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2,3-Dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one and 3,4-dihydro-2*H*,6*H*[1,3]thiazino[2,3-*b*]-quinazolin-6-one have been synthesized in one step by the reaction of methyl anthranilate with chloroalkyl isothiocyanates.

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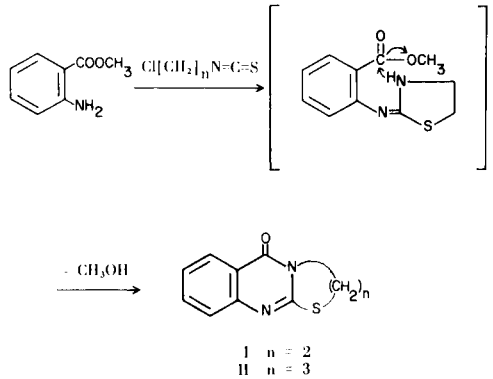
In connection with a general study of the chemistry of heterocyclic compounds, we became interested in developing an improved synthesis of 2,3-dihydro-5*H*-thiazolo-[2,3-*b*]quinazolin-5-one (I) and 3,4-dihydro-2*H*,6*H*[1,3]-thiazino[2,3-*b*]quinazolin-6-one (II). These compounds may be considered "fused" thiazolo and thiazino analogues of febrifugine, which has been found to possess interesting antimalarial activity (1).

Although a method for preparation of I and II using methyl *o*-isothiocyanatobenzoate as a starting material has been reported (2a-b), it requires thiophosgene and vigorous conditions which limit its potential usefulness.

We have developed a new, one-step synthesis of I by reaction of methyl anthranilate with 2-chloroethyl isothiocyanate (3). It involves the intermediate formation of a thiazoline and the elimination of methanol to give I *via* an intramolecular cyclization. The reaction proceeds smoothly. Thus, methyl anthranilate in boiling ethanol reacted with 2-chloroethyl isothiocyanate in the presence of triethylamine to give I directly in good yield.



I n = 2
II n = 3

The reaction was then extended to the synthesis of the homologous II by using 3-chloropropyl isothiocyanate (4). The yield of analytically pure product was at least 68% in each example and can be easily scaled up. The approach offered herein may well constitute the method of choice for synthesizing the title compounds.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were run as Nujol mulls using a Perkin-Elmer 297 infrared spectrophotometer. The ^{1}H nuclear magnetic resonance spectra were obtained in DMSO-d_6 with a Varian T-60A spectrometer. The electron-impact mass spectra were determined with a LKB-9000 mass spectrometer (70 eV). Microanalyses were done by the Analytical Section, Merck Sharp and Dohme Research Laboratories, under the supervision of Mr. J. P. Gilbert.

2,3-Dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (I).

Methyl anthranilate (3.78 g., 0.025 mole) and triethylamine (2.53 g., 0.025 mole) were dissolved in 80 ml. of ethanol to which 2-chloroethyl isothiocyanate (3.04 g., 0.025 mole) was added. The mixture was heated under reflux for 20 hours. After concentrating the reaction mixture under reduced pressure, the product was precipitated by the addition of water. Recrystallization of the crude product from ethyl acetate gave 3.45 g. (68% yield) of 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (I), m.p. 157.0-157.5° [lit. (2a), m.p. 156-157°]; ir (Nujol): ν max 1665 (C=O) and 1605 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ (ppm) 3.55 (t, 2H, CH_2S), 4.55 (t, 2H, CH_2N), 7.25-8.21 (m, 4H, ArH); ms (electron impact, 70 eV): m/e 204 (M^+, base).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.81; H, 3.95; N, 13.71; S, 15.70. Found: C, 58.84; H, 3.80; N, 13.77; S, 15.93.

When the reaction was carried out in xylene using anthranilic acid (3.43 g., 0.025 mole) instead of the ester, it afforded a diminished yield (1.58 g., 31%) of I.

3,4-Dihydro-2*H*,6*H*[1,3]thiazino[2,3-*b*]quinazolin-6-one (II).

This compound was prepared in a manner similar to the synthesis of I. From 9.07 g. (0.06 mole) of methyl anthranilate, 8.13 g. (0.06 mole) of 3-chloropropyl isothiocyanate and 6.07 g. (0.06 mole) of triethylamine, 9.10 g. (70%) of 3,4-dihydro-2*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazolin-6-one (II) was obtained. Recrystallization from ethanol gave white prisms, m.p. 120-121° [lit. (2b), m.p. 121.5-122.0°]; ir (Nujol): ν max 1680 (C=O) and 1610 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ (ppm) 2.25 (m, 2H, C-CH_2-C), 3.20 (t, 2H, CH_2S), 4.10 (t, 2H, CH_2N), 7.25-8.10 (m, 4H, ArH); ms (electron impact 70 eV): m/e 218 (M^+, base).

Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.49; H, 4.58; N, 12.81; S, 14.54.

REFERENCES AND NOTES

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