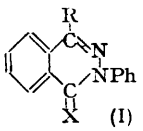
Some Compounds related to 1 : 2-*Dihydro*-4-*hydroxy*-1-*oxo*-2-*phenylphthalazine.*

By David J. Drain and Donald E. Seymour.

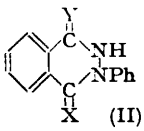
[Reprint Order No. 5800.]

A series of compounds derived from 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine by replacement of one or both oxygen atoms by sulphur has been prepared for testing against *Mycobacterium tuberculosis*. Several related phthalazines are described.

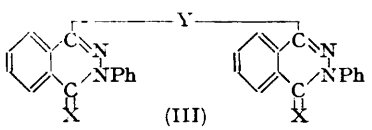
As part of a research relating to the chemotherapy of tuberculosis, 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (I; R = OH, X = O) was prepared and found to exhibit fairly high tuberculostatic activity both *in vitro* and *in vivo* (Bavin, Drain, Seiler, and Seymour, *J. Pharm. Pharmacol.*, 1952, **4**, 844). Although this compound has usually been regarded as existing in the keto-form (II; X = Y = O) the hydroxyphthalazone structure (I; R = OH, X = O) will be used throughout this paper, both for uniformity of nomenclature and because it more truly represents the properties and reactions of the compound.



(I)



(II)



(III)

Because of a certain resemblance between the structure of this compound and that of the tuberculostatic thiosemicarbazones, it was of interest to investigate the biological activity of a series of related compounds in which one or both of the oxygen atoms were replaced by sulphur.

Treatment of 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine with phosphorus pentasulphide in xylene gave the diphthalazinyl sulphide (III; X = Y = S) in addition to the expected 1 : 2-dihydro-4-mercapto-2-phenyl-1-thiophthalazine (I; R = SH, X = S). On oxidation with hydrogen peroxide in alkaline solution the former product was converted

into the corresponding diketo-sulphide (III; X = O, Y = S) which on further oxidation with hydrogen peroxide in acetic acid yielded the diketo-sulphone (III; X = O, Y = SO_2). The thio-thiol (I; R = SH, X = S) was readily alkylated by treatment of its sodium derivative with alkyl halides, and its structure was confirmed by conversion of its *S*-benzyl derivative (I; R = S·CH_2Ph, X = S) with alkaline hydrogen peroxide into the corresponding oxo-compound (I; R = S·CH_2Ph, X = O) also obtained by reaction of 4-chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (I; R = Cl, X = O) with sodium benzyl sulphide.

4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (I; R = Cl, X = O) was readily prepared by the action of phosphoryl chloride on (I; R = OH, X = O). Reaction with sodium alkoxides or sodium alkyl sulphides gave the corresponding alkoxy- or alkylthio-compounds in good yields. The preparation of the alkoxy-compounds by alkylation of (I; R = OH, X = O) was described by Rowe, Gillan, and Peters (*J.*, 1935, 1808) and their formulation of these compounds as *O*-alkyl rather than *N*-alkyl derivatives is confirmed by the above method of preparation.

The chloro-compound with potassium hydrogen sulphide in refluxing ethylene glycol (no reaction occurred in boiling ethanol) yielded 1 : 2-dihydro-4-mercapto-1-oxo-2-phenylphthalazine (I; R = SH, X = O).

Treatment of the 4-alkoxy-compounds (I; R = OAlk, X = O) with phosphorus pentasulphide in boiling xylene yielded a series of 4-alkoxy-1 : 2-dihydro-2-phenyl-1-thiophthalazines (I; R = OAlk, X = S). De-ethylation of the ethoxy-compound gave, in good yield, 1 : 2-dihydro-4-hydroxy-2-phenyl-1-thiophthalazine (I; R = OH, X = S).

Experimental

1 : 2-*Dihydro*-4-*hydroxy*-1-*oxo*-2-*phenylphthalazine* (I; R = OH, X = O).—Refluxing equimolar quantities of phenylhydrazine and phthalic anhydride for 24 hr. in ethanol yielded 79% of *N*-anilinophthalimide together with 11% of 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (cf. Biquard and Grammaticakis, *Bull. Soc. chim. France*, 1942, **9**, 657, who claim a good yield of the phthalazine by an identical method). *N*-Anilinophthalimide was rearranged to 1 : 2-dihydro-4-hydroxy-1-oxo-2-phenylphthalazine in 92% yield by ethanolic sodium ethoxide (Chattaway and Tesh, *J.*, 1920, **117**, 711).

4-*Chloro*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I; R = Cl, X = O).—1 : 2-Dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (20 g.) in phosphoryl chloride (20 c.c.) was heated under reflux for 4 hr., and the mixture poured into 5N-sodium hydroxide (200 c.c.) containing crushed ice. After 1 hr. the solid (17·8 g.; m. p. 124—127°) was collected, washed with water, and recrystallised from aqueous ethanol from which the *chloro*-compound separated as needles, m. p. 130° (Found: C, 65·3; H, 3·45; N, 10·7; Cl, 14·2. $C_{14}H_9ON_2Cl$ requires C, 65·6; H, 3·5; N, 10·9; Cl, 13·9%).

Reaction of 1 : 2-*Dihydro*-4-*hydroxy*-1-*oxo*-2-*phenylphthalazine with Phosphorus Pentasulphide*.—1 : 2-Dihydro-4-hydroxy-1-oxo-2-phenylphthalazine (11·9 g.) in dry xylene (200 c.c.) was refluxed with stirring for 6 hr., during which phosphorus pentasulphide (11·1 g.) was added in six portions. The hot solution was decanted from a small residue and allowed to cool overnight, the yellow crystals which had separated [Solid (A); 4·1 g.; m. p. 250—254°] were collected, and the xylene liquors (B) worked up as described below. Solid (A) was triturated with dilute aqueous sodium hydroxide, and the insoluble material (2·9 g.) was recrystallised from acetic acid from which *di*-(1 : 2-*dihydro*-2-*phenyl*-1-*thio*-4-*phthalazinyl*) *sulphide* (III; X = Y = S) separated as orange needles, m. p. 256·5° (decomp.) (Found: C, 66·8; H, 3·35; N, 10·5; S, 19·1. $C_{28}H_{18}N_4S_3$ requires C, 66·4; H, 3·55; N, 11·1; S, 19·0%). The xylene liquors (B) were steam-distilled to remove xylene, and the residue, an orange-red oil which solidified, was ground with dilute sodium hydroxide solution. Acidification of the alkaline filtrate gave a yellow solid (2·5 g.) which after two recrystallisations from alcohol yielded yellow needles, m. p. 167—168°, of 1 : 2-*dihydro*-4-*mercapto*-2-*phenyl*-1-*thiophthalazine* (I; R = SH, X = S) (Found: C, 62·8; H, 3·7; N, 10·4; S, 22·4. $C_{14}H_{10}N_2S_2$ requires C, 62·2; H, 3·7; N, 10·4; S, 23·7%).

Di-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *Sulphide* (III; X = O, Y = S).—To a suspension of di-(1 : 2-dihydro-2-phenyl-1-thio-4-phthalazinyl) sulphide (0·27 g.) in ethanol (100 c.c.) at 60°, 30% hydrogen peroxide (2 c.c.) was added, followed by methanolic 2N-potassium hydroxide (3 c.c.). After 1 hr. at 60° the mixture was evaporated to dryness *in*

vacuo, the residue triturated with water, and the solid collected (0·23 g.). After two recrystallisations from alcohol *di*-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *sulphide* formed yellow needles, m. p. 198—200° (Found : C, 70·45; H, 3·7; N, 11·5; S, 7·1. $C_{28}H_{18}O_2N_4S$ requires C, 70·9; H, 3·8; N, 11·8; S, 6·75%).

Di-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *Sulphone* (III; X = O, Y = SO_2).—Di-(1 : 2-dihydro-1-oxo-2-phenyl-4-phthalazinyl) sulphide (0·2 g.) in acetic acid (10 c.c.) was heated at 100° with hydrogen peroxide (2 c.c. of 30%). An orange colour, formed initially, faded after a few seconds to give a colourless solution from which crystals soon began to separate. After 1 hr. the mixture was cooled and the product (0·2 g.; m. p. 262—264°) collected. On crystallisation from acetic acid *di*-(1 : 2-*dihydro*-1-*oxo*-2-*phenyl*-4-*phthalazinyl*) *sulphone* was obtained as feathery needles, m. p. 265° (Found : C, 65·0; H, 3·8; N, 10·9; S, 6·2. $C_{28}H_{18}O_4N_4S$ requires C, 66·4; H, 3·55; N, 11·1; S, 6·3%).

4-*Benzylthio*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* (I; R = S·CH_2Ph, X = S).—1 : 2-Dihydro-4-mercapto-2-phenyl-1-thiophthalazine (0·27 g.) in ethanol (5 c.c.) was treated with ethanolic N-sodium ethoxide (1 c.c.) followed by benzyl chloride (0·126 g.). After 1 hour's heating under reflux the solution was cooled and the yellow crystals (0·32 g.; m. p. 134°) were collected and washed with water to remove inorganic material. After recrystallisation from ethanol, 4-*benzylthio*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* separated as yellow needles, m. p. 135° (Found : C, 70·4; H, 4·7; N, 7·8; S, 17·5. $C_{21}H_{16}N_2S_2$ requires C, 70·0; H, 4·45; N, 7·8; S, 17·8%). Similarly prepared were : 4-*Ethylthio*-, yellow needles, m. p. 151°, from ethanol (Found : C, 64·1; H, 4·7; N, 9·3; S, 20·9. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4; S, 21·5%), and 4-(2 : 4-*dinitrophenylthio*)-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine*, orange prisms, m. p. 206°, from acetic acid (Found : C, 54·95; H, 2·9; N, 12·8; S, 14·6. $C_{20}H_{12}O_4N_4S_2$ requires C, 55·05; H, 2·75; N, 12·8; S, 14·7%).

4-*Benzylthio*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I; R = S·CH_2Ph, X = O).—(*a*) To 4-chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (0·18 g.) in ethanol (2 c.c.) was added a solution of sodium benzyl sulphide (from 0·087 g. of the thiol), and the solution heated under reflux. After 30 min. the mixture was diluted with water till turbidity developed, and cooled to yield a solid (0·2 g.). After crystallisation from ethanol, 4-*benzylthio*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* separated as needles, m. p. 117—118° (Found : C, 73·6; H, 4·85; N, 8·1; S, 9·0. $C_{21}H_{16}ON_2S$ requires C, 73·25; H, 4·65; N, 8·15; S, 9·3%).

(*b*) 4-Benzylthio-1 : 2-dihydro-2-phenyl-1-thiophthalazine (0·18 g.) in ethanol (30 c.c.) was heated to 60° and treated with hydrogen peroxide (0·25 c.c. of 30%) followed by methanolic 2N-potassium hydroxide (0·5 c.c.). After 30 min. at 60° the solvents were removed *in vacuo* and the residue was treated with water and acidified with hydrochloric acid. The gum which separated solidified on trituration with ethanol. After recrystallisation from ethanol the compound formed needles, m. p. 116—118° undepressed on admixture with a specimen prepared by method (*a*).

4-*Ethoxy*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I; R = OEt, X = O).—4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (0·25 g.) in ethanol (1 c.c.) was heated under reflux with ethanolic N-sodium ethoxide (1 c.c.) for 60 min. Water was added to the hot solution till turbidity developed and, on cooling, the product (0·2 g.) crystallised. After recrystallisation from light petroleum the ethoxy-compound formed needles, m. p. 104° undepressed on admixture with a specimen prepared by the method of Rowe, Gillan, and Peters (*loc. cit.*).

4-*Ethoxy*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* (I; R = OEt, X = S).—4-Ethoxy-1 : 2-dihydro-1-oxo-2-phenylphthalazine (8·8 g.) in dry xylene (100 c.c.) was treated with phosphorus pentasulphide (7·5 g.) and heated under reflux with stirring for 1 hr. The hot solution was decanted from some gum, the xylene removed by steam-distillation, and the residual orange oil, which solidified, was crystallised from ethanol from which 4-*ethoxy*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine* (8·3 g.) separated as orange-yellow rods, m. p. 153° (Found : C, 67·6; H, 5·05; N, 10·0; S, 11·3. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·9; S, 11·35%).

Similarly prepared were : 1 : 2-*dihydro*-2-*phenyl*-4-*propoxy*-1-*thiophthalazine*, yellow needles, m. p. 128°, from ethanol (Found : C, 69·3; H, 5·5; N, 9·75; S, 10·7. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·45; S, 10·8%), and 4-*butoxy*-1 : 2-*dihydro*-2-*phenyl*-1-*thiophthalazine*, yellow plates, m. p. 96°, from ethanol (Found : C, 69·9; H, 5·8; N, 9·0; S, 10·1. $C_{18}H_{18}ON_2S$ requires C, 69·7; H, 5·8; N, 9·0; S, 10·3%).

1 : 2-*Dihydro*-4-*hydroxy*-2-*phenyl*-1-*thiophthalazine* (I; R = OH, X = S).—4-Ethoxy-1 : 2-dihydro-2-phenyl-1-thiophthalazine (1 g.) in acetic acid (5 c.c.) was boiled under reflux with 48% hydrobromic acid (15 c.c.) for 1 hr. After dilution with water (30 c.c.) the solution was cooled, the solid was collected and dissolved in dilute sodium hydroxide, and the solution was

filtered from a small amount of insoluble matter and acidified with hydrochloric acid. The product (0·65 g.) after recrystallisation from alcohol, formed yellow needles, m. p. 227—230° (Found: C, 66·35; H, 4·1; N, 10·7; S, 12·2. $C_{14}H_{10}ON_2S$ requires C, 66·15; H, 3·95; N, 11·0; S, 12·6%).

1 : 2-*Dihydro*-4-*mercapto*-1-*oxo*-2-*phenylphthalazine* (I; R = SH, X = O).—4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (2·5 g.) and potassium hydrogen sulphide (2·5 g.) in ethylene glycol (25 c.c.) were boiled under reflux for 2 hr. On cooling and dilution with water a yellow solution was obtained which on acidification gave a pale yellow solid (1·2 g.). After recrystallisation from alcohol the *mercapto*-compound formed yellow needles, m. p. 135° (Found: C, 65·8; H, 4·3; N, 10·4; S, 12·1. $C_{14}H_{10}ON_2S$ requires C, 66·15; H, 3·95; N, 11·0; S, 12·6%).

4-*Hydrazino*-1 : 2-*dihydro*-1-*oxo*-2-*phenylphthalazine* (I; R = $NH{\cdot}NH_2$, X = O).—4-Chloro-1 : 2-dihydro-1-oxo-2-phenylphthalazine (0·25 g.), hydrazine hydrate (0·5 c.c. of 100%), and hydrazine sulphate (0·25 g.) were refluxed in ethylene glycol (5 c.c.) for 3 hr. The solution was cooled and water (5 c.c.) added. The product (0·2 g.) separated as needles, m. p. 188—190°. After recrystallisation from aqueous ethylene glycol the *hydrazino*-compound formed pale yellow prismatic needles, m. p. 190° (Found: C, 66·7; H, 4·7; N, 21·9. $C_{14}H_{12}ON_4$ requires C, 66·7; H, 4·75; N, 22·2%).

The p-*nitrobenzylidene derivative* was prepared in alcohol containing a drop of acetic acid; it separated from ethanol in yellow needles, m. p. 237—238° (Found: C, 65·05; H, 4·1. $C_{21}H_{15}O_3N_5$ requires C, 65·4; H, 4·0%). Similarly prepared was the p-*acetamidobenzylidene derivative*, pale yellow, m. p. 246—247°, from aqueous ethanol (Found: C, 69·4; H, 4·75. $C_{23}H_{19}O_2N_5$ requires C, 69·5; H, 4·8%).

We thank Miss J. Layton for experimental assistance and the Directors of Herts Pharmaceuticals Ltd. for permission to publish these results.

CHEMICAL DIVISION, SMITH & NEPHEW RESEARCH LTD.
(FORMERLY CHEMICAL LABORATORIES, HERTS PHARMACEUTICALS LTD.),
HUNSDON LABORATORIES, WARE, HERTS. [*Received, October 12th*, 1954.]