CCA-451

615.778.2
Note

N^4-Acylsulphonamides. II. Derivatives of 4-(α-Methyl-α-ethylsuccinimido) and 4-(α-Ethyl-α-phenylglutarimido) Benzenesulphamide*

A. Junašević-Holjevac and B. Glunčić

Research Department »Pliva«, Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia

Received September 16, 1966

In continuation of our investigation[1] into the relationship between structure and physiological activity in substances containing a moiety derived from the established pharmacologically active acid amides and a group derived from the therapeutically employed sulphonamides[2], we have now prepared a series of such compounds related to the well-known sedative α-ethyl-α-phenylglutarimide[3] and the antiepileptic α-methyl-α-ethylsuccinimide[4], respectively.

The preparation of 4-(α-metyl-α-ethylsuccinimido) benzenesulphamide and its N^1-substituted derivatives (I—VIII, Table I) was performed by condensation in pyridine of α-methyl-α-ethylsuccinic anhydride with sulphanylamide or a corresponding sulphonamide, respectively, according to the method decribed by Miller *et al.*[5] for the preparation of 4-succinimido-benzenesulphonamide.

The same procedure was applied to the attempted preparation of 4-(α-ethyl--α-phenyl glutarimido) benzene-sulphamides starting with α-ethyl-α-phenylglutaric anhydride and the same suplhonamides. However, in these cases, α-ethyl-α-phenylglutaric anhydride reacted unexpectedly to give the corresponding anilic acids instead of the imides. The same results were also obtained for the reaction of α-methyl-α-ethylsuccinic anhydride with certain sulphonamides, *i. e.* with 5-sulphanilylamido-3,4-dimethyl-iso-öxazole, 2-sulphanilylamido-4,6-dimethyl-pyrimidyne and 4-sulphanilylamido-2,4-dimethoxy-pyrimidyne, respectively.

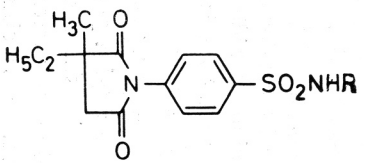
We intend in our future experiments to determine which of the two carboxylic groups is engaged in the formation of the amide bond of these anilic acids. Newertheless, the characteristic data for both groups of the anilic acids are presented in Tables II and III. Most of these compounds readily react with acetyl chloride undergoing cyclization to the imides IX—XI (Table I), and XXVII—XXXII (Table IV), respectively.

Compounds I—XI showed no anticonvulsive effect when tested on mice previously treated with Metrazole, nor any bacteriostatic activity against *St. aureus, B. subtilis* and *E. coli in vitro*.

---

* Taken from the thesis submitted by A. Junašević-Holjevac, in partial fulfilment of the requirements for the degree of Doctor of Chemistry at the University of Zagreb.

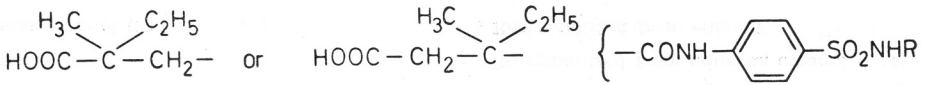
TABLE I



Compound	R	Yield of crude prod. %	m. p. °C	Formula	Calc'd.			Found		
					C	H	N	C	H	N
I	H	49.7	172[a]	$C_{13}H_{16}N_2O_4S$	52.68	5.44	9.45	52.50	5.23	9.67
II	2-thiazolyl	84.1	211[b]	$C_{16}H_{17}N_3O_4S_2$	50.64	4.51	11.08	50.34	4.33	11.21
III	1-phenyl-5-pyrazolyl	61.0	158[b]	$C_{22}H_{22}N_4O_4S$	60.26	5.05	12.78	60.52	4.98	12.70
IV	5-methyl-3-iso-öxazolyl	100.0	203[c]	$C_{17}H_{19}N_3O_5S$	54.10	5.07	11.13	53.96	5.01	11.20
V	2-pyrimidinyl	76.4	260[b]	$C_{17}H_{18}N_4O_4S$	54.53	4.84	14.97	54.45	4.83	15.05
VI	4-methyl-2-pyrimidinyl	60.8	209[c]	$C_{18}H_{20}N_4O_4S$	55.66	5.19	14.43	55.75	5.05	14.31
VII	6-methoxy-3-pyridazinyl	78.8	176[b]	$C_{18}H_{20}N_4O_5S$	53.45	4.98	13.85	53.38	4.96	13.70
VIII	5-methoxy-2-pyrimidinyl	83.4	243[b]	$C_{18}H_{20}N_4O_5S$	53.45	4.98	13.85	53.45	4.76	14.09
IX	3,4-dimethyl-5-iso-öxazolyl	73.0	170[c]	$C_{18}H_{21}N_3O_5S$	55.23	5.40	10.74	55.00	5.20	10.71
X	4,6-dimethyl-2-pyrimidinyl	90.0	187[b]	$C_{19}H_{22}N_4O_4S$	56.70	5.51	13.92	56.98	5.58	13.81
XI	2,6-dimethoxy-4-pyrimidinyl	90.6	191[b]	$C_{19}H_{22}N_4O_6S$	52.52	5.10	12.90	52.42	5.05	12.83

[a] Recrystallized from aqueous dimethylformamide (1 : 1)
[b] Recrystallized from methanol
[c] Recrystallized from ethanol

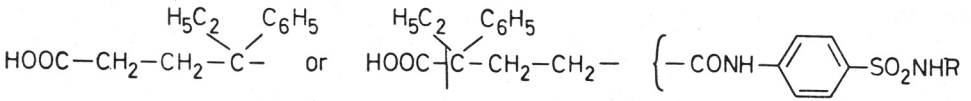
TABLE II



Compound	R	Yield of crude prod. %	m. p. °C	Formula	Calc'd.			Found		
					C	H	N	C	H	N
XII	3,4-dimethyl-5-iso-öxazolyl	71.0	189[a]	$C_{18}H_{23}N_3O_6S$	52.80	5.66	10.26	52.61	5.40	10.54
XIII	4,6-dimethyl-2-pyrimidinyl	72.5	213[b]	$C_{19}H_{24}N_4O_5S$	54.27	5.75	13.33	54.27	5.60	12.90
XIV	2,6-dimethoxy-4-pyrimidinyl	59.4	210[a]	$C_{19}H_{24}N_4O_7S$	50.42	5.34	12.38	50.18	5.07	12.58

[a] Recrystallized from ethanol
[b] Recrystallized from methanol

TABLE III



Compound	R	Yield of crude prod. %	m. p. °C	Formula	Calc'd.			Found		
					C	H	N	C	H	N
XV	2-thiazolyl	91.0	233[b]	$C_{22}H_{23}N_3O_5S_2$	55.79	4.89	8.87	55.50	4.60	9.13
XVI	H	37.2	201[a]	$C_{19}H_{22}N_2O_5S$	58.45	5.81	7.49	58.39	5.56	7.22
XVII	1-phenyl-5-pyrazolyl	58.8	115[c]	$C_{28}H_{28}N_4O_5S$	63.14	5.29	10.52	63.19	5.15	10.26
XVIII	3,4-dimethyl-5-iso-öxazolyl	98.4	146[d]	$C_{24}H_{27}N_3O_6S$	59.37	5.60	8.65	59.32	5.71	8.86
XIX	5-methyl-3-iso-öxazolyl	83.0	204[d]	$C_{23}H_{25}N_3O_6S$	58.58	5.34	8.91	58.69	5.16	9.10
XX	2-pyrimidinyl	62.0	230[b]	$C_{23}H_{22}N_4O_5S$	58.96	5.16	11.96	58.88	4.99	11.65
XXI	4-methyl-2-pyrimidinyl	73.7	125[c]	$C_{24}H_{26}N_4O_5S$	59.73	5.43	11.61	59.51	5.59	11.54
XXII	4,6-dimethyl-2-pyrimidinyl	88.7	210[e]	$C_{25}H_{28}N_4O_5S$	60.47	5.68	11.28	60.20	5.41	10.99
XXIII	6-methoxy-3-pyridazinyl	92.2	226[e]	$C_{24}H_{26}N_4O_6S$	57.82	5.25	11.24	57.87	5.08	11.10
XXIV	5-methoxy-2-pyrimidinyl	90.0	130[e]	$C_{24}H_{26}N_4O_6S$	57.82	5.25	11.24	57.61	5.47	11.08
XXV	2,6-dimethoxy-4-pyrimidinyl	37.9	209[d]	$C_{25}H_{28}N_4O_7S$	56.81	5.34	10.60	56.64	5.18	10.73
XXVI*	guanyl	80.0	153[f]	$C_{20}H_{24}N_4O_5S$	55.54	5.59	12.96	55.41	5.48	12.75

[a] Recrystallized from ethanol (1 : 1)

[b] Recrystallized from methanol

[c] Recrystallized from aqueous ethanol (1 : 3)

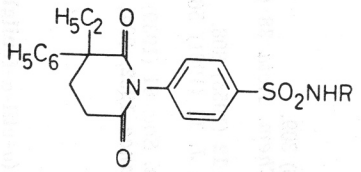
[d] Recrystallized from aqueous ethanol (1 : 2.5)

[e] Recrystallized from aqueous ethanol (1 : 2)

[f] Recrystallized from ethanol

* We are obliged to Mrs K. Grba for the preparation.

TABLE IV



Compound	R	Yield of crude prod. %	m. p. °C	Formula	Calc'd.			Found		
					C	H	N	C	H	N
XXVII	2-thiazolyl	89.0	206[a]	$C_{22}H_{21}N_3O_4S_2$	58.00	4.64	9.23	57.79	4.36	9.33
XXVIII	1-phenyl-5-pyrazolyl	82.6	184[a]	$C_{28}H_{26}N_4O_4S$	65.35	5.09	10.89	65.18	5.28	10.81
XXIX	2-pyrimidinyl	89.0	247[a]	$C_{23}H_{22}N_4O_4S$	61.32	4.92	12.44	61.18	4.89	12.14
XXX	4-methyl-2-pyrimidinyl	56.0	233[a]	$C_{24}H_{24}N_4O_4S$	62.05	5.20	12.06	61.92	4.98	11.83
XXXI	6-methoxy-3-pyridazinyl	94.0	180[a]	$C_{24}H_{24}N_4O_5S$	59.98	5.03	11.66	59.72	4.80	11.76
XXXII	5-methoxy-2-pyrimidinyl	89.6	255[b]	$C_{24}H_{24}N_4O_5S$	59.98	5.03	11.66	60.04	5.28	11.87

[a] Recrystallized from methanol, [b] Recrystallized from aqueous ethanol (1 : 2)

EXPERIMENTAL

All melting points are uncorrected. Samples of pure comercial N^1-substituted sulphonamides were used as starting materials. α-Methyl-α-ethylsuccinic and α-ethyl-α-phenylglutaric anhydride were prepared (by a known method) from the corresponding acid and acetic anhydride.

General Method for the Preparation of N^4-acyl Sulphonamides

A mixture of 0.01 mole of α-methyl-α-ethylsuccinic or α-ethyl-α-phenylglutaric anhydride, 0.01 mole of the corresponding sulphonamide and 50—250 ml. of pyridine was refluxed for 2 hrs., the solvent evaporated *in vacuo*, and the residue triturated with cold diluted hydrochloric acid (3 : 10). The separated solid was collected by filtration, and washed with water until neutral.

By this method, crude imido derivatives I—VIII (Table I), and anilic acids XII—XIV (Table II), XV—XXVI (Table III) were prepared.

Using the method described by Legagneur and Neven[6], a mixture of 0.01 mole of an anilic acid and 40—50 ml. of acetyl chloride was refluxed for 0.5 hr., cooled and poured into 400 g. of crushed ice. The separated solid was filtered off, and washed with water and saturated bicarbonate solution.

By this method, crude imido derivatives IX—XI (Table I) and XX—XXXII (Table IV) were prepared.

Acknowledgments. The authors wish to express their gratitude to Mr. E. Guštak for his keen interest in this work.

REFERENCES

1. V. Bedenko and B. Glunčić, *Croat. Chem. Acta* **38** (1966) 309.
2. A. Junašević-Holjevac and B. Glunčić, *Croat. Chem. Acta* **38** (1966) 123.
3. K. A. Jochheim and I. Geberding, *Med. Monatsschf.* **12** (1955) 808.
4. K. W. Heathfield and E. C. Jewesbury, *Brit. Med. J.* **11** (1961) 565, cf. *Subsidia Medica* **14** (1962) 17.
5. E. Miller, H. J. Rock, and M. L. Moore, *J. Am. Chem. Soc.* **61** (1939) 1198.
6. F. S. Legagneur and C. Neven, *Bull. Soc. Chim. France* **1952**, 994; *ibid.* **1953**, 70.

IZVOD

Acilsulfonamidi. II. Derivati 4-(α-metil-α-etilsukcinimido) i 4-(α-etil-α-fenilglutarimido) benzensulfamida

A. Junašević-Holjevac i B. Glunčić

Kondenzacijom anhidrida α-metil-α-etil jantarne i α-etil-α-fenil glutarne kiseline s poznatim sulfonamidima dobiveni su ciklički imidi I—VIII (Tabela I) i anilne kiseline XII—XV (Tabela II), kao i XV—XXIV (Tabela III). Zagrijavanjem s acetilkloridom neke od ovih anilnih kiselina su prevedene u cikličke imide IX—XI (Tabela I) i XXVII—XXXII (Tabela IV).

Preliminarni farmakološki pokusi su pokazali da spojevi I—XI ne pokazuju aktivnost protiv konvulzija izazvanih metrazolom na miševima, kao ni antibakterijalnu aktivnost *in vitro* protiv *St. aureus, B. subtilis,* i *E. coli.*

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 16. rujna, 1966.