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SHORT COMMUNICATIONS

Michael Addition of *N,N′*-Dibenzylmalonamide to *N*-Aryl(alkyl)crotonamides

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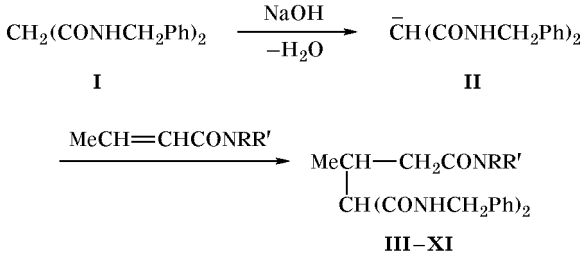
We previously [1] developed preparative procedures for synthesizing promising pharmaceuticals, alkyl, amino, heteryl, and ylidene derivatives of *N*,*N′*-dibenzylmalonamide (**I**). With the goal of obtaining new biologically active substances on the basis of amide **I** we have examined its reactions with crotonamides. We expected that a combination of two pharmacophoric moieties in a single molecule with simultaneous increase of the number of amide groups should lead to enhancement of biological activity [2].

We have found that *N*,*N′*-dibenzylmalonamide (**I**) adds to *N*-aryl(alkyl)crotonamides [3] according to Michael, affording *N*,*N′*,*N″*-trisubstituted 2-methyl-1,1,3-propanetricarboxylic acid amides **III**–**XI** in high yields (Table 1, Scheme 1).

The active intermediate, carbanion **II**, was generated by the action of alkali under heterogeneous conditions [4, 5]. The best yields of the products were obtained in anhydrous dimethylformamide in the presence of an equimolar amount of crystalline sodium hydroxide as catalyst.

Scheme 1.



III–**X**, R = H; **III**, R′ = 4-$CH_3C_6H_4$; **IV**, R′ = 3-$CH_3C_6H_4$; **V**, R′ = 2-$CH_3C_6H_4$; **VI**, R′ = 4-$CH_3OC_6H_4$; **VII**, R′ = 3-$CH_3OC_6H_4$; **VIII**, R′ = 2-$CH_3OC_6H_4$; **IX**, R′ = 1-naphthyl; **X**, R′ = CH_2Ph; **XI** R = R′ = Ph.

Table 1. Yields, melting points, R_f values, and elemental analyses of N-substituted 2-methyl-1,1,3-propanetricarboxamides **III**–**XI**

Comp. no.	Yield, %	mp, °C	R_f[a]	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
III	99	243–245	0.58	73.67	6.85	9.35	$C_{28}H_{31}N_3O_3$	73.49	6.83	9.18
IV	63	245–247	0.60	73.54	6.84	9.36	$C_{28}H_{31}N_3O_3$	73.49	6.83	9.18
V	53	255–257	0.56	73.60	6.85	9.29	$C_{28}H_{31}N_3O_3$	73.49	6.83	9.18
VI	57	232–234	0.54	71.30	6.57	8.95	$C_{28}H_{31}N_3O_4$	71.00	6.59	8.87
VII	62	245–246	0.50	71.21	6.58	8.99	$C_{28}H_{31}N_3O_4$	71.00	6.59	8.87
VIII	64	240–242	0.60	71.28	6.59	8.97	$C_{28}H_{31}N_3O_4$	71.00	6.59	8.87
IX	66	250–252	0.50	75.69	6.14	8.78	$C_{31}H_{31}N_3O_3$	75.58	6.13	8.53
X	81	236–238	0.55	73.64	6.83	9.40	$C_{28}H_{31}N_3O_3$	73.49	6.82	9.18
XI	92	242–244	0.58	76.43	6.41	8.26	$C_{33}H_{33}N_3O_4$	76.27	6.40	8.08

[a] Silufol UV-254 plates; 1-butanol–acetic acid–water, 10 : 40 : 1.

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Table 2. IR and ^{1}H NMR spectra of N-substituted 2-methyl-1,1,3-propanetricarboxamides **III**–**XI**

Comp. no.	IR spectrum, ν(C=O), cm^{-1}	^{1}H NMR spectrum, δ, ppm							
		NHAr	NHC**H**$_2$Ph	CH$_2$**Ph**	C**H**$_2$Ph	COCHCO	C**H**CH$_3$	CH$_2$	CH$_3$
III	1666, 1605	10.22 s	8.23 t	7.26 s	4.22 d	3.11 d	2.58 m	2.21 m	0.99 m
IV	1692, 1661	9.89 s	8.13 t	7.25 s	4.24 d	3.08 d	2.48 m	2.31 m	0.97 m
V	1668, 1632	9.91 s	8.41 t	7.25 s	4.20 d	3.22 d	2.52 m	2.27 m	0.93 m
VI	1668, 1652	10.11 s	8.40 t	7.28 s	4.28 d	3.12 d	2.60 m	2.24 m	0.96 m
VII[a]	1658, 1632	9.67 s	8.41 t	7.25 s	4.30 d	3.14 d	2.65 m	2.37 m	0.98 m
VIII[b]	1660, 1625	9.81 s	8.32 t	7.22 s	4.22 d	3.15 d	2.44 m	2.12 m	0.98 m
IX[c]	1662, 1610	9.94 s	8.14 t	7.26 s	4.20 d	3.11 d	2.58 m	2.20 m	0.97 m
X	1664, 1640	10.08 s	8.27 t	7.25 s	4.26 d	3.09 d	2.61 m	2.31 m	0.99 m
XI	1658, 1626	10.14 s	8.30 t	7.26 s	4.20 d	3.17 d	2.59 m	2.33 m	0.96 m

[a] δ(MeO) 3.72 ppm, s. [b] δ(MeO) 3.42 ppm, s. [c] δ(MeO) 3.54 ppm, s.

The structure of the products was confirmed by elemental analysis and spectral methods (Table 2) [6]. Unlike initial crotonamides [2], the IR spectra of Michael addition products **III**–**XI** lack C=C absorption band at 1590–1606 cm^{-1}. The ^{1}H NMR spectra of triamides **III**–**XI** contained signals from the *N*-substituent in the initial crotonamide [2], including those from aromatic protons, whereas no signals from olefinic protons were present. The *N*,*N*′-dibenzylmalonamide fragment gives rise to aromatic proton signals and signals from the amide and methylene groups (a singlet at δ 7.22–7.28 ppm, a triplet at δ 8.13–8.41 ppm, and a doublet at 4.20–4.30 ppm, respectively); also, a signal from the malonic CH group was present at δ 3.08–3.22 ppm (Table 2).

Compounds **III**–**XI** were found to exhibit pronounced anticonvulsant activity and moderate toxicity.

***N*^{1},*N*$^{1'}$-Dibenzyl-*N*^{3}-substituted 2-methyl-1,1,3-propanetricarboxamides III–XI.** To 1.41 g (5 mmol) of dibenzylamide **I** we added 5 mmol of appropriate N-substituted crotonamide and 10 ml of DMF, the mixture was heated to 40°C, and 0.2 g (5 mmol) of powdered sodium hydroxide was added. The mixture was vigorously stirred for 10 h at 80°C, poured into water, and acidified with hydrochloric acid to pH 5. The precipitate was filtered off, washed with water, dried, and recrystallized from a mixture of 2-propanol with DMF.

The IR spectra were recorded on a Specord M-80 spectrophotometer in KBr. The ^{1}H NMR spectra were measured on a Varian WXR-400 instrument operating at 400 MHz; a mixture of DMSO-d_6 with CCl_4 was used as solvent, and TMS, as internal reference.

REFERENCES

1. Bezuglyi, P.A., Georgiyants, V.A., and Rakhimova, M.V., *Russ. J. Org. Chem.*, 2000, vol. 36, no. 3, pp. 396–398.
2. Bezuglii, P.O., Georgiyants, V.A., Perekhoda, L.O., Garna, N.V., and Sich, I.A., *Visn. Farm.*, 2000, no. 3, pp. 7–10.
3. Georgiyants, V.A., *Naukovi osnovi rozrobki likars'kikh preparativ: Materiali naukovoi sesii viddilennya NAN Ukraini* (Scientific Principles of Drug Design: Proc. Scientific Session of National Academy of Sciences of Ukraine), Kharkiv: Osnova, 1998, pp. 307–310.
4. Sykes, P., *A Guidebook to Mechanism in Organic Chemistry*, Harlow, Essex, England: Longman, 1986, 6th ed. Translated under the title *Mekhanizmy reaktsii v organicheskoi khimii*, Moscow: Khimiya, 1991, p. 222.
5. Mackie, R.K. and Smith, D.M., *Guidebook to Organic Synthesis*, London: Longman, 1982. Translated under the title *Putevoditel' po organicheskomu sintezu*, Moscow: Mir, 1985, p. 76.
6. Brown, D.W., Floyd, A.J., and Sainsbury, M., *Organic Spectroscopy*, Chichester: Wiley, 1988. Translated under the title *Spektroskopiya organicheskikh veshchestv*, Moscow: Mir, 1992, p. 66.