Synthesis of 5*H*-[1,2]-Benzisothiazolo[2,3-*a*]quinazolin-5-one

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In a previous paper (1) we have reported the conversion of 2*H*-1,3-benzothiazine-2-thion-4(3*H*)one and of 2*H*-1,3-benzoxazine-2-thion-4(3*H*)one into 4-quinazolinones by means of arylamides. On the basis of these results we have experimentally confirmed a possible reaction pathway between 2-hydroxy and 2-chlorobenzoyl chlorides and amides in the synthesis of 4-quinazolinones (2).

A comparative study however, of the reactive behaviour of amides showed that anthranilamide reacts with 2*H*-1,3-benzothiazine-2-thion-4(3*H*)one in a different way to give a complex reaction mixture, from which it was possible to isolate the following compounds: 3*H*-1,2-benzodithiole-3-thione (I), 3*H*-1,2-benzodithiol-3-one (II), quinazolino[2,1-*b*]quinazoline-5(6*H*),8-dione (III), 1,2,3,4-tetrahydro-2-thioquinazolin-4-one (IV), 1,2,3,4-tetrahydroquinazoline-2,4-dione (V) and 5*H*-[1,2]-benzisothiazolo[2,3-*a*]quinazolin-5-one (VI).

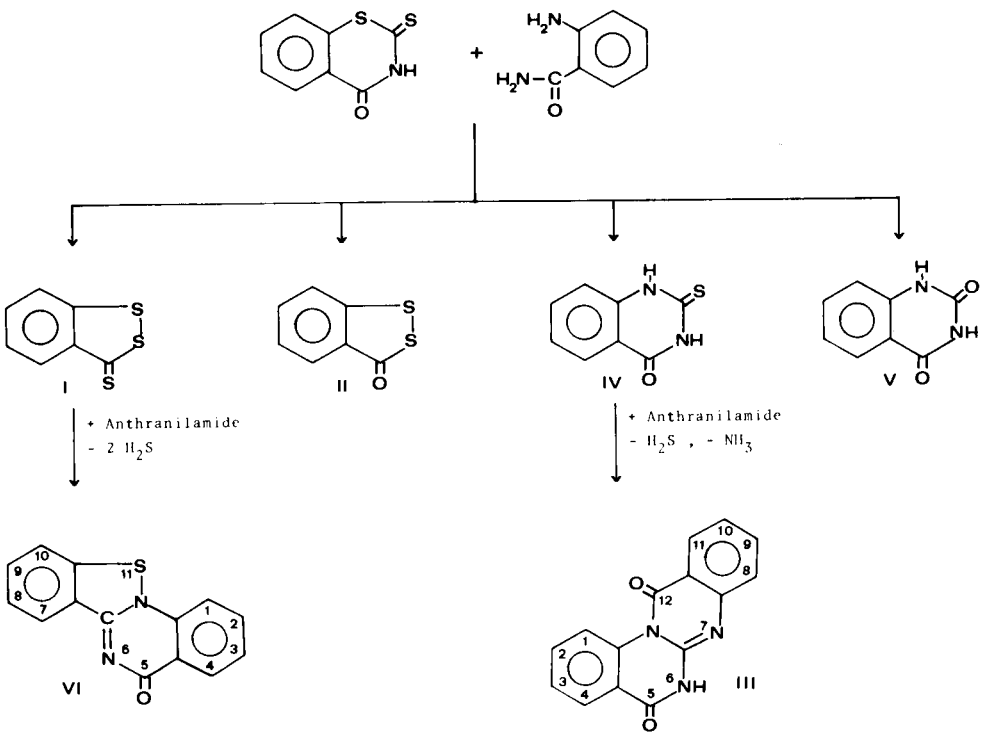
Compound VI is of particular interest because it has not been reported in the literature.

Wagner and Richter (3) demonstrated that 1,3-thiazines in alkaline medium are converted into 3*H*-1,2-benzodithiole-3-thione (I) and 3*H*-1,2-benzodithiol-3-one (II), and our research confirms such behaviour (4).

Moreover McClelland and co-workers observed that 3*H*-1,2-benzodithiole-3-thione (I) reacts with primary amines to yield benzisothiazolone derivatives (5).

In the present investigation compound I was isolated, thus we propose the following reaction sequence for the formation of compounds III and VI:

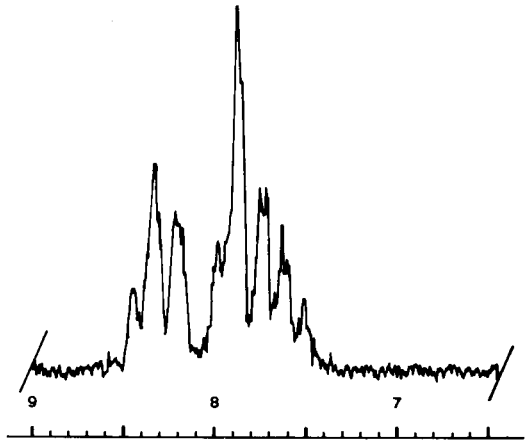
SCHEME I



This has been confirmed by obtaining VI from the reaction of 3*H*-1,2-benzodithiole-3-thione (I) with anthranilamide.

Furthermore compound III was obtained by reacting 2*H*-1,3-benzothiazine-2-thion-4(3*H*)one and anthranilic acid, under the same experimental conditions.

FIGURE I



EXPERIMENTAL

Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Melting points were determined on a Büchi-Tottoli capillary apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer model 157 infrared spectrometer as nujol mulls. The uv spectra were determined on a Beckmann DB ultraviolet spectrometer in 95% ethanol. The nmr spectra were recorded using a Jeol C-60H, 60 MHz instrument using TMS as the internal standard. The purity of the compounds was confirmed by tlc on silica gel Merck platten 0.25 mm with fluorescent indicator, using the two following solvent systems: cyclohexane:benzene (1:9) or benzene:ethylacetate (3:7).

Reaction of 2*H*-1,3-Benzothiazine-2-thion-4(3*H*)one and Anthranilamide.

2*H*-1,3-Benzothiazine-2-thion-4(3*H*)one (19.5 g., 0.1 mole) and anthranilamide (13.6 g., 0.1 mole) were heated under reflux for 1 hour, during which time the reaction mixture became dark brown and hydrogen sulfide was evolved. The separation of compounds from the reaction mixture was accomplished by column chromatography (400 g. of silica gel Merck 0.05-0.2 mm in a column of 4 cm diameter and 75 cm length), using different eluents:

a) 3*H*-1,2-Benzodithiole-3-thione (I).

Elution with 5400 ml. of petroleum ether (b.p. 40-70°) afforded a red-orange product (1.2 g.) as needles (ethanol), m.p. 93-94° undepressed with an authentic sample.

Anal. Calcd. for $C_7H_4S_3$: C, 45.65; H, 2.17; S, 52.17. Found: C, 45.82; H, 2.08; S, 52.10.

b) 3*H*-1,2-Benzodithiol-3-one (II).

Elution with 8250 ml. of the same solvent gave subsequently a yellow compound (0.8 g.) as needles (ethanol), m.p. 78-80°, which did not depress when mixed with an authentic sample.

Anal. Calcd. for $C_7H_4OS_2$: C, 50.00; H, 2.38; S, 38.09. Found: C, 50.18; H, 2.42; S, 38.12.

c) Quinazolino[2,1-*b*]quinazoline-5(6*H*),8-dione (III).

Elution with 4500 ml. of petroleum ether (b.p. 40-70°): ethyl ether (1:1) afforded a pale yellow product (3.5 g.) (benzene or ethanol), m.p. 260-262° (Butler and Partridge (6) gave m.p. 255-255.5°); ir: 3100 (inflexion NH), 1695 (C=O), 1610, 1585 cm^{-1} (NH); uv: λ max 235, 283, 320, 331 nm; nmr (DMSO): 7.15, 7.98 δ (5H, m, C_2-H, C_3-H, C_8-H, C_9-H, C_{10}-H), 8.02, 8.28 δ (2H, dd, C_4-H, C_{11}-H), 9.99, 10.16 δ (1H, d, C_1-H), 12.9, 13.45 δ (1H, s, NH exchanged with deuterium oxide).

Anal. Calcd. for $C_{15}H_9N_3O_2$: C, 68.44; H, 3.42; N, 15.97. Found: C, 68.52; H, 3.51; N, 16.02.

d) 1,2,3,4-Tetrahydro-2-thioquinazolin-4-one (IV).

Subsequently the same eluent phase (5400 ml.) yielded crude IV (3.0 g.) which was crystallized from acetic acid to give a colourless compound, m.p. 320-322°.

Anal. Calcd. for $C_8H_6N_2OS$: C, 53.93; H, 3.37; N, 15.73; S, 17.97. Found: C, 54.08; H, 3.42; N, 15.80; S, 18.05.

e) 1,2,3,4-Tetrahydroquinazoline-2,4-dione (V).

Elution with 7500 ml. of petroleum ether (b.p. 40-70°):ethyl ether (5:95) yielded a colourless product (3.2 g.) which was crystallized from ethanol, m.p. 355-358°.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.33; H, 3.68; N, 17.31.

f) 5*H*-[1,2]Benzisothiazolo[2,3-*a*]quinazolin-4-one (VI).

From the eluent phase ethyl ether:chloroform (1:1) (6100 ml.) a yellow compound (2.2 g.) was separated which, after crystallization from ethanol, melted at 245-247°; ir: 1650 (C=O), 1625 cm^{-1} (C=N); uv: λ max (log ε) 218 (4.52), 240 (4.36), 262 (4.19), 284 (3.95), 298 nm (4.00); nmr (DMSO): 7.45-8.54 δ (8H aromatic) (see Figure I).

Anal. Calcd. for $C_{14}H_8N_2OS$: C, 66.66; H, 3.17; N, 11.11; S, 12.70. Found: C, 66.73; H, 3.21; N, 11.15; S, 12.82.

Reaction of 3*H*-1,2-Benzodithiole-3-thione and Anthranilamide.

3*H*-1,2-Benzodithiole-3-thione (I) (1.84 g., 0.01 mole) and anthranilamide (1.36 g., 0.01 mole) were heated under reflux for 10 minutes. During the reaction hydrogen sulphide was evolved. The analytical sample (0.9 g.) was obtained by column chromatography (20 g. of silica gel Merck 0.05-0.2 mm in a column of 2 cm diameter and 38 cm length) eluted with ethyl ether:chloroform (1:1). It was found to be identical with VI.

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