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61.* REACTION OF MALONYL DICHLORIDE WITH AROMATIC AMIDES

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In the reaction of malonyl dichloride with substituted -enzamides, cyclic and linear products and their mixtures form, depending on the solvent and the ratio and concentrations of reagents. When the reaction is carried out in dilute dichloroethane solution, pure 2-aryl-1,3-oxazin-4,6-diones without a substituent at C(s) are obtained in good yield. These materials are extremely unstable, and in the presence of traces of water are converted to the respective N-aroylmalonamic acids.

Mono- and disubstituted malonyl dichlorides react wi $\dot{}$ aromatic amides to form the respective 5-mono- and 5,5-disubstituted 2-aryl-1,3-oxazine-4,6-diones (III) [2-4]. At the same time compounds without a substituent at heterocycle position 5 could not be synthesized by this method. It has been shown that the reaction of amides II with unsubstituted malonyl dichloride I forms pyranooxazines IV by dimerization of I [2, 3]. It is also known that in the case of thiobenzamides the corresponding 1,3-thiazine-4,6-diones are obtained in high yield [5]. It was therefore of interest to study this reaction in greater detail, in order to elucidate its possible use for the synthesis of oxazine-diones not substituted at position 5.



Dimerization of malonyl dichloride leading to bicyclic products can take place because the reaction is carried out under relatively severe conditions (heating in xylene or without solvent). It could therefore be expected that greater dilution of the reaction mixture and moderate heating would give the compounds III in which we were interested. Preliminary tests showed that when malonyl dichloride I and benzamide IIa react in THF over quite a wide concentration range (0.3-2.6 mole/liter), only one product is ever obtained; according to its properties it is the corresponding pyrano-oxazine IVa, the structure of which has been considered in detail in [3, 6]. The PMR spectrum of this compound in DMSO contains signals of the OH proton (12.6 ppm) the 8-H proton (5.45 ppm), and multiplets of the benzene ring protons (7.5 and 8.2 ppm).

Substance IVb, which is similar in spectral properties (see Table 1), was obtained in THF from malonyl dichloride and p-nitrobenzamide (IIb). Replacement of THF by ethyl acetate gave a compound of composition $C_{1,7}H_{1,2}N_4O_8$. The IR spectrum of this compound contained a band at 3250 cm⁻¹ ($v_{\rm NH}$) and bands in the carbonyl region at 1705, 1690, and 1673 cm⁻¹. The PMR spectrum showed, besides the aromatic proton quadruplet (8.2 ppm), the NH (11.6 ppm) and

*For Communication 60, see [1].

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TABLE 1. Properties of Compounds III-VI

% ,bjsiY		74	11	67	73	85	44	42	40	63	76	69
Calculated, 껴	zĵ	7,4	12,0	6,3	5,5	9,3	4,9	14,0	7,6	6,6	11,1	5,8 (14,7)
	н	3,7	2,6	2,7	2,7	2,0	3,2	3,0	4,9	4,3	3,2	3,3
	ပ	63,5	51,3	53,7	60,7	51,7	58,6	51,0	61,6	58,0.	47,6	49,7
Empirical formula		C ₁₀ H ₇ NO ₃	C ₁₀ 11 ₆ N ₂ O ₅	C ₁₀ H ₆ CINO ₃	C ₁₃ H ₇ NO ₅	$C_{13}H_6N_2O_7$	C ₁₄ H ₉ NO ₆	C ₁₇ H ₁₂ N4C **	C ₁₉ H ₁₈ N ₂ C ***	C ₁₀ H ₉ NO ₄	$C_{10}H_8N_2O_6$	C ₁₀ H _s CINO ₄
Found, %	2() 2	7,1	11,8	6,3	5,6	9,3	4,7	14,2	7,5	6,6	11,3	6,1 (15,8)
	H	3,6	2,6	3,0	2,9	1,8	3,1	2,9	5,0	4,2	3,6	3,3
	υ	63,2	51,5	54,2	60,8	51,8	58,1	50,9	61,7	58,2	47,6	49,7
PMR spectrum (in DMSO- D ₆), 6, pp m		12,8 (s. 1H); 8,1 (m,2H); 7,6 (m, 2H); 5,30 (c. 1H);	12,9 (a, 1H); 8,3 (m, 4H);	12,8 (s, 1H); 7,6 (d, 2H); 12,8 (s, 1H); 7,6 (d, 2H); s, 7, 6,01); 6,9,7,7,1H)	12,6 (s, 1H); 7,5 (m,3H); 8,9 (m, 3H); 8,9 (m, 3H); 8,9 (m, 3H); 7,5 (m, 3H);	13,2 (s, 1H); 8,2 (m, 4H);	7.2 (5, 1H); 8,2 (d, 2H); 7,2 (5, 2H); 5,47 (s, 1H);	11,60 (s, 2H); 8,2 (q., 8H);	$\begin{array}{c} 11,05 (s, 2H); 7,95 (d, 4H); \\ 11,05 (s, 2H); 7,95 (d, 4H); \\ 0.95 (d, 4H); 4,16 (s, 2H); \\ 2 76 (d, 4H); 4,16 (s, 2H); \end{array}$	2,5 (br. s, 1H); 11,2 (s, 1H); 7,4 (m, 3H); 7,9 (m, 2H); 7,4 (m, 3H); 7,9 (m, 2H);	12,7 (br, s, 2H); 11,5 (s, 1H); 12,7 (br, s, 1H); 11,5 (s, 1H); 260 (z, 2H); 260 (z, 3H)	0.20 (bt. 5, 1H); 0.03 (5, 1H); 12.6 (bt. 5, 1H); 11,3 (5, 1H); 7,93 (d, 2H); 7,55 (d, 2H); 369 (s. 2H)
IR spectrum, ν, cm ⁻¹		1659, 1628, 1600, 1580, 1550	1730, 1625, 1597, 1560, 1525	1675, 1655, 1630, 1598, 1570,	1347 1785, 1700, 1675, 1625, 1605,	1260, 1350, 1320 1790, 1720, 1690, 1605 sh, 1600,	1574, 1555, 1510 1574, 1555, 1510	3250, 1705, 1690, 1673, 1602	3250, 1715, 1690, 1678, 1610, 1580	3285, 1720, 1677, 1645, 1598, 1577	3255, 1720, 1683, 1605, 1530	3420, 3260, 1730, 1712, 1679, 1595
R,		l	1	I	0,39	0,51	0,38	0,67	0,53	0,51	0,49	0,52
mp, °C (decomp.)•		164-166	205-207	192-192,5	222-223	224-226	202203	187-189	176-178	122-123 (139-140 [7])	215-217	121-122
Com- pound		IIIa	qIII	pIII	IVa	IVb	IVc	۷b	Vc	Vla	VIb	ρIΛ

*Compounds IVa-c were recrystallized from dioxane, Vb from THF, Vc from dichloroethane. **Found (ebullioscopic): M 410. Calculated: M 400 ***Found (ebullioscopic): M 370. Calculated: M 370.

the CH_2 (4.19 ppm) protons at a 1:1 ratio of integrated intensities. From these data we may ascribe the structure of N,N'-bis(p-nitrobenzoyl)malondiamide (Vb) to this compound. Similar compounds were isolated in low yield as byproducts of the reaction of monosubstituted malonyl dichlorides with amides [3]. In benzene even after prolonged boiling, malonyl dichloride did not react appreciably with amide IIb, probably because of the low solubility of the latter.

The use of more dilute reagents (1-3% solutions) and reverse order of mixing (excess amide in the mixture should favor formation of malondiamides V) in THF or its mixture with dichloroethane in the case of amides IIb, d was also unsuccessful. We obtained a mixture of products in which IV and V were identified; we also separated malonamic acids VI which are the hydrolysis products of oxazinediones III (see below). In these cases it is impossible to establish unequivocally whether oxazinediones III formed, or whether VI is obtained by hydrolysis (during isolation) of the intermediate N-aroylmalonamic acid chlorides.

Addition of a 1% solution of p-methoxybenzamide (IIc) to a 2% solution of malonyl dichloride in dichloroethane at 50°C gave a mixture of IVc and Vc, from which the individual compounds were separated in comparable yields. Their IR and PMR spectra agreed with those of IVa, b and Vb (Table 1).

At the same time it was found that when 0.8% solution of benzamide IIa is added to 3% solution of malonyl dichloride in dichloroethane the reaction goes unequivocally to form oxazinedione IIIa. Changing the order of addition of reagents did not affect the course of the reaction or the product yield. Compound IIIa was identical in melting point and IR spectrum with the product that we obtained by a known method from benzoyl isocyanate and ketene [7]. This material is extremely unstable and even in the presence of atmospheric moisture is converted to N-benzoylmalonamic acid (VIa), which could not be excluded in [7]. Use of the conditions described above enabled us to obtain other oxazinediones IIIb, d in good yield. These are yellowish crystalline materials, almost insoluble in low-polar aprotic solvents; their chromatograms show the spots of the respective acids VI due to rapid hydrolysis. The cyclic structure of III is confirmed by the absence from the IR spectra of the crystalline samples, of the N-H vibration bands (3250 cm^{-1}) that are typical of VI, and the presence of bands in the 1610-1630 and 1550-1560 cm⁻¹ regions corresponding to heterocyclic C=C and C=N vibrations. The vibration bands of enolic hydroxyl are not very characteristic; as a rule there is absorption over a wide frequency range from 2400 to 3100 cm^{-1} . The PMR spectra of freshly prepared solutions in DMSO* have signals of benzene ring protons, 5-H protons (5.22 ppm), and a weak-field proton (12.8 ppm) that are evidence for enolization of one carbonyl group. The PMR spectra of acid VI solutions in DMSO contain signals of OH, NH, and CH₂ protons in the 12.5-12.7, 11.2-11.5, and 3.7 ppm regions, respectively. The IR spectra of these materials have several carbonyl vibration bands in the 1640-1730 cm⁻¹ region.

Thus the reaction of malonyl dichloride with aromatic amides forms oxazinediones III, unsubstituted at $C_{(s)}$, provided the reaction is carried out in dilute dichloroethane solution. Under other conditions the formation of both bicyclic (IV) and linear (V) reaction products is possible.

EXPERIMENTAL

IR spectra of mineral oil suspensions were obtained with a Specord IR-75 instrument; PMR spectra, on a Tesla BS 487-C spectrometer (80 MHz), HMDS internal standard. The course of the reaction and product purity were monitored with TLC on Silufol UV-254 plates, with ethyl acetate eluent.

<u>2-Phenyl-5,6-dihydro-4H-1,3-oxazine-4,6-dione (IIIa)</u>. To a solution of 2 g (16 mmole) of benzamide in 250 ml of dry dichloroethane was added 2.8 g (20 mmole) of malonyl dichloride in 100 ml of dichloroethane dropwise with stirring at 60° over 3-3.5 h. The mixture was stirred for 1 h at 60° and cooled, and solvent was distilled off in vacuum to leave 50-70 ml. The precipitate was filtered off, washed with dichloroethane, and dried in a vacuum desiccator over P_2O_5 .

2-p-Nitrophenyl-5,6-dihydro-4H-1,3-oxazine-4,6-dione (IIIb) and 2-p-chlorophenyl-5,6dihydro-4H-1,3-oxazine-4,6-dione (IIId) were synthesized analogously. In the former case

*Oxazinediones III are unstable in DMSO.

malonyl dichloride was added at 80° (p-nitrobenzamide is not completely soluble at a lower temperature), and the mixture was stirred for 4 h at 60°.

<u>2-Phenyl-7-hydroxypyrano[3,4-e]oxazine-4,5-dione (IVa)</u>. To a solution of 7.3 g (60 mmole) of benzamide in 50 ml of THF was added 10 g (70 mmole) of malonyl dichloride in 25 ml of THF with stirring so that the temperature never exceeded 30°. The mixture was stirred for 8 h at 20°, and the yellow precipitate was filtered off, washed with THF, and dried in vacuum.

<u>2-p-Nitrophenyl-7-hydroxypyrano[3,4-e][1,3]oxazine-4,5-dione (IVb)</u>. To a solution of 2 g (12 mmole) of p-nitrobenzamide in 60 ml of THF was added 1.97 g (14 mmole) of malonyl dichloride in 40 ml of THF dropwise over 1 h at 20°. The mixture was stirred for 4 h at 20° and left over night. The solvent was distilled off in vacuum, the residue was treated with ethyl acetate, and the precipitate was filtered off.

<u>N,N'-Bis(p-nitrobenzoyl)malondiamide (Vb).</u> To a suspension of 3 g (19 mmole) of p-nitrobenzamide in 100 ml of ethyl acetate was added 2.54 g (19 mmole) of malonyl dichloride in 50 ml of ethylacetate with stirring at 15° over 1 h. The mixture was stirred for 2.5 h at 15°, then for 9 h at 75°, then left overnight. The crystalline precipitate was filtered off (0.7 g), and the mother liquor was partially evaporated to give another 0.85 g of amide Vb.

<u>2-p-Methoxyphenyl-7-hydroxypyrano[3,4-e][1,3]oxazine-4,5-dione (IVc) and N,N'bis(p-methoxybenzoyl)malondiamide (Vc).</u> To a solution of 3.73 g (26 umole) of malonyl dichloride in 200 ml of dichloroethane was added a warm solution of 4 g (26 mmole) of p-methoxybenza-mide in 400 ml of dichloroethane with stirring at 50° over 3.5 h. The mixture was then stirred 30 min and left over night. The solvent was distilled off at atmospheric pressure until the volume was reduced to 100 ml, then in vacuum to 30 ml, and 1.9 g of amide Vc was filtered off. Further evaporation of the filtrate gave 1.65 g of compound IVc.

N-Aroylmalonamic acids VIa, b, d were obtained by recrystallization of the respective oxazinediones III from 1:1 aqueous acetonitrile.

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