New Compounds

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

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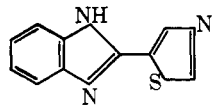
In view of the potent anthelmintic activity[3] shown by a large series of benzimidazole compounds, a few new thiazol-5-ylbenzimidazoles were synthesized.



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.

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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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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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