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Synthesis, Physicochemical and Pharmacological Properties of N,N',N'', N'''-Substituted Amides of 1,1,3,3-Propanetetracarboxylic Acid

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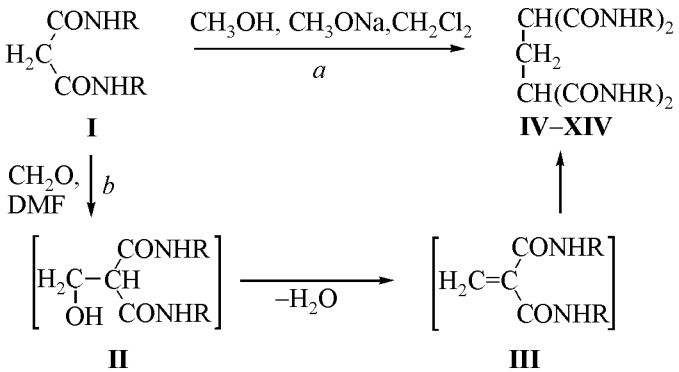
Abstract—By condensation of symmetrical malonic acid diamides with dichloromethane (method *a*) and with paraform (method b) N,N',N'',N'''-substituted amides of 1,1,3,3-propanetetracarboxylic acid were synthesized. Better yields of the target products (68–80%) and the use of less toxic reagents indicate that method *b* is more feasible. The primary pharmacological screening revealed that the compounds obtained possess pronounced anticonvulsant activity at moderate toxicity.

The search for new anticonvulsant preparations is carried out among wide range of organic compounds. The high anticonvulsant activity of heterocyclic compounds prepared from malonic acid (Phenobarbital, Gluferal, Fall-Lepsin, Didepil, Pagluferal) [1] stimulated our search for anticonvulsants among its acyclic derivatives. Published data suggest that the presence in a molecule of an aromatic fragment, especially if it contains electron-donor substituents, results in significantly increased protective activity at convulsions initiated by chemical agents [2]. The other publications indicate that this effect is favored by the presence of an amide group in a molecule [3].

In earlier publications on the synthesis [4, 5] and investigation of the biological activity [6, 7] of symmetrical malonic acid dianilides was mentioned a high pharmacological potential of this class compounds, in particular, with respect to the central nervous system. It was also established formerly that the anticonvulsant activity in the series of malonic acid amides is favored by increased number of aryl(alkyl)amide moieties in the molecule provided in the methylene group at least one free proton is conserved required for to compounds synthesized to take part in biochemical processes [8].

Aiming at increasing the number of amide moieties we synthesized amides of 1,1,3,3-propanetetracarboxylic acid by two procedures.



R = H (**IV**), $CH_2C_6H_5$ (**V**), 4-$CH_3OC_6H_4$ (**VI**), 4-$CH_3C_6H_4$ (**VII**), 2,4-$(CH_3)_2C_6H_3$ (**VIII**), 3,4-$(CH_3)_2C_6H_3$ (**IX**), 2,4,6-$Br_3C_6H_2$ (**X**), 4-$COOHC_6H_4$ (**XI**).

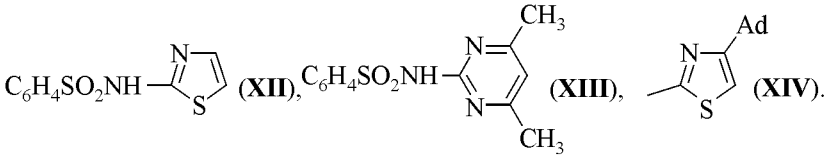


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Table 1. Yields, physical constants, and elemental analyses of substituted amides of 1,1,3,3-propanetetracarboxylic acid **IV**–**XIV**

Compd. no.	Yield, %		mp, °C	R_f[a]	Found, %			Formula	Calculated, %		
	a	b			C	H	N		C	H	N
IV	35	75	263–265	0.56	38.68	5.40	25.61	C7H12N4O4	38.89	5.59	25.88
V	38	68	256–258	0.77	72.63	6.47	9.53	C35H36N4O4	72.89	6.30	9.71
VI	41	80	284–285	0.58	56.41	5.82	8.54	C35H36N4O8	56.6	5.66	8.70
VII	40	74	284–286	0.60	72.60	6.20	9.54	C35H36N4O4	72.81	6.29	9.72
VIII	38	73	254–256	0.59	74.21	6.84	8.75	C39H44N4O4	74.01	7.01	8.82
IX	39	70	253–255	0.58	74.19	7.17	8.97	C39H44N4O4	74.01	7.01	8.82
X	36	72	280–282	0.54	25.51	1.27	3.97	C31H16N4O4Br12	25.32	1.09	3.81
XI	35	71	253–255	0.60	56.21	3.41	15.07	C35H24N8O12	56.13	3.22	14.91
XII	38	72	240–242	0.56	43.91	3.00	14.22	C43H36N12O12S8	44.13	3.12	14.31
XIII	37	73	258–260	0.57	52.48	4.54	17.91	C55H56N16O12S4	52.31	4.42	17.73
XIV	35	70	230–232	0.60	65.18	7.17	10.38	C59H76N8O4S4	65.02	7.03	10.21

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

Table 2. Spectral characteristics of compounds **IV**–**XIV**

Compd. no.	IR spectrum ν(C=O), cm^{-1}	^{1}H NMR spectrum, δ, ppm				
		H arom, m	NHCO, 4H	CH_2, 2H	CH, 2H	Proton signals of other functional groups
IV	1646, 1605	–	9.45 s (8H, NH_2)	4.40 t	3.11 t	–
V	1684, 1621	7.20–7.10 (20H)	9.35 t	4.25 t	3.18 t	–
VI	1640, 1628	7.18–6.75 (12H)	9.68 s	4.45 t	3.14 t	2.20 m (12H, OCH_3)
VII	1633, 1612	7.10–6.98 (12H)	9.76 s	4.28 t	3.12 t	2.24 m (12H, CH_3)
VIII	1658, 1629	6.57–6.30 (12H)	9.29 s	4.27 t	3.13 t	2.33 m (24H, CH_3)
IX	1680, 1617	7.10–7.00 (12H)	9.85 s	4.40 t	3.35 t	2.19 m (24H, CH_3)
X	1662, 1626	7.20–7.05 (8H)	9.50 s	4.30 t	3.15 t	–
XI	1664, 1630	7.85–6.75 (12H)	9.80 s	4.40 t	3.20 t	13.65 s (1H, COOH)
XII	1655, 1618	7.25–7.10 (16H)	9.30 s	4.20 t	3.17 t	–
XIII	1670, 1610	7.85–7.75 (12H)	9.50 s	4.40 t	3.00 t	2.20 m(24H, CH_3), 10.5 m (4H, NH–Ar)
XIV	1653, 1620	–	9.75 s	4.36 t	3.16 t	–

N,N',N'',N'''-substituted amides of propanetetracarboxylic acid were obtained by condensation of two molecules of malonic acid symmetrical amides with excess dichloromethane in anhydrous methanol in the presence of sodium methylate (procedure *a*). The yields of the target products were about 35–40%. Taking into account the toxicity and volatility of dichloromethane we guessed that it would be appropriate to synthesize the malonic acid tetrabenzylamide and a series of its analogs along another method: by condensation of malonic acid symmetrical amides with paraform (procedure *b*).

The latter is two-stage process [9]. The firs stage of reaction proceeds similarly to Knoevenagel condensation. Symmetrical dianilides **I** where the methylene group is bonded to two electron-withdrawing substituents play in this reaction the role of methylene component, and paraform acts as a carbonyl component. The acidity of the hydrogen in the methane group of compound **II** is very high, therefore the water molecule elimination occurs easily affording a crotonic type compound **III** [9].

Compound **III** further reacts with one more dianilide molecule by a process similar to Michael

reaction (reaction with unsaturated compounds). This specific behavior of paraform is apparently due to the higher accessibility of the methylene group in the ylidene derivative **III** for the carbanion formed from the second dianilide molecule. We studied the effect of the reaction medium, base catalyst, temperature, and reaction duration on the rate of the corresponding reaction. Sufficient yields were obtained in reaction carried out in DMF solution. The presence of base catalysts did not affect significantly the reaction rate. The yield was not increased at higher temperature because of tarring, but at low temperature yields were reduced.

The mixed sample of compounds prepared by procedures *a* and *b* melted without depression of the melting point.

Sufficiently high yields of target products obtained by procedure *b* (Table 1) show its advantages and promising features for the synthesis of potential medicines. The structures, composition, and purity of compounds synthesized were confirmed by spectral methods (Table 2) and elemental analyses.

IR spectra of all compounds obtained contain a band of stretching vibrations belonging to carbonyl group (amide-**I**).

^{1}H NMR spectra of compounds synthesized contain a general set of proton signals: The singlet in the region 9.29–9.80 ppm corresponds to the amide group proton of the anilide moiety, the multiplet at 6.75–7.85 ppm belongs to aromatic protons (compounds **V**–**XIV**), the triplet at 4.20–4.45 ppm corresponds to the free methylene group, and the triplet at 3.00–3.35 ppm arises because of the presence of methine group proton (Table 2).

Amides of 1.1..3-propanetetracarboxylic acid obtained were subjected to primary pharmacological screening with respect to anticonvulsant activity. It was established that almost all compounds synthesized possessed a pronounced anticonvulsant activity combined with low toxicity. The anticonvulsant activity of the compounds was compared with that of the drugs most often used in medical practice to stop the convulsions, namely, with Phenobarbital and Diphenin. All compounds prevented convulsions induced by Corazol and electroshock. The pharmacological activity was found to depend on the structure of the respective molecule.

EXPERIMENTAL

IR spectra of compounds obtained were recorded on spectrometer Specord M-80 from samples pelletized with KBr, concentration of compound studied 1%. ^{1}H NMR spectra were registered on Varian WXR-400 instrument in DMSO-*d*6 + CCl_4 at operating frequency 100 MHz, chemical shifts were presented in the δ scale from TMS as internal reference.

N,N′,N″,N‴-substituted tetraamides of 1,1,3,3-propanetetracarboxylic (IV–XIV). *General procedure.* (a) In 70 ml of anhydrous methanol was dissolved 0.46 g (2 mmol) of metal sodium. To the solution was added 2 mmol of symmetrical malonic acid diamide, and the mixture was heated for 1 h. Then to the reaction mixture was added several crystals of phenolphthalein and 5 ml of dichloromethane. The reaction mixture was heated at reflux till the solution became colorless (38 h). On cooling the excess dichloromethane was distilled off, the reaction mixture was poured into water acidified to pH 5 with hydrochloric acid. The separated precipitate was filtered off and recrystallized from a mixture of 2-propanol and DMF. Melting points and ^{1}H NMR spectra of compounds synthesized are listed in Tables 1, 2.

(b) To a solution of 2 mmol of symmetrical malonic acid diamide in 10 ml of DMF was added 0.06 g (2 mmol) of paraform, and the mixture was heated at reflux for 18 h, the reaction mixture was poured into water acidified to pH 5 with hydrochloric acid. The separated precipitate was filtered off and recrystallized from a mixture of 2-propanol and DMF.

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