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EXOTIC AMINO ACIDS. 8*. SYNTHESIS OF MONOMETHYL ESTERS OF N-ARYL-AMINOMETHYLENEMALONIC ACIDS

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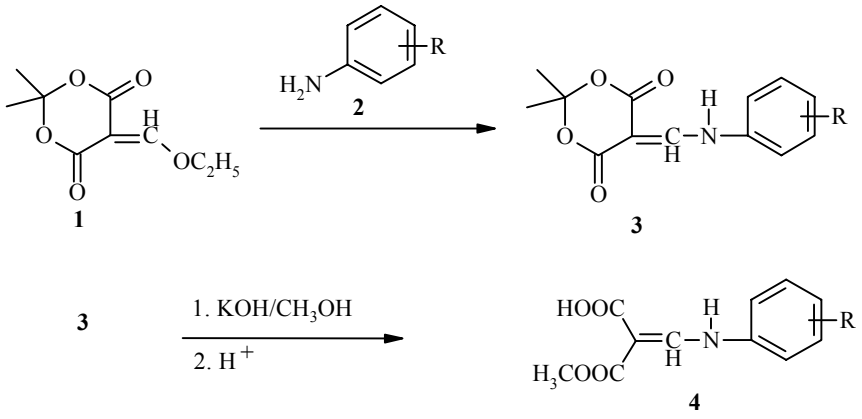
N-Arylaminomethyleneisopropylidenemalonates, obtained from ethoxymethyleneisopropylidenemalonate and aromatic amines, underwent methanolysis to form monomethyl esters of N-arylaminomethylenemalonic acids. The conditions of their formation and their yields depend on the nature and positions of the substituents in the aromatic ring of the initial amine.

Keywords: N-arylaminomethyleneisopropylidenemalonates, aromatic amines, monomethyl esters of N-arylaminomethylenemalonic acids, ethoxymethyleneisopropylidenemalonate.

We have previously [2] established that N-hetarylaminomethyleneisopropylidenemalonates are valuable sources for the synthesis of substituted β-amino acids.

Since β-amino acids are of great interest because of their biological activity [1-5], we have extended the search for new methods for the synthesis of non-proteinogenic (exotic) amino acids and in this study we have investigated the methanolysis of aromatic aminomethyleneisopropylidenemalonates **3**. Compounds **3a-k** (Tables 1 and 2) were synthesized from ethoxymethyleneisopropylidenemalonate (**1**) and aromatic amines **2a-k** in ethanol at room temperature [6, 7].



2–4 **a** R = H; **b** R = CH_3(*o-, m-, p-*); **c** R = NO_2 (*o-, m-, p-*); **d** R = OH (*o-, m-, p-*); **e** R = OCH_3 (*o-, m-, p-*); **f** R = COOH (*o-, m-, p-*); **g** R = *o*-$COOCH_3$; **h** R = *o*-Cl; **i** R = *o*-Br; **j** R = Br(*o-*), NO_2(*p-*); **k** R = *p*-$COCH_3$

* For part 7 see [1].

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TABLE 1. Characteristics of Compounds **3a-k***

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*[2]	Yield, %
		C	H	N	Hal		
3a	$C_{13}H_{13}NO_4$					158-160 (CCl_4) 154-156 [8] (Ethanol)	77 79 [8]
3b(*o*-)	$C_{14}H_{15}NO_4$					125-126 120.2-121.8 [8] (Ethanol)	85 76 [8]
3b(*m*-)	$C_{14}H_{15}NO_4$					119-120 115-116.6 [8] (Ethanol)	62 75 [8]
3b(*p*-)	$C_{14}H_{15}NO_4$					151-152 150-152 [8] (Ethanol)	85.5 67 [8]
3c(*o*-)	$C_{13}H_{12}N_2O_6$					185-186 (dec.) (Ethanol) 180-181(dec.) [8] (Acetonitryle)	96 48 [8]
3c(*m*-)	$C_{13}H_{12}N_2O_6$					200-203 (dec.) 197-203.8 (dec.) [8] (Acetonitryle)	84.5 78 [8]
3c(*p*-)	$C_{13}H_{12}N_2O_6$					217-218 (dec.) 215-216(dec.) [8] (Acetonitryle)	99 67 [8]
3d(*o*-)	$C_{13}H_{13}NO_5$	59.50 59.31	5.07 4.98	5.50 5.32		213-214 (dec.) (Ethanol)	70
3d(*m*-)	$C_{13}H_{13}NO_5$	59.11 59.31	4.81 4.93	5.50 5.32		208-210 (dec.) (Ethanol)	77
3d(*p*-)	$C_{13}H_{13}NO_5$					214-215 (dec.) (Ethanol) 207-209 (dec.) [9]	85 21 [9]
3e(*o*-)	$C_{14}H_{15}NO_5$					150-151 154-155.8 [8] (Ethanol)	89 83[8]
3e(*m*-)	$C_{14}H_{15}NO_5$	60.72 60.64	5.51 5.45	5.25 5.05		115-117	69
3e(*p*-)	$C_{14}H_{15}NO_5$					164-165 163-165 [8] (Ethanol)	87 55 [8]
3f(*o*-)	$C_{14}H_{13}NO_6$					245-246 (dec.) (Ethanol) 233-235 (dec.) [7]	70 78 [7]
3f*(m*-)	$C_{14}H_{13}NO_6$	57.89 57.73	4.56 4.50	4.90 4.81		248-250 (dec.)	98
3f(*p*-)	$C_{14}H_{13}NO_6$					239-241 (dec.) (Ethanol) 236-238 (dec.) [7]	89 55 [7]
3g	$C_{15}H_{15}NO_6$	58.93 59.02	5.03 4.95	4.70 4.59		169-171 (Ethanol)	95
3h	$C_{13}H_{12}ClNO_4$	55.48 55.43	4.36 4.29	5.03 4.97	12.64 12.58	125-126 (Ethanol)	82
3i	$C_{13}H_{12}BrNO_4$	48.02 47.88	3.86 3.71	4.20 4.29	27.53 27.43	157-158	85
3j	$C_{13}H_{11}BrN_2O_6$	42.11 42.06	2.90 2.98	3.81 3.77	21.70 21.52	233-234 (dec.)	55
3k	$C_{15}H_{15}NO_5$	62.31 62.28	5.30 5.23	4.88 4.84		209-210 (dec.)	58

* Elemental analyses are cited for compounds synthesized for the first time.
*[2] The recrystallization solvent is given in brackets.

The aromatic amines used were aniline **2a** and anilines with substituents in the aromatic ring **2b-k**. Methanolysis of the aminomethyleneisopropylidenemalonates **3a-k** was carried out in methanol in the presence of an equimolar quantity (for compounds **3f** (*o-, m-, p-*) 2 moles) of potassium hydroxide with subsequent acidification of the solution of the potassium salts of compounds **4a-k**.

It was established experimentally that the conditions of formation and the yield of the monomethyl N-arylaminomethylenemalonates **4a-k** (N-aryl-substituted β-amino acids) depends on both the nature of the substituents on the aromatic ring and their dispositions.

Most of the methyl esters of the arylaminomethylenemalonic acids (**4b** (*o-, m-, p-*), **4c** (*o-*), **4d** (*m-*), **4e** (*o-, m-, p-*), **4f** (*o-, m-, p-*), **4g-i,k**) are formed over a few hours at room temperature, while for splitting of the 1,3-dioxane ring in compounds containing aniline **3a**, *m-* and *p*-nitroaniline **3c** (*m-, p-*), *o-* and *p*-aminophenol **3d** (*o-, p-*), and *o*-bromo-*p*-nitroaniline **3j** it was necessary to boil the components in methanol for 2 h.

The yields of compounds **4a-k** ranged from 37-82%. The decreased yields of compounds **4d** (*o-, p-*) containing hydroxy groups in the *o-* and *p*-positions of the benzene ring explained by the formation of secondary products during their formation and is connected with the necessity to carry out two recrystallization to obtain pure compounds.

Characteristics of the monomethyl N-arylaminomethylenemalonates **4a-k** are given in Table 3, and their structures are given on the basis of the ^{1}H NMR spectra (see Table 4). The spectroscopic data for the arylaminomethyleneisopropylidenemalonate starting materials **3a-k** are cited in Table 2. The presence of a six proton singlet for two methyl groups in the region 1.63-1.77 ppm is characteristic of the spectra of compounds

TABLE 2. Spectroscopic Characteristics of Compounds **3a-k**

Compound	^{1}H NMR spectrum, δ, ppm			Coupling constants, $^3J_{=CHNH}$, Hz
	$2CH_3$(6H, s)	HC=(1H, d)	NH(1H, d)	
3a	1.73	8.51	11.13	14
3b(*o-*)	1.67	8.51	11.42	14
3b(*m-*)	1.71	8.49	11.27	14.5
3b(*p-*)	1.68	8.44	11.39	15
3c(*o-*)	1.72	8.66	12.94	14.5
3c(*m-*)	1.74	8.60	11.31	14
3c(*p-*)	1.77	8.73	11.46	14
3d(*o-*)	1.64	8.58	11.44	15
3d(*m-*)	1.71	8.53	11.07	15
3d(*p-*)	1.67	8.45	11.18	14
3e(*o-*)	1.71	8.62	11.49	15
3e(*m-*)	1.69	8.49	11.11	15
3e(*p-*)	1.68	8.44	11.18	15
3f(*o-*)	1.73	8.76	11.36	15
3f(*m-*)	1.68	8.53	11.28	14
3f(*p-*)	1.63	8.68	11.42	15
3g	1.76	8.68	13.10	14
3h	1.73	8.60	11.62	14
3i	1.67	8.54	11.51	14
3j	1.71	8.80	11.73	14
3k	1.71	8.67	11.18	15

TABLE 3. Characteristics of Compounds of Compounds **4a-k***

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*[2]	Yield, %
		C	H	N	Hal		
4a	$C_{11}H_{11}NO_4$	59.81 / 59.72	5.11 / 5.01	6.50 / 6.33		127-130 (2:1 ethanol–water)	45
4b(*o*-)	$C_{12}H_{13}NO_4$	61.40 / 61.27	5.70 / 5.57	5.83 / 5.95		112-113	70
4b*(m*-)	$C_{12}H_{13}NO_4$	61.03 / 61.27	5.43 / 5.57	5.90 / 5.95		154-156	73
4b(*p*-)	$C_{12}H_{13}NO_4$	61.40 / 61.27	5.42 / 5.57	5.90 / 5.95		122-124	74
4c(*o*-)	$C_{11}H_{10}N_2O_6$	49.67 / 49.63	3.84 / 3.79	10.64 / 10.52		195-196 (Ethanol)	75
4c(*m*-)	$C_{11}H_{10}N_2O_6$	49.71 / 49.63	3.85 / 3.79	10.57 / 10.52		206-207 (dec.) (Methanol)	62
4c(*p*-)	$C_{11}H_{10}N_2O_6$	49.71 / 49.63	3.64 / 3.79	10.61 / 10.52		183-185 (dec.)	79
4d(*o*-)	$C_{11}H_{11}NO_5$	55.81 / 55.70	4.81 / 4.67	5.96 / 5.90		186-187 (dec.) (2·diisopropyl ether)	40
4d(*m*-)	$C_{11}H_{11}NO_5$	55.96 / 55.70	4.71 / 4.67	5.98 / 5.90		177-178 (dec.) (Ethanol)	51
4d(*p*-)	$C_{11}H_{11}NO_5$	55.45 / 55.70	4.79 / 4.67	5.96 / 5.90		204-206 (2·ethanol–water, 1:1)	37
4e(*o*-)	$C_{12}H_{13}NO_5$	57.50 / 57.37	5.18 / 5.22	5.47 / 5.58		147-148 (Ethyl acetate–hexane)	61
4e(*m*-)	$C_{12}H_{13}NO_5$	57.77 / 57.37	5.14 / 5.22	5.64 / 5.58		101-102 (Diisopropyl ether)	56
4e(*p*-)	$C_{12}H_{13}NO_5$	57.10 / 57.37	5.14 / 5.22	5.65 / 5.58		129-130 (Ethyl acetate-hexane)	55.5
4f(*o*-)	$C_{12}H_{11}NO_6$	54.12 / 54.35	4.34 / 4.18	5.08 / 5.28		189-191 (dec.) (Ethanol)	73
4f(*m*-)	$C_{12}H_{11}NO_6$	54.13 / 54.35	4.31 / 4.18	5.33 / 5.28		189-191 (dec.) (Ethanol)	79
4f(*p*-)	$C_{12}H_{11}NO_6$	54.13 / 54.35	4.10 / 4.18	5.18 / 5.28		250-251 (dec.) (1:2 DMF–ethanol)	65
4g	$C_{13}H_{13}NO_6$	55.64 / 55.92	4.70 / 4.69	5.24 / 5.02		163-165 (Ethanol)	72
4h	$C_{11}H_{10}ClNO_4$	51.97 / 51.68	3.72 / 3.94	5.26 / 5.48	13.69 / 13.87	140-141 (Ethanol)	56
4i	$C_{11}H_{10}BrNO_4$	44.29 / 44.02	3.26 / 3.36	4.75 / 4.67	27.12 / 26.63	140-141	82
4j	$C_{11}H_9BrN_2O_6$	38.50 / 38.28	2.87 / 2.63	8.12 / 8.12	22.92 / 23.15	195-196 (dec.)	50
4k	$C_{13}H_{13}NO_5$	59.56 / 59.31	4.80 / 4.98	5.55 / 5.32		174-175	53

* Elemental analysis data are given only for compounds described for the first time.

*[2] Recrystallization solvents are given in brackets.

3a-k. This signal has disappeared in the spectra of compounds **4a-k** to be replaced by a three proton singlet in the region 3.22-3.89 ppm, which is characteristic for monomethyl esters, and also by broad weak field signal of the –COOH proton. The remaining proton signals of the fixed *trans* fragments of the aminomethylene groups, which appear as two doublets =CH– (δ 8.3-8.8) and –NH (δ 11.07-13.31 ppm) with J = 12-15 Hz.

TABLE 4. Spectroscopic Characteristics of Compounds **4a-k**

Compound	^{1}H NMR spectrum, δ, ppm				Coupling constants, $^3J_{=CHNH}$, Hz
	CH_3 (3H, s)	HC= (1H, s)	NH (1H, s)	COOH (1H, s)	
4a	3.83	8.43	11.67	7.22	14
4b(*o*-)	3.86	8.47	11.83	12.83	13.75
4b(*m*-)	3.78	8.44	11.60	7.21	14
4b(*p*-)	3.89	8.39	11.72	12.86	13.5
4c(*o*-)	3.84	8.74	13.31	12.71	13.5
4c(*m*-)	3.52	8.57	11.40	12.56	14
4c(*p*-)	3.64	8.65	11.70	14.28	14
4d(*o*-)	3.75	8.68	11.92	13.19	14
4d(*m*-)	3.83	8.43	11.67	12.86	15
4d(*p*-)	3.86	8.37	11.70	12.83	15
4e(*o*-)	3.86	8.52	11.90	12.80	15
4e(*m*-)	3.80	8.59	11.35	12.72	14
4e(*p*-)	3.80	8.38	11.38	12.80	14
4f(*o*-)	3.78	8.76	12.60	13.16	12
4f(*m*-)	3.78	8.57	11.56	13.05	12.5
4f(*p*-)	3.22	8.58	11.39	12.83	12
4g	3.88	8.61	13.30	12.63	15
4h	3.83	8.51	12.0	12.69	13.75
4i	3.86	8.48	12.15	12.75	13.75
4j	3.81	8.51	12.23	7.46	15
4k	3.80	8.30	11.75	12.80	15

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ and DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker WH-90/DS (90 MHz) instrument. Homogeneity of the compounds synthesized was monitored by TLC on Silufol plates with the solvent systems: 9:1 chloroform–methanol (compounds **4a,d** (*o*-), **4e** (*o-, m*-), **4f** (*o-, m-, p*-), **4i-k**), chloroform (compounds **4b** (*o-, m-, p*-)), 4:1:1 butanol–glacial acetic acid–water (compounds **4d** (*m-, p*-), **4h**), 35:35:7:23 butanol–acetone–glacial acetic acid–water (compound **4g**), ethyl acetate (compounds **4c** (*o-, m-, p*-), **4e** (*p*-)).

N-Arylaminomethyleneisopropyildenmalonates (3a-k) were prepared analogously to N-hetaryl-aminomethyleneisopropylidenemalonates [2]. Compounds **3b** (*o-, m-, p*-), **3c** (*m-, p*-), **3e** (*o-, m-, p*-), **3f** (*m*-), and **3i-k** were chromatographically homogeneous without recrystallization, whereas recrystallization was necessary for compounds **3a**,**c** (*o*-), **3d** (*o-, m-, p*-), **3f** (*o-, p*-), **3g** and **h**.

Monomethyl Esters of N-Arylaminomethylenemalonic Acids (4a-k). An equimolar quantity of the aminomethylenemalonates **3a-k** was added to a solution of potassium hydroxide (2 mmol, 4 mmol for compounds **3f** (*o-, m-, p*-)) in methanol (20 ml). In the cases of compounds **3b** (*o-, m-, p*-), **3c** (*o*-), **3d** (*m*-), **3e** (*o-, m-, p*-), **3f** (*o-, m-, p*-), **3g-k** the reaction mixture was stirred at room temperature for 3h, then kept at the same temperature for 12 h. In the case of compounds **3a**,**c** (*m-, p*-), **3d** (*o-, p*-) and **3j** the mixture was boiled for 2h. The potassium salts of compounds **4c** (*m-, p*-), **4d** (*p*-), **4f** (*o-, p*-), and **4k** were filtered off, whereas the methanol solutions containing the potassium salts of compounds **4a**,**b** (*o-, m-, p*-), **4c** (*o*-), **4d** (*o-, m*-), **4e** (*o-, m-, p*-) and **4g-j** were evaporated. The residues after filtration and evaporation were dissolved in water and acidified with 1N hydrochloric acid. The precipitates of the monomethyl esters **4a**,**b** (*o-, m-, p*-), **4c** (*o-, m-, p*-), **4d** (*o-, m*-), **4e** (*p*-), **4f** (*o-, m-, p*-), **4g-i** and **4k** were filtered off, while the acid solutions containing compounds **4d** (*p*-), **4e** (*o-, m*-), and **4j** were extracted with ethyl acetate, the extract was dried over $MgSO_4$, filtered, and the

ethyl acetate was evaporated. Compounds **4b** (*o-, m-, p-*), **4c** (*p-*), **4i-k** were chromatographically homogeneous without recrystallization, while compounds **4a**,**c** (*o-, m-*), **4d** (*o-, m-, p-*), **4e** (*o-, m-, p-*), **4f** (*o-, m-, p-*), **4g,h** were chromatographically homogeneous after recrystallization from the solvents noted in Table 3.

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