New Compounds

Possible Anthelmintic Thiazol-5-ylbenzimidazoles. III[1]

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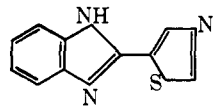
Received February 23, 1968

In view of the potent anthelmintic activity[3] shown by a large series of benzimidazole compounds, a few new thiazol-5-ylbenzimidazoles were synthesized.



Experimental Section

2-Chloro-4-methyl-5-carbethoxythiazole.[4]—2-Amino-4-methyl-5-carbethoxythiazole (5 g) in a cooled solution of 80% H_3PO_4 (25 ml) was treated with concentrated HNO_3 (14 ml), cooled to −5°, diazotized with a solution of $NaNO_2$ (4 g) with stirring over 1 hr, and added to a solution of $CuSO_4$ (9 g) and NaCl (9 g) in water (40 ml); N_2 evolution ceased in 10 min. After standing an additional 1 hr, the mixture on neutralization and steam distillation afforded a cream-colored product which was recrystallized from absolute alcohol; yield 40%, mp 191–192° dec.[5a] *Anal.*[5b] ($C_7H_8NO_2SCl$) N, Cl; S: calcd, 15.57; found, 15.82.

2-Bromo-4-methyl-5-carbethoxythiazole.—The above procedure using NaBr instead of NaCl afforded the compound recrystallized from ethyl acetate; yield 45%, mp 210–211° dec. *Anal.* ($C_7H_8NO_2SBr$) N, S; Br: calcd, 32.00; found, 31.

2-Propylamino-4-methyl-5-carbethoxythiazole.—2-Amino-4-methyl-5 carbethoxythiazole (5 g), propyl alcohol[6] (25 ml) and 80% H_2SO_4 (20 ml) was heated at 70° for 5 hr. The solution on pouring onto ice and neutralizing with NH_4OH gave a colorless product which was recrystallized from dioxane, yield 45%, mp 176–177° dec. *Anal.* ($C_{10}H_{16}N_2O_2S$) S; N: calcd, 12.28; found, 12.38.

2-Isopropylamino-4-methyl-5-carbethoxythiazole.—The above procedure using isopropyl alcohol gave a product which was recrystallized from a mixture of ethanol and ethyl acetate, yield 45%, mp 195–196° dec. *Anal.* ($C_{10}H_{16}N_2O_2S$) N; S: calcd, 14.03; found 14.90

2-(2-Chloro-4-methylthiazol-5-yl)benzimidazole.—A mixture of 2-chloro-4-methyl-5-carbethoxythiazole (0.01 mole) and *o*-phenylenediamine (0.01 mole) in polyphosphoric acid (40 ml) was heated for 6 hr at 250°, cooled to 90°, poured onto crushed ice, neutralized with NH_4OH, and filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue on extraction with ethanol (50 ml) and concentration under reduced pressure gave a product which was recrystallized from dioxane, yield 42%, mp 176–177° dec. *Anal.* ($C_{11}H_8N_3SCl$) N, Cl, S.

2-(2-Bromo-4-methylthiazol-5-yl)benzimidazole.—The above procedure gave a product which was recrystallized from acetone; yield 40%, mp 190–191° dec. *Anal.* ($C_{11}H_8N_3SBr$) N; S: calcd, 10.88; found, 10.98.

2-(2-Propylamino-4-methylthiazol-5-yl)benzimidazole was recrystallized from dioxane, yield 42%, mp 182–184° dec. *Anal.* ($C_{14}H_{16}N_4S$) N, S.

2-(2-Isopropylamino-4-methylthiazol-5-yl)benzimidazole was recrystallized from ethyl acetate, yield 45%, mp 176–177° dec *Anal.* ($C_{14}H_{16}N_4S$) N, S.

Acknowledgment.—The author expresses his gratitude to the Head, Chemistry Department, Meerut College, Meerut, for providing necessary facilities.

(1) Part II: J. M. Singh and S. P. Gupta, *J. Indian Chem. Soc.*, **42**, 337 (1965).

(2) Defence Science Laboratory, Delhi-6, India.

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(5) (a) All melting points are uncorrected. (b) Where analyses are given by symbols of the elements, analytical results were within ±0.4% of theory.

(6) During propylation in the presence of H_2SO_4 the ester group remains unchanged as confirmed by infrared spectrum (5.85-μ peak).

Synthesis of Some New 6-Chloro-S-substituted 2-Mercapto-3-aryl- (or -alkyl-) 4(3H)-quinazolones as Antimalarials

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Received November 12, 1968

The antimalarial activity of febrifugine, an alkaloid having the 3-substituted 4(3H)-quinazolinone structure, created interest in the preparation and testing of a number of quinazolines.[1] Compounds having the side chain CH_2COCH_2R (where R = ω-N-piperidyl-*n*-butyl or ω-N-morpholinylpropyl) at position 3 of the 4(3H)-quinazolinone nucleus were shown to have significant antimalarial activity.[2] Gujral, *et al.*, observed the hypnotic activity of 2-alkyl-3-aryl-4(3H)-quinazolones in rats.[3] A potent anticonvulsant property of 2-methyl-3-*p*-bromophenyl-4-quinazolone hydrochloride has been reported against pentylenetetrazole-induced convulsions in mice.[4] These activities led to the synthesis of 2-S-substituted thio-3-aryl- (or -alkyl-) 4(3H)-quinazolones[5,6] as possible antimalarials and ataractic agents.[7] In the present work, the synthesis of 6-chloro-2-mercapto-3-aryl- (or -alkyl-) 4(3H)-quinazolones and their S-substituted derivatives from 5-chloroanthranilic acid,[8] aryl (or alkyl) isothiocyanates, and alkyl halides has been studied.

Experimental Section

6-Chloro-2-mercapto-3-benzyl-4(3H)-quinazolone.—Equimolar quantities of 5-chloroanthranilic acid (19 g) and benzyl isothiocyanate (13.5 ml) in the presence of absolute EtOH (100 ml) were refluxed on a water bath for 4–5 hr. The product was cooled and dissolved (10% NaOH), filtered, and reprecipitated by dilute HCl. The precipitate was filtered, washed (H_2O), and crystallized (AcOH). Similarly, other 6-chloro-2-mercapto-3-aryl- (or -alkyl-) 4(3H)-quinazolones were prepared from the corresponding isothiocyanates and 5-chloroanthranilic acid (Table II).

6-Chloro-2-methylthio-3-benzyl-4(3H)-quinazolone.—MeI (3 ml) was added to a solution of 6-chloro-2-mercapto-3-benzyl-4(3H)-quinazolone (7.6 g) prepared in 10% alcoholic NaOH. The resulting mixture was stirred for 1 hr at room temperature and the separated crystalline product was washed (H_2O, EtOH) and

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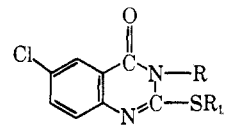
TABLE I

6-CHLORO-S-SUBSTITUTED 2-MERCAPTO-3-ARYL- (OR -ALKYL-) 4(3H)-QUINAZOLONES

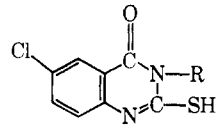


R	% yield	Mp, °C[a]	Formula[b]
	R_1 = Me		
C_6H_5	40	186	$C_{15}H_{11}ClN_2OS$
o-MeC_6H_4	55	210	$C_{16}H_{13}ClN_2OS$
m-MeC_6H_4	65	147	$C_{16}H_{13}ClN_2OS$
p-MeC_6H_4	60	248	$C_{16}H_{13}ClN_2OS$
m-ClC_6H_4	65	160	$C_{15}H_{10}Cl_2N_2OS$
p-ClC_6H_4	55	241	$C_{15}H_{10}Cl_2N_2OS$
p-$EtOC_6H_4$	63	211	$C_{17}H_{15}ClN_2O_2S$
o-$MeOC_6H_4$	54	160	$C_{16}H_{13}ClN_2O_2S$
p-$MeOC_6H_4$	80	189	$C_{16}H_{13}ClN_2O_2S$
Et	66	124	$C_{11}H_{11}ClN_2OS$
Me	75	158	$C_{10}H_9ClN_2OS$
$C_6H_5CH_2$	76	97	$C_{16}H_{13}ClN_2OS$
	R_1 = Et		
C_6H_5	65	238	$C_{16}H_{13}ClN_2OS$
o-MeC_6H_4	60	250	$C_{17}H_{15}ClN_2OS$
m-MeC_6H_4	58	223	$C_{17}H_{15}ClN_2OS$
p-$EtOC_6H_4$	55	146	$C_{18}H_{17}ClN_2OS$
p-ClC_6H_4	70	182	$C_{16}H_{12}Cl_2N_2OS$
o-$MeOC_6H_4$	70	154	$C_{17}H_{15}ClN_2O_2S$
p-$MeOC_6H_4$	68	172	$C_{17}H_{15}ClN_2O_2S$
Me	65	95	$C_{11}H_{11}ClN_2OS$
n-Bu	55	74	$C_{14}H_{17}ClN_2OS$
	R_1 = $C_6H_5CH_2$		
o-MeC_6H_4	65	235	$C_{22}H_{17}ClN_2OS$
m-MeC_6H_4	69	130	$C_{22}H_{17}ClN_2OS$
p-MeC_6H_4	80	193	$C_{22}H_{17}ClN_2OS$
m-ClC_6H_4	70	130	$C_{21}H_{14}Cl_2N_2OS$
p-ClC_6H_4	65	181	$C_{21}H_{14}Cl_2N_2OS$
p-$EtOC_6H_4$	75	158	$C_{23}H_{19}ClN_2O_2S$
o-$MeOC_6H_4$	48	135	$C_{22}H_{17}ClN_2O_2S$
p-$MeOC_6H_4$	73	160	$C_{22}H_{17}ClN_2O_2S$
	R_1 = $C_6H_5CH_2$ (*Continued*)		
Et	49	122	$C_{17}H_{15}ClN_2OS$
Me	85	123	$C_{16}H_{13}ClN_2OS$
n-Bu	85	100	$C_{19}H_{19}ClN_2OS$
$C_6H_5CH_2$	80	113	$C_{22}H_{17}ClN_2OS$
	R_1 = *n*-Pr		
C_6H_5	45	149	$C_{17}H_{15}ClN_2OS$
o-MeC_6H_4	37	251	$C_{18}H_{17}ClN_2OS$
m-MeC_6H_4	40	125	$C_{18}H_{17}ClN_2OS$
p-MeC_6H_4	50	131	$C_{18}H_{17}ClN_2OS$
m-ClC_6H_4	40	155	$C_{17}H_{14}Cl_2N_2OS$
p-ClC_6H_4	45	176	$C_{17}H_{14}Cl_2N_2OS$
p-$EtOC_6H_4$	55	134	$C_{19}H_{19}ClN_2O_2S$
o-$MeOC_6H_4$	38	187	$C_{18}H_{17}ClN_2O_2S$
p-$MeOC_6H_4$	70	158	$C_{18}H_{17}ClN_2O_2S$
Et	45	197	$C_{13}H_{15}ClN_2OS$
Me	50	224	$C_{12}H_{13}ClN_2OS$
n-Bu	46	71	$C_{15}H_{19}ClN_2OS$
$C_6H_5CH_2$	42	237	$C_{18}H_{17}ClN_2OS$
	R_1 = *n*-Bu		
C_6H_5	47	233	$C_{18}H_{17}ClN_2OS$
o-MeC_6H_4	50	258	$C_{19}H_{19}ClN_2OS$
m-MeC_6H_4	48	221	$C_{19}H_{19}ClN_2OS$
p-MeC_6H_4	45	117	$C_{19}H_{19}ClN_2OS$
m-ClC_6H_4	50	239	$C_{18}H_{16}Cl_2N_2OS$
p-ClC_6H_4	45	278	$C_{18}H_{16}Cl_2N_2OS$
p-$EtOC_6H_4$	60	141	$C_{20}H_{21}ClN_2O_2S$
o-$MeOC_6H_4$	70	112	$C_{19}H_{19}ClN_2O_2S$
p-$MeOC_6H_4$	49	155	$C_{19}H_{19}ClN_2O_2S$
Et	45	121	$C_{14}H_{17}ClN_2OS$
Me	40	122	$C_{13}H_{15}ClN_2OS$
$C_6H_5CH_2$	85	77	$C_{19}H_{19}ClN_2OS$

[a] Uncorrected. [b] Crystallization solvent: EtOH. All compounds were analyzed for N, S. The analytical results were within ±0.3% of the calculated values.

TABLE II

6-CHLORO-2-MERCAPTO-3-ARYL- (OR -ALKYL-) 4(3H)-QUINAZOLONES



R	% yield	Mp, °C[a]	Formula[b]
$C_6H_5CH_2$	75	265	$C_{15}H_{11}ClN_2OS$
p-$EtOC_6H_4$	80	328	$C_{16}H_{13}ClN_2O_2S$
Me	70	214	$C_9H_7ClN_2OS$
Et	60	217	$C_{10}H_9ClN_2OS$
n-Bu	65	220	$C_{12}H_{13}ClN_2OS$

[a] Uncorrected. [b] Crystallization solvent: AcOH. All compounds were analyzed for N, S. The analytical results were within ±0.4% of the calculated values.

crystallized (95% EtOH). Similarly, various 6-chloro-S-substituted 2-mercapto-3-aryl- (or -alkyl-) 4(3H)-quinazolones were prepared (Table I).

Hydrolysis of 6-Chloro-2-methylthio-3-*m*-tolyl-4(3H)-quinazolone.—A mixture of 6 *N* HCl (30 ml), 6-chloro-2-methylthio-3-*m*-tolyl-4(3H)-quinazolone (2.40 g), and EtOH (30 ml) was refluxed on a water bath for 6 hr. A trap containing 0.8 g of NaOH was connected to the top of the reflux condenser during this period. The resulting product was cooled, filtered, washed (H_2O), and finally crystallized (EtOH), mp 298°, yield 70%. *Anal.* ($C_{15}H_{11}ClN_2O_2$) N.

The content of the NaOH trap on treatment with $Pb(OAc)_2$ and $HgCl_2$ solution separately gave a yellow precipitate, confirming the presence of MeSH.

Acknowledgment.—The authors thank the Council of Scientific and Industrial Research, New Delhi, for the award of a Junior Research Fellowship to one of them (V. N. C.).