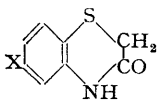
142. *Preparation of* 2 : 3-*Dihydro*-3-*ketobenzo*-1 : 4-*thiazine Derivatives as Possible Anthelmintics.*

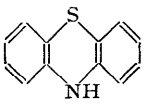
By Alexander Mackie and John Raeburn.

Derivatives of 2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine have been prepared, mainly from the diazonium compound from the 6-amino-derivative, for test against parasitic worms *in vitro*. Nearly all the derivatives produced a paralysant effect on liver fluke (*Fasciola hepatica*).

2 : 3-Dihydro-3-ketobenzo-1 : 4-thiazine (I; X = H) and some derivatives thereof have been prepared, as it was considered that they might show some anthelmintic properties: these compounds have some features of phenothiazine (II), extensively used in veterinary practice, and of filicic acid (III), an important constituent of *Filix mas*.

Few derivatives of 2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine have been synthesised. Friedlaender and Chwala (*Monatsh.*, 1907, **28**, 252) showed that when (*o*-nitroarylthio)-acetic acids were reduced, the resulting aminoarylthio-acids split off a molecule of water with extraordinary ease, with ring closure to benzo-1 : 4-thiazine derivatives.


(I)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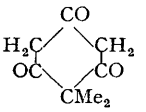
(III)

2 : 3-Dihydro-3-ketobenzo-1 : 4-thiazine and its 6 : 7-dimethoxy-derivative were obtained by reduction of the appropriate (nitrophenylthio)acetic acids (Claasz, *Ber.*, 1912, **45**, 751; Baldick and Lions, *J. Roy. Soc. N.S.W.*, 1937—38, **71**, 113).

Most of the derivatives described in this investigation were prepared by way of the diazonium compound from 6-amino-2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine (I; X = NH_2), obtained by reduction of (2 : 4-dinitrophenylthio)acetic acid (Friedlaender and Chwala, *loc. cit.*, p. 276). Many of the yields were small, principally owing to the difficulty in obtaining the compounds analytically pure. The amino-group was replaced successfully by F, Cl, I, CNS, N_3, NO_2, NO, SH, H_2AsO_3, H_2SbO_3, and HgCl, and decomposition of the diazonium compound by copper bronze afforded the bis-derivative. The 6-bromo-compound was not obtained by Sandmeyer reaction, but by decomposition of the perbromide. The 6-hydroxy-derivative could not be prepared from the diazonium compound. A deep red colour was obtained, which indicated self-coupling. The 6 : 7-dihydroxy-compound was, however, easily prepared from the 6 : 7-dimethoxy-derivative. The amino-group could not be replaced by the cyanogen group by Sandmeyer reaction, and attempts to produce a Grignard reagent from the iodo-derivative were fruitless.

The derivatives described herein have been tested against and had practically no effect on the round worm, *Ascaris lumbricoides*, but nearly all showed a paralysant effect on liver fluke (*Fasciola hepatica*) *in vitro*. Full details will be published elsewhere. The 6-chloro-derivative was the most effective.

Experimental

M. p.s are uncorrected.

6-*Amino*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Reduction of (2 : 4-dinitrophenylthio)-acetic acid, m. p. 172° (Friedlaender and Chwala, *loc. cit.*, record m. p. 167—168°), with tin and hydrochloric acid afforded the 6-amino-compound. Contrary to the findings of Friedlaender and Chwala (*loc. cit.*) who preferred using iron and acetic acid, the former reagents proved superior. Reduction in alcohol with iron and hydrochloric acid (West's method, *J.*, 1925, **127**, 494) was unsatisfactory.

The hydrochloride decomposed at 272—274°, and the acetyl derivative had m. p. 257°. Friedlaender and Chwala (*loc. cit.*) give m. p. 257° for the latter compound, but record few experimental details. Satisfactory yields were only obtained after 16 hours' refluxing with acetic anhydride.

The amino-compound was easily diazotised below 10°, and for each of the derivatives prepared by way of the diazo-reaction, 4·5 g. of amino-derivative were used.

6-*Fluoro*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Fluoroboric acid (40% solution; 20 c.c.) was added to the cold diazonium solution. The mixture was stirred for 2 hours, a pale yellow precipitate of the diazonium fluoroborate separating, which was filtered off, washed with water, ethanol, and ether, and finally dried (6 g.). The diazonium fluoroborate was decomposed at 135° (vapour from boiling xylene) and the 6-*fluoro*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine* in the residue was extracted with boiling absolute ethanol. An orange-brown impurity, which separated when the alcoholic extract cooled, was removed, and the fluoro-compound in the filtrate was isolated and recrystallised from aqueous ethanol in pale yellow platelets (1 g.), m. p. 184° (Found: C, 52·4; H, 3·2; N, 7·7. C_8H_6ONFS requires C, 52·5; H, 3·3; N, 7·7%).

6-*Chloro*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—The amino-group was replaced by chlorine in a Sandmeyer reaction (Friedlaender and Chwala, *loc. cit.*).

6-*Bromo*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Decomposition of the perbromide at 155° afforded a compound, m. p. 220° (Found : N, 5·0. Calc. for C_8H_6ONBrS : N, 5·7%). A purer product could not be obtained.

6-*Iodo*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—A saturated aqueous solution of potassium iodide (8 g.) was added to the cold diazonium solution. The reaction mixture was stirred during 5 hours, then refluxed for 1 hour with ethanol (200 c.c.), and the solution filtered hot. The crystals obtained on cooling of the filtrate were recrystallised from aqueous ethanol, giving the 6-*iodo*-compound as feathery orange needles (3·5 g.), m. p. 208—210° (Found : I, 43·5; N, 5·1. C_8H_6ONIS requires I, 43·6; N, 4·8%).

2 : 3-*Dihydro*-3-*keto*-6-*thiocyanatobenzo*-1 : 4-*thiazine*.—Potassium thiocyanate (4 g.) in aqueous solution, followed by a paste containing cuprous thiocyanate, was added to the cold diazonium solution. The paste was prepared by adding potassium thiocyanate (4 g.) in aqueous solution to a solution containing copper sulphate (8 g.) and ferrous sulphate (16 g.), filtering, and making the residue into a paste with water. The mixture was vigorously agitated for 9 hours, then the reaction product was refluxed with ethanol (200 c.c.) for 1·5 hours. After filtration, the filtrate deposited orange crystals which were recrystallised from aqueous ethanol. 2 : 3-*Dihydro*-3-*keto*-6-*thiocyanatobenzo*-1 : 4-*thiazine* was obtained as pale yellow needles (3 g.), m. p. 180° (Found : C, 48·4; H, 3·1; N, 12·3. $C_9H_6ON_2S_2$ requires C, 48·6; H, 2·7; N, 12·6%).

6-*Azido*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Sodium azide (2 g.) in aqueous solution was slowly added to the cold diazonium solution. Nitrogen was evolved and a white precipitate formed. The mixture was stirred below 10° for 5 hours, and then allowed to attain room temperature. The precipitate was filtered off, washed, and recrystallised from aqueous ethanol. 6-*Azido*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine* was obtained as pale yellow feathery needles (5 g.), becoming yellowish-brown with slight decomposition on exposure to light, m. p. 176° (decomp.) (Found : N, 27·0. $C_8H_6ON_4S$ requires N, 27·2%).

2 : 3-*Dihydro*-3-*keto*-6-*nitrobenzo*-1 : 4-*thiazine* (cf. Hodgson and Marsden, *J.*, 1944, 22).—The diazonium solution was neutralised with calcium carbonate and filtered. Finely powdered sodium cobaltinitrite (11 g.) was then added to the filtrate and the diazonium cobaltinitrite which separated was filtered off and dried. The diazonium cobaltinitrite (10 g.) was added in portions at room temperature to an aqueous solution containing sodium nitrite (10 g.) and copper sulphate (10 g.), in which cuprous oxide (4 g.) was suspended. After evolution of nitrogen was complete, the product was filtered off. The greenish residue was recrystallised from ethanol, giving the 6-*nitro-thiazine* as golden-brown feathery needles (1 g.), m. p. 243—244° (Found : N, 13·6. $C_8H_6O_3N_2S$ requires N, 13·3%).

2 : 3-*Dihydro*-3-*keto*-6-*nitrosobenzo*-1 : 4-*thiazine*.—The diazonium solution was run into a saturated solution of potassium permanganate (70 c.c.) below 10° and the mixture rendered alkaline with aqueous potassium hydroxide. After 3 hours' stirring, the mixture was extracted with ether, and on removal of the ether the residue was recrystallised from aqueous ethanol, giving 2 : 3-*dihydro*-3-*keto*-6-*nitrosobenzo*-1 : 4-*thiazine* as pale yellow platelets (0·2 g.), m. p. 134° (Found : N, 14·7. $C_8H_6O_2N_2S$ requires N, 14·4%).

2 : 3-*Dihydro*-3-*keto*-6-*mercaptobenzo*-1 : 4-*thiazine*.—Aqueous potassium xanthate (4 g.) was added to the cold diazonium solution. After 2 hours, a bright yellow precipitate was obtained, the temperature of the reaction mixture was gradually raised, and decomposition completed on the water-bath (1·5 hours). The yellow precipitate was filtered off and refluxed with alcoholic potassium hydroxide until hydrolysis of the ethyl thiocarbonic acid derivative was complete (1 hour). After removal of the ethanol, the residue was dissolved in water, and the solution filtered and acidified with dilute sulphuric acid. The yellow precipitate was filtered off and recrystallised from aqueous ethanol; the *mercapto-thiazine* was obtained as pale yellow needles (3 g.), m. p. 174° (Found : C, 48·9; H, 3·2; N, 7·4. $C_8H_7ONS_2$ requires C, 48·7; H, 3·6; N, 7·1%).

2 : 3-*Dihydro*-3-*ketobenzo*-1 : 4-*thiazine*-6-*arsonic Acid*.—A solution of sodium arsenite (25 c.c.; 20%) was added to the cold diazonium solution, and the mixture rendered alkaline with aqueous sodium hydroxide. After being stirred (3—4 hours), the solution was filtered, the filtrate acidified and boiled with animal charcoal, and the purified filtrate made strongly acid. Brownish crystals were obtained on cooling and were recrystallised from hot water. The *arsonic acid* formed pale yellow plates (0·5 g.), decomp. >300° (Found : C, 33·3; H, 2·7; N, 5·0. $C_8H_8O_4NSAs$ requires C, 33·2; H, 2·8; N, 4·8%).

2 : 3-*Dihydro*-3-*ketobenzo*-1 : 4-*thiazine*-6-*stibonic Acid*.—A solution of antimony trioxide (8 g.) in concentrated hydrochloric acid, added to the ice-cold diazonium solution, gave the *stibonic acid*. This was purified by dissolution in aqueous sodium carbonate and reprecipit-

ation with acid, and then formed a reddish-brown amorphous powder (1 g.), decomp. >270° (Found : C, 28·8; H, 2·5; N, 3·9. $C_8H_8O_4NSSb$ requires C, 28·6; H, 2·4; N, 4·2%).

6-*Chloromercuri*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—The diazonium solution was added to a solution of mercuric chloride (7 g.) in concentrated hydrochloric acid (7 c.c.) mixed with ice (7 g.). After 2 hours' stirring at 0°, the diazonium mercurichloride was filtered off, dried, and decomposed with copper bronze (6 g.) in presence of acetone (80 c.c.) at 0° (3 hours). The temperature was then raised slowly and decomposition completed on the water-bath (1 hour). On cooling, the product was filtered off and recrystallised from nitrobenzene. The *chloromercuri-thiazine* was obtained as pale yellow needles (1 g.), m. p. 263—264° (decomp.) (Found : C, 24·3; H, 1·2; N, 3·4. $C_8H_6ONClSHg$ requires C, 24·0; H, 1·5; N, 3·5%).

Bis-(2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazin*-6-*yl*).—An aqueous alcoholic solution of the diazonium compound was decomposed with copper bronze (5 g.) introduced slowly, the temperature being kept below 30°. After 1 hour, the temperature was raised gradually to 75°, whereupon a vigorous reaction took place, and the resulting reddish-brown precipitate was filtered off. Excess copper was removed, and the residue was purified by refluxing it with absolute ethanol. The *dithiazinyl* was obtained as a brown amorphous powder (3·5 g.), m. p. >330° (Found : N, 8·3. $C_{16}H_{12}O_2N_2S_2$ requires N, 8·5%).

2 : 3-*Dihydro*-6 : 7-*dihydroxy*-3-*ketobenzo*-1 : 4-*thiazine*.—2 : 3-Dihydro-3-keto-6 : 7-dimethoxybenzo-1 : 4-thiazine (5 g.) (Baldick and Lions, *loc. cit.*) was refluxed with a large excess of constant-boiling hydriodic acid for 2 hours. On removal of methyl iodide and addition of a large volume of water, brown crystals separated, which were purified by recrystallisation from distilled water out of contact of air. The *dihydroxy-thiazine* crystallised as pale pink rectangular plates (1 g.), decomp. >240°, becoming deep pink on exposure to air. A purple colour, changing quickly to sky blue, developed with aqueous sodium hydroxide, but no colour with ferric chloride (Found : C, 48·8; H, 3·2; N, 7·0. $C_8H_7O_3NS$ requires C, 48·7; H, 3·6; N, 7·1%).

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