not the amino group (as was observed in the formation of compound IV) participates in the reaction with the β -carbon atom.



Comparison of the results obtained indicates in our opinion that the endocyclic nitrogen atom is the more reactive in the molecule of II, but in the presence of protonating agents (as occurs in the reaction of amine II with benzylidenemalonic acid) initial protonation of the azole ring leads to deactivation of its endocyclic center, and thereby causes the formation of an amide with subsequent cyclization and decarboxylation. That decarboxylation is the final step in the formation of product IIIa from acid VIII and amine II in DMF is also shown by the fact that cinnamic acid does not condense with amine II under analogous conditions.

EXPERIMENTAL

The IR spectra were recorded on a Specord M 82 spectrometer for KBr disks. The ¹H NMR spectra were recorded on a Varian 300 spectrometer, solvent was DMSO-d₆, and internal standard TMS. The mass spectra were obtained on a MSBC SELMI spectrometer (source was 10 μ Ci ²⁵²Cf) for positive and negative ions at an accelerating voltage of ± 20 kV. A check on the progress of reactions and the purity of the compounds obtained, and also identification of aldehydes VI and amide V, were performed by TLC on Silufol UV 254 plates in the system ethyl acetate–benzene–methanol, 2:2:1.

7-Phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-5-one (IIIa). A mixture of 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (Ia) (0.23 g, 1 mmol) and triazole II (0.08 g, 1.1 mmol) in nitrobenzene (1 ml) was boiled for 3 h. After cooling, ether (5 ml) was added to the reaction mixture, and the precipitate filtered off. Product IIIa (0.16 g, 66%) was obtained and was purified by recrystallization from a DMF–propan-2-ol (1:2) mixture.

Compounds IIIb-d were obtained analogously from the appropriate diones Ib-d.

3-Phenyl-N-(2H-1,2,4-triazol-3-yl)-3-(2H-1,2,4-triazol-3-ylamino)propionamide (IVa). A mixture of dione Ia (2.32 g, 0.01 mol) and triazole II (0.84 g, 0.01 mol) in DMF (2 ml) was boiled for 15 min. The reaction mixture was cooled and methanol (5 ml) added. The mixture of products IVa and V was filtered off, and was separated by recrystallization from a 1:1 mixture of DMF–methanol. Product IVa (0.6 g, 20%) and product V (0.16 g, 13%) were obtained. The presence of benzaldehyde in the filtrate after the separation of the crystalline products was established by TLC, visualizing with an alcohol solution of 2,4-dinitrophenylhydrazine.

B. A mixture of benzaldehyde (1.44 g, 0.01 mol), 2,2-dimethyl-1,3-dioxane-4,6-dione (1.06 g, 0.01 mol), and triazole II (1.68 g, 0.02 mol) in DMF (2 ml) was boiled for 15 min. The mixture was cooled and methanol (10 ml) added. Product IVa (1.26 g, 12%) was filtered off. Compound V was detected in the filtrate by TLC (R_f 0.3).

Compounds IVb-d were obtained analogously from the corresponding substituted benzaldehyde.

N-(2H-1,2,4-Triazol-3-yl)acetamide (V). A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (1.44 g, 0.01 mol) and triazole II (0.84 g, 0.01 mol) in DMF (1 ml) was boiled for 15 min. The mixture was cooled, methanol was added, and product V (0.76 g, 60.3%) was filtered off.

Bis(2,2-dimethyl-1,3-dioxane-4,6-dion-5-yl)phenyl-methane (VII). A solution of dione Ia (0.23 g, 1 mmol) in DMF (1 ml) was boiled for 30 min. The reaction mixture was cooled to 0-5°C, water (5 ml) added, and product VII (0.15 g, 40%) filtered off. It had mp 177°C (literature mp 177°C [7]). 2,4-Dinitrophenyl-hydrazine (0.4 g) in 13% H₂SO₄ solution in alcohol (15 ml) was added to the filtrate. Benzaldehyde 2,4-dinitrophenylhydrazone (0.2 g, 69% calc. on the initial compound Ia) was isolated; mp 243°C, literature mp 243°C [6].

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