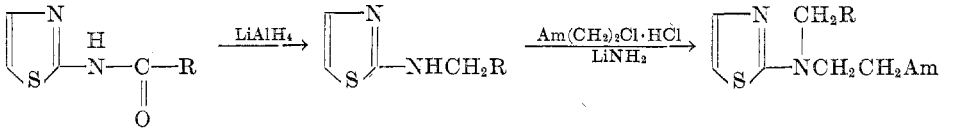
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

SOME 2-THIAZOLYLAMINES FOR ANTIHISTAMINIC EVALUATION

IRVING ALLAN KAYE AND CHESTER L. PARRIS

Received August 9, 1951

Although the thiazole analog (I: R = benzyl, Am = dimethylamino) of Pyribenzamine [N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)ethylenediamine] is the subject of a recent patent (1), the preparation of other N,N-dialkyl-N′-aralkyl-N′-(2-thiazolyl)ethylenediamines (I) has not been described thus far. In this communication four such compounds are reported, one (I C) of which had been investigated previous to this work as a histamine antagonist (2, 3) and, together with I D, had been included in a study of the effect of radical substitution on the optical properties of antihistaminics (4). Our products were obtained by alkylating 2-aralkylaminothiazoles, prepared by lithium aluminum hydride reduction of correspondingly substituted 2-benzamidothiazoles, with N,N-disubstituted *beta*-aminoethyl chloride hydrochlorides in the presence of lithium amide. In preliminary tests on the isolated guinea pig ileum strip, I D appeared to be



I

A; R = C_6H_5, Am = N-pyrrolidyl
B; R = C_6H_5, Am = N-morpholino
C; R = C_6H_4 (OCH_3)-4, Am = dimethylamino
D; R = C_6H_4Cl-4, Am = dimethylamino

the most potent histamine antagonist, having the same order of activity as Pyribenzamine. The other diamines, I C, I A and I B were, respectively, 50%, 7.5% and 0.3% as active.

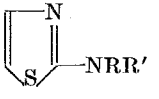
Acknowledgement. The authors wish to thank Endo Products, Inc. for support (in part) of this project and Dr. Harold Bloomberg and Mr. Eric Meyer for the information on the antihistaminic activity of the products.

EXPERIMENTAL

All melting points are corrected; boiling points are not. Anisoyl chloride and *p*-chlorobenzoyl chloride were supplied through the generosity of the Heyden Chemical Corp. Lithium amide, lithium aluminum hydride, 2-aminothiazole and *beta*-dimethylaminoethyl chloride hydrochloride were obtained from commercial sources. *beta*-(N-Pyrrolidyl)ethyl chloride hydrochloride (5), *beta*-(N-morpholino)ethyl chloride hydrochloride (6) and 2-benzylaminothiazole (7) were prepared by previously described methods.

2-(p-Chlorobenzamido)thiazole (Method A). To a stirred solution of 50 g. (0.5 mole) of 2-aminothiazole in 85 ml. of ether and an equal volume of pyridine, 96.3 g. (0.55 mole) of *p*-chlorobenzoyl chloride was added dropwise, with external cooling, at such a rate that the reaction-temperature did not exceed 10°. The reaction-mixture was refluxed gently

TABLE I

2-THIAZOLYL AMINES AND AMIDES OF FORMULA  —NRR′

R	R′	METHOD	B.P. °C.	B.P. Mm.	YIELD, %	M.P., °C.	N ANAL. Formula	N ANAL. Calc'd	N ANAL. Found
$COC_6H_4(OCH_3)$-4	H	A			70[a, b]	207–209[c, d]			
COC_6H_4Cl-4	H	A			82[a]	212.5–213[c]	$C_{10}H_7ClN_2OS$	11.74	11.70
$CH_2C_6H_4(OCH_3)$-4	H	B			82[a, e]	147.5–148[c]	$C_{11}H_{12}N_2OS$	12.72	12.65
$CH_2C_6H_4Cl$-4	H	B			90[a]	132–133[c]	$C_{10}H_9ClN_2S$	12.47	12.40
$CH_2C_6H_5$	$(CH_2)_2NC_4H_8$[f]	C	152–155	0.5	83[g]	165–166.5[h]	$C_{16}H_{21}N_3S$	14.62	14.55
							$C_{16}H_{21}N_3S \cdot H_2C_2O_4$	11.12	10.98
$CH_2C_6H_5$	$(CH_2)_2NC_4H_8O$[i]	C	164–165	0.1	95[g]	172–173[h]	$C_{16}H_{21}N_3OS$	13.85	13.11[j]
							$C_{16}H_{21}N_3OS \cdot H_2C_2O_4$	10.68	10.51
$CH_2C_6H_4(OCH_3)$-4	$(CH_2)_2N(CH_3)_2$	C	153–155	0.4	85[g]	146.5–147.5[h]	$C_{15}H_{21}N_3OS$	14.42	14.16
							$C_{15}H_{21}N_3OS \cdot H_2C_2O_4$	11.02	10.95
$CH_2C_6H_4Cl$-4	$(CH_2)_2N(CH_3)_2$	C	142–143	0.3	86[g]	147–148[h]	$C_{14}H_{18}N_3SCl$	14.21	13.95
							$C_{14}H_{18}N_3SCl \cdot H_2C_2O_4$	10.89	10.79

[a] The yield given is based on the weight of product obtained after one recrystallization from isopropanol. [b] M. p. 201–208°. [c] Recrystallized from isopropanol. [d] The same melting point has been reported by Stoll, Morf and Peyer, U. S. Patent 2,401,522, June 4, 1946, and by Sandoz Ltd., Swiss Patent 233,735, Nov. 16, 1944. [e] M.p. 139–144°. [f] NC_4H_8 is the N-pyrrolidyl group. [g] The yield is based on the weight of distillate. [h] Oxalate, recrystallized from isopropanol. [i] NC_4H_8O is the N-morpholino group. [j] Analysis of redistilled base. The nitrogen value was not improved by further distillation.

for 15 minutes and then poured into ice and water. The precipitated product was washed with water, dilute aqueous sodium carbonate solution and finally with water until the washings were neutral to litmus. After recrystallization from *ca.* one liter of isopropanol, the amide melted at 205.5–208.5° and weighed 97.8 g. (82%). Recrystallized twice more from the same solvent, the compound melted at 212.5–213°.

2-(p-Chlorobenzyl)aminothiazole (Method B). To a stirred solution of 13.6 g. (0.36 mole) of lithium aluminum hydride in 400 ml. of dry ether, in an ice bath, was added 71.6 g. (0.3 mole) of 2-(*p*-chlorobenzamido)thiazole in small portions. After refluxing for 10 minutes, the mixture was decomposed by the dropwise addition of a solution of 113 g. (0.4 mole) of Rochelle salt in 250 ml. of water. A bulky yellow precipitate appeared and was washed with water and redissolved in dilute hydrochloric acid. The acid solution was decolorized with charcoal and made alkaline with ammonium hydroxide. The white solids were washed with water, dried at 80°, powdered and extracted repeatedly with hot ethanol. The combined ethanolic extracts were concentrated on a steam bath to incipient crystallization. On chilling, there was obtained 60.7 g. (90%) of 2-(*p*-chlorobenzyl)aminothiazole, m.p. 121–127°. Three recrystallizations from isopropanol raised the melting point to 132–133°.

N,N-Dimethyl-N'-(p-chlorobenzyl)-N'-(2-thiazolyl)ethylenediamine (Method C). A mixture of 11.3 g. (0.05 mole) of 2-(*p*-chlorobenzyl)aminothiazole, 2.9 g. (0.12 mole) of lithium amide (98% purity), 8.7 g. (0.06 mole) of *beta*-dimethylaminoethyl chloride hydrochloride and 100 ml. of dry benzene was refluxed for 24 hours. The lithium chloride was removed by filtration and washed with benzene. The filtrate, on distillation, initially at atmospheric pressure to remove solvent and finally *in vacuo*, yielded 14.8 g. of product (86%), b.p. 142–143°. (0.3 mm.).

SUMMARY

Lithium aluminum hydride reduction of 2-(*p*-chloro- and *p*-methoxy-benzamido)thiazoles gave the 2-(*p*-chloro- and *p*-methoxy-benzylamino)thiazoles which, together with 2-benzylaminothiazole, were condensed with some N,N-disubstituted *beta*-aminoethyl chloride hydrochlorides in the presence of lithium amide. Of the products, N,N-dimethyl-N'-(*p*-chlorobenzyl)-N'-(2-thiazolyl)ethylenediamine, appeared, in a preliminary study, to be the most potent histamine antagonist.

BROOKLYN 10, NEW YORK

REFERENCES

(1) SONDERN AND BREIVOGEL, *U. S. Patent* 2,440,703, May 4, 1948.
(2) BERNSTEIN AND FEINBERG, *J. Lab. Clin. Med.*, **34**, 1007 (1949).
(3) FEINBERG, MALKIEL, BERNSTEIN AND HARGIS, *J. Pharmacol Exp. Therap.*, **99**, 195 (1950).
(4) KEENAN AND HALEY, *J Am. Pharm. Assoc.*, **39**, 333 (1950).
(5) WRIGHT, KOLLOFF, AND HUNTER, *J. Am. Chem. Soc.*, **70**, 3098 (1948).
(6) MASON AND BLOCK, *J. Am. Chem. Soc.*, **62**, 1143 (1940).
(7) KAYE AND PARRIS, *J. Am. Chem. Soc.*, in press.