Experimental Section[a]

Condensations with Indole-3-acetic Acid Hydrazide.—Equimolar quantities of indole-3-acetic acid hydrazide and the appropriate carbonyl compounds were dissolved in a minimum of EtOH and heated on a steam bath for 30 min. After cooling, and in some cases standing for several days the products described in Table I were obtained by filtration.

Condensations with Amines.—In a similar manner equimolar quantities of isatin, indole-3-carboxaldehyde, or 1-benzylindole-3-carboxaldehyde were allowed to react in EtOH with the appropriate amines to give the compounds in Table II.

Indole-3-acetic Acid Hydrazide and Succinic Anhydride.—A mixture of 1.89 g (0.01 mole) of indole-3-acetic acid hydrazide and 1.00 g (0.01 mole) of succinic anhydride in Me_2CO (5 ml) was refluxed for 15 min and allowed to stand overnight at room temperature. Filtration gave 2.30 g (80%) of I, mp 203–204° from EtOH; ir(KBr): 3400, 3240, 2945, 1700 (broad), 1610 cm^{-1}. *Anal.* ($C_{14}H_{15}N_3O_4$): C, H.

Tolualdehyde Mustard and 3-Aminocarbazole.—A mixture of 1.82 g (0.01 mole) of 3-aminocarbazole and 2.60 g (0.01 mole) of 4-[bis-(2-chloroethyl)amino]-*o*-tolualdehyde was refluxed in EtOH to give 3.22 g (76%) of imine, mp 188° from EtOH. *Anal.* ($C_{24}H_{23}Cl_2N_3$): N.

[a] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points were taken in capillaries and are corrected.

Studies of the Chemistry of Azole Derivatives. XII. Possible Anticonvulsant Thiazolo[3,2-*a*]benzimidazoles

J. M. SINGH

Defence Science Laboratory, Delhi-6, India

Received February 13, 1970

In view of the potent pharmacological activity of a large number of heterocyclic thioureas[1-3] additional thioureidothiazolo[3,2-*a*]benzimidazoles were synthesized. These compounds have been tested for anticonvulsant activity (Table I).

Experimental Section

2-Aminothiazolo[3,2-*a*]benzimidazol-3-(2*H*)-one.—A solution of thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one[4] (5 g) in AcOH (20 ml) was slowly added at 0° to a solution of PhN_2Cl with stirring. The mixture was kept for 1 hr at (0–5°) and the product obtained was crystallized from EtOH. The azo compound (5 g) was dissolved in hot EtOH (25 ml). A solution of $Na_2S_2O_4$ (25 g) in H_2O (50 ml) was added and the mixture was refluxed for 30 min and then cooled. The amino compound obtained was recrystallized from EtOH, yield 57%, mp 185°. *Anal.* ($C_9H_7N_3S$): N,S.

Synthesis of Thioureas.—Equimolecular quantities of 2-aminothiazolo[3,2-*a*]benzimidazol-3(2*H*)-one and an aryl isothiocyanate were refluxed in abs EtOH for 5 hr and cooled. The precipitated thioureas were crystalized (C_4H_9). The hydrochlorides were prepared in Et_2O solution.

Acknowledgment. The author is thankful to Dr. Kartar Singh, Director, Defence Science Laboratory for encouragement and Dr. H. K. Acharya for providing facilities.

(1) Paper XI: J. M. Singh, *J. Med. Chem.*, **12**, 962 (1969).

A Reinvestigation of the Reaction of Monosodium Urea with Various Substituted Pyrazinecarboxylate Esters

J. WILLIAM HANIFIN, ROSEMARY CAPEZZI, AND ELLIOTT COHEN

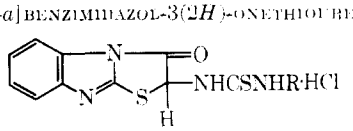
Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received March 30, 1970

We have reinvestigated the reaction of monosodium urea with methyl 3,5-diamino-6-chloropyrazinecarboxylate[1] as well as the 5-methylamino analog and found that a small amount of the desired *N*-carbamoylpyrazinecarboxamide is produced in each case. The products were isolated by liquid–liquid partition chromatography (llpc) and shown to be the desired compounds by comparison of ir, mass spectrum, tlc,

TABLE I

2-AMINOTHIAZOLO[3,2-*a*]BENZIMIDAZOL-3(2*H*)-ONETHIOUREA HYDROCHLORIDES



No.	R	Formula	Mp, °C	Yield, %	Activity	LD_{50} (toxicity)
1	Ph	$C_{16}H_{13}ClN_4S_2$	220–221	60	++	200
2	*o*-MePh	$C_{17}H_{15}ClN_4S_2$	195–197	65	++	260
3	*p*-MePh	$C_{17}H_{15}ClN_4S_2$	175–177	59	++	240
4	*m*-MePh	$C_{17}H_{15}ClN_4S_2$	198–200	58	++	280
5	*o*-BrPh	$C_{16}H_{12}ClBrN_4S_2$	210	60	+++	300
6	*p*-BrPh	$C_{16}H_2ClBrN_4S_2$	165–166	65	+++	280
7	*m*-BrPh	$C_{16}H_{12}ClBrN_4S_2$	189	58	+++	290
8	*o*-ClPh	$C_{16}H_2Cl_2N_4S_2$	202–204	62	++++	300
9	*p*-ClPh	$C_{16}H_{12}Cl_2N_4S_2$	211	59	++++	350
10	*m*-ClPh	$C_{16}H_{12}Cl_2N_4S_2$	215	64	+++++	330

[a] All new compounds were analyzed for N,S and the analytical values were within ±0.4% of the calculated values. [b] Mice were used for the experiments for anticonvulsant activity following the method in Putnam and H. H. Merritt, *Science*, **85**, 525 (1937). A +++++ rating was given if the convulsive threshold is elevated more than 60 ma, ++++ is raised to 60 ma, +++ is raised by 40 ma, ++ is raised by 15–20 ma and + is raised by 10–15 ma, 3.5 hr after treatment.

(1) L. Goldman, U. S. Patent 2,617,804, *Chem. Abstr.*, **48**, 2124 (1954).
(2) T. N. Ghosh and A. R. Chaudhuri, *J. Indian Chem. Soc.*, **28**, 268 (1951).
(3) H. F. Kaufmann and P. Schultz, *Arch. Pharm.*, **273**, 22 (1935).
(4) J. William Hanifin, Rosemary Capozzi, and Elliott Cohen, *J. Med. Chem.*, **12**, 1102 (1969).

and llpc with an authentic sample. In both cases the reaction mixture consisted mostly of unreacted ester which masked the product in the initial investigation.

Experimental Section

Substituted *N*-Carbamoylpyrazinecarboxamides.—To 15 ml of dry DMF was added 1.2 g (0.02 mole) of urea. To the stirred solution cooled to −15° was added 1.0 g (0.02 mole) of NaH (50% in oil). The mixture was left to stir for 2 hr. To the cooled mixture was then added 0.005 mole of the pyrazinecarboxylate ester. The mixture was left to stir for 2 hr, and poured onto 40 g of ice–H_2O (acidified to pH 6 with HOAc). On standing a precipitate formed which was filtered and shown by tlc to contain starting ester and product. The product was isolated by liquid–liquid partition chromatography on a Celite column using a heptane–THF–MeOH–H_2O (150:100:10:5) solvent system. The yield of product was about 50 mg (4%) in both cases.

Acknowledgments.—We thank Mr. C. Pidacks and staff for the liquid–liquid partition chromatography.

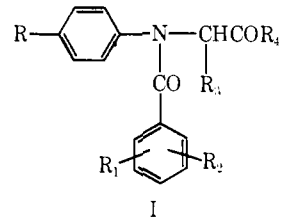
N-Aryl-*N*-aroylamino Acid Derivatives

A. Larizza, G. Lettieri, and R. Viterbo

Research Laboratories, Richardson-Merrell S.p.A., Naples, Italy

Received January 26, 1970

We have synthesized *N*-aryl-*N*-aroylamino acid derivatives of the general formula I. Recently, compounds of this type have been disclosed,[1] but only compounds



I

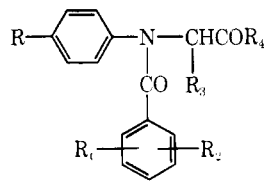
and analgetic activities were found in compounds **3**, **4**, and **5**.

Experimental Section[2]

Ethyl Esters of *N*-Aryl-*N*-aroylamino Acids. General Procedure.—A solution of 0.1 mole of the appropriate aroyl chloride[3] in 50 ml of dry PhH was added dropwise with stirring to a solution of 0.1 mole of the ethyl ester of the appropriate *N*-arylamino acid and 0.1 mole of NEt_3 in 200 ml of dry PhH. The reaction mixture was set aside at room temperature overnight and then filtered in order to remove the formed NEt_3·HCl. The filtrate was shaken with 0.5 *N* HCl, then with satd aq $NaHCO_3$, and, finally, with H_2O to neutral pH. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Generally, a gummy residue was obtained, which was directly converted into the acid derivative by hydrolysis (see below). In some cases, the ethyl esters were isolated and characterized (Table I).

***N*-Aryl-*N*-aroylamino Acids (I, R_4 = OH). General Procedure.**—EtOH (30–50 ml) was added to a mixture of 0.05 mole of the Et ester of the appropriate *N*-aryl-*N*-aroylamino acid in 150 ml of 0.5 *N* NaOH until a clear solution resulted. This solution was refluxed for 4 hr, shaken with Et_2O, and made acid by addition of 4 *N* HCl. The oily precipitate was extracted with Et_2O or EtOAc. The organic solution was washed (H_2O) and dried (Na_2SO_4). The residue obtained after evaporation of the

Table I



R	R_1	R_2	R_3	R_4	Mp, °C	Formula	Analyses[a]
H	H	H	Ph	OH	183–184	$C_{21}H_{17}NO_4$	C, H, N
CH_3O[b]	H	H	H	OH	125–126	$C_{16}H_{15}NO_4$	C, H, N
H[g]	H	4-Cl	H	OH	153–154	$C_{13}H_{12}ClNO_3$	C, H, N, Cl
Cl	H	4-Cl	H	OH	161–163	$C_{15}H_{11}Cl_2NO_3$	C, H, N, Cl
Cl[c]	H	H	H	OH	140–142	$C_{15}H_{12}ClNO_3$	C, H, N, Cl
H	H	2-Cl	H	OH	124–126	$C_{15}H_{12}ClNO_3$	C, H, N, Cl
C_2H_5O	H	2-OH	H	OH	137–138	$C_{17}H_{17}NO_5$	C, H, N
C_2H_5O	H	H	H	OH	92–93	$C_{17}H_{17}NO_4$	C, H, N
Cl[d]	H	2-Cl	H	OH	137–138	$C_{15}H_{11}Cl_2NO_3$	C, H, N, Cl
CH_3O	2-Cl	4-Cl	H	OH	172–174	$C_{16}H_{13}Cl_2NO_4$	C, H, N, Cl
$CH_3(CH_2)_6O$[e]	H	4-Cl	H	OH	115–116	$C_{22}H_{26}ClNO_4$	C, H, N, Cl
C_2H_5O[f]	H	H	CH_3	OH	128–129	$C_{18}H_{19}NO_4$	C, H, N
H	H	2-Cl	H	OC_2H_5	87–88	$C_{17}H_{16}ClNO_3$	C, H, N, Cl
CH_3O	H	2-Cl	H	OC_2H_5	97–98	$C_{18}H_{18}ClNO_4$	C, H, N, Cl
H	4-Cl	3-H_2NSO_2	H	OC_2H_5	113–115	$C_{17}H_{17}ClN_2O_5S$	C, H, N, Cl, S
C_2H_5O	4-Cl	3-H_2NSO_2	H	OC_2H_5	101–103	$C_{19}H_{21}ClN_2O_6S$	C, H, N, Cl, S
CH_3O	4-Cl	3-H_2NSO_2	H	OC_2H_5	123–124	$C_{18}H_{19}ClN_2O_6S$	C, H, N, Cl, S
CH_3O	H	4-Cl	H	$NH(CH_2)_2CH_3$	97–98	$C_{19}H_{21}ClN_2O_3$	C, H, N, Cl
C_2H_5O	H	4-Cl	H	$NH(CH_2)_2CH_3$	90–92	$C_{20}H_{23}ClN_2O_3$	C, H, N, Cl

[a] The analytical results obtained for the indicated elements are within ±0.3% of the theoretical values. [b] Compound **1**. [c] Compound **2**. [d] Compound **4**. [e] Compound **5**. [f] Compound **3**. [g] This is compound **28** in Table II of D. Evans, A. S. L. Mackintosh, and S. S. Szinai, *J. Med. Chem.*, **12**, 1006 (1969). They report mp 154–156°.

not yet described are now reported (Table I). Considerable choleretic activity was found in compounds **1**, **2**, and **3**. Moreover, meaningful diuretic

(1) Netherlands Application 6805246; SOGESPAR S.A. (1968).

(2) Melting points were determined in open capillary tubes and are uncorrected.

(3) In the preparation of *N*-*p*-ethoxyphenyl-*N*-salicyloylglycine *o*-acetoxybenzoylchloride was used.