ORGANIC SULFUR COMPOUNDS

PART I. BENZOTHIAZINE HYDROXAMIC ACIDS AND RELATED COMPOUNDS

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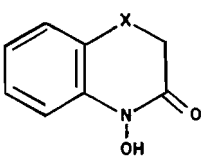
ABSTRACT

2*H*-1,4-Benzothiazine hydroxamic acids of type V (see Table I) are readily prepared by reducing suitably substituted (*o*-nitrophenylthio)acetates (II, R″ = Me or Et) by means of sodium borohydride and palladium–charcoal. The ester precursors can be prepared by the interaction of *o*-nitrothiophenols and α-bromoesters, but such a method is limited in scope. Diethyl bromomalonate, for example, reacts atypically with *o*-nitrothiophenol. The ester precursors are better prepared by Fischer–Speier esterification of the corresponding acids (II, R″ = H) which, in turn, are the products of nucleophilic attack by α-mercaptoacids on suitable *o*-chloro- (or bromo-) nitrobenzenes. This general preparative method failed in two instances. When *o*-chloronitrobenzene or 4-chloro-3-nitrotoluene was reacted with α-mercaptoisobutyric acid, the only acidic product obtained was α,α′-dithiodiisobutyric acid.

Reduction of methyl 2-(*o*-nitrophenylthio)benzoate (VI) with sodium borohydride and palladium–charcoal gave an azoxy compound, namely 2,2′-bis((*o*-methoxycarbonyl)phenylthio)azoxybenzene (VII).

When suitably substituted aromatic *o*-nitroesters are reduced with sodium borohydride and palladium–charcoal, the nitro group is converted into a hydroxylamino group which then cyclizes with the ester group, and cyclic hydroxamic acids are the result. Using this method of reduction, we have prepared a variety of such compounds (1, 2) including 3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine (I*a*), the related sulfone (I*b*) and the corresponding benzoxazine (I*c*). Many cyclic hydroxamic acids possess antibacterial properties (2, 3, 4); Dimboa (3,4-dihydro-2,4-dihydroxy-7-methoxy-3-oxo-2*H*-1,4-benzoxazine) exhibits antimetabolic activity (5) and benzothiazines related to I have been shown to possess anthelmintic properties (6, 7). For these reasons, it was of interest to prepare simple derivatives of I*a* and test them initially for antibacterial activity and for their

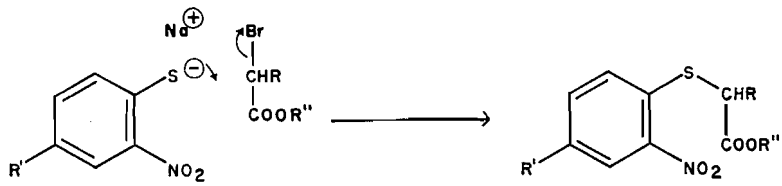


I

(*a*) X = S
(*b*) X = SO_2
(*c*) X = O

action on selected enzymes. This investigation also offered an opportunity to study further the reducing properties of sodium borohydride in the presence of palladium–charcoal.

For the preparation of the precursors (II) required for reduction to 2-substituted 3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazines, the initial method chosen was to condense the appropriate sodium *o*-nitrothiophenolate with suitable α-bromoesters (Scheme 1). This reaction, however, proved to be unsatisfactory. In the first place, the yields of pure *o*-nitrothiophenol obtained by mild reduction of bis(*o*-nitrophenyl) disulfide (III*a*) according to the methods of Claass (8, 9) and Mills and Whitworth (10) were poor, as were the yields of products; in addition, the scope of the reaction was limited by the

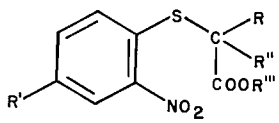


SCHEME 1.

nature of the substituent R on the α-carbon of the bromoester. Using this method, 2-(*o*-nitrophenylthio)propionic acid, its ethyl ester (II*a*), ethyl 2-(*o*-nitrophenylthio)butyrate (II*b*), and methyl (2,4-dinitrophenylthio)acetate (II*c*) were prepared from either the disulfides (III*a* or III*b*) or from sodium *o*-nitrothiophenolate. An unsuccessful attempt to extend this reaction to the preparation of the compound in which R was an ethoxycarbonyl group (II*d*) is described in detail later in this paper.

Numerous attempts were made to prepare (4-trifluoromethyl-2-nitrophenylthio)acetic acid (II*e*) from bis(4-trifluoromethyl-2-nitrophenyl) disulfide (III*c*). Using Claass' method of converting disulfides to thiophenols, the disulfide (III*c*) was reduced to 4-trifluoromethyl-2-nitrothiophenol, which was not isolated before being reacted with chloroacetic acid. By this method, very poor yields of II*e* were obtained. The presence of the trifluoromethyl group and its effect on the solubility in water of the product contributed to the poor yield (11). An attempt to isolate 4-trifluoromethyl-2-nitrothiophenol in pure form, prior to condensing with chloroacetic acid, was unsuccessful.

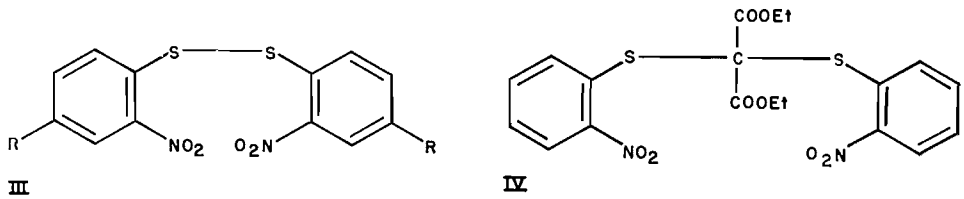
o-Chloronitrobenzene is an alternative starting material for the preparation of compounds of type II. This substance and its simple derivatives are known to react with thioglycollic acid and give (*o*-nitrophenylthio)acetic acids in good yields (12, 13, 14). Using this method, (4-trifluoromethyl-2-nitrophenylthio)acetic acid (II*e*) was prepared from 4-chloro-α,α,α-trifluoro-3-nitrotoluene and was isolated in a yield vastly superior to that obtained as described above. The related 4-bromo and 4-methyl derivatives of (*o*-nitrophenylthio)acetic acid (II*f* and II*g*) were also obtained by this method from 2,5-dibromonitrobenzene and 4-chloro-3-nitrotoluene respectively. This approach to the syntheses of precursors of benzothiazine hydroxamic acids is capable of extension to give the starting materials necessary for the preparation of products substituted in the 2-position of the benzothiazine ring. These starting materials were readily obtained by reacting various *o*-chloro- (or bromo-) nitrobenzenes with α-mercapto acids in the presence of sodium bicarbonate (Scheme 2). Generally, longer reaction times were necessary than when thioglycollic acid was employed in the reaction. Thus, when α-mercaptosuccinic acid and α-mercaptopropionic acid were each condensed with *o*-chloronitrobenzene, 4-chloro-α,α,α-trifluoro-3-nitrotoluene, 2,5-dibromonitrobenzene, and 4-chloro-3-nitrotoluene, a further selection of compounds of type II (II*h*–II*o*) were obtained, usually in good yield. The deactivating effect of the methyl group on the reactivity of 4-chloro-3-nitrotoluene to nucleophilic substitution was clearly illustrated by the fact that the yields of products obtained using this compound were appreciably lower than when the other *o*-nitrochloro (or bromo) compounds were employed in the reactions with α-mercapto acids. The major limitation, however, to this preparative method would seem to be the availability of α-mercapto acids, although the nature of the other substituents on the α-carbon of the mercapto acid and their effect on the reactivity of the thiol group also limits its scope. When, for example, α-mercaptoisobutyric acid is condensed with 4-chloro-α,α,α-trifluoro-3-nitrotoluene or with 2,5-dibromonitrobenzene, the nucleophilic reaction is typical and



II

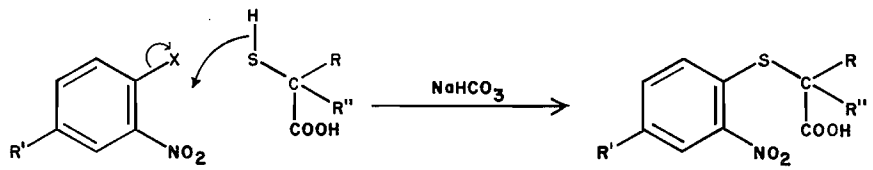
Compound	R	R′	R″	R‴	Compound	R	R′	R″	R‴
a	Me	H	H	Et	*l*	Me	H	H	H
b	Et	H	H	Et	*m*	Me	CF_3	H	H
c	H	NO_2	H	Me	*n*	Me	Br	H	H
d	COOEt	H	H	Et	*o*	Me	Me	H	H
e	H	CF_3	H	H	*p*	Me	CF_3	Me	H
f	H	Br	H	H	*q*	Me	Br	Me	H
g	H	Me	H	H	*r*	Me	H	Me	H
h	CH_2COOH	H	H	H	*s*	Me	Me	Me	H
i	CH_2COOH	CF_3	H	H	*t**	Me	H	H	Me
j	CH_2COOH	Br	H	H	*u*	Me	H	H	Me
k	CH_2COOH	Me	H	H					

*SO_2 replaces S in II.



III IV

a, R = H; *b*, R = NO_2; *c*, R = CF_3.



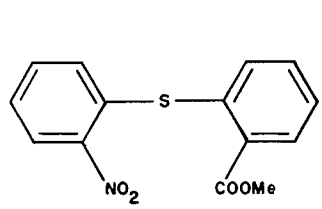
SCHEME 2.

α-(4-trifluoromethyl-2-nitrophenylthio)isobutyric acid (II*p*) and α-(4-bromo-2-nitrophenylthio)isobutyric acid (II*q*) are readily obtained in good yield. No α-(*o*-nitrophenylthio)isobutyric acids were obtained, however, when *o*-chloronitrobenzene and 4-chloro-3-nitrotoluene were reacted with α-mercaptoisobutyric acid. Under the conditions used, neither the thiol group of the α-mercapto acid nor the ortho-chlorine atom of the nitrobenzene employed in the reaction were sufficiently activated to promote a nucleophilic substitution reaction, and, in both cases, the same product, α,α′-dithiodiisobutyric acid, was the only acidic material isolable.

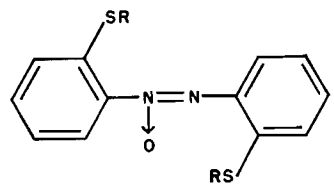
The acids II*e*–II*q* were readily esterified using Fischer–Speier conditions, before being reduced. Reductive cyclization of the esters of type II by means of sodium borohydride and palladium–charcoal produced good yields of cyclic hydroxamic acids (Table I) in most cases. Two attempts to reduce methyl (4-methyl-2-nitrophenylthio)acetate, however, resulted in poor yields of the expected hydroxamic acid (V*g*); the main product of this atypical reaction was the acid (II*g*) of the starting material. Reduction of methyl (2,4-dinitrophenylthio)acetate (II*c*) was also unsatisfactory. A dark brown amphoteric oil was obtained in an amount insufficient for characterization. It gave the color tests expected of

both a primary aromatic amine and a hydroxamic acid which suggested that the isolated nitro group (R′ in formula II) had, as expected, reduced beyond the hydroxylamino stage (15).

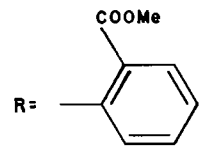
Condensation of methyl *o*-mercaptobenzoate with *o*-chloronitrobenzene produced methyl 2-(*o*-nitrophenylthio)benzoate (VI). This compound was reduced with sodium borohydride and palladium–charcoal in an attempt to prepare a cyclic hydroxamic acid with a seven-membered ring system. Hitherto, reduction of nitro groups with this reagent has produced either primary amines (15) or, as a result of cyclization at the hydroxylamino stage of reduction, cyclic *N*-oxy or *N*-hydroxy compounds (1, 2). In the present case, reduction did occur but the product was neither a primary amine nor a cyclic hydroxamic acid. Instead, an azoxy compound (VII) was obtained. In a different series of reactions, we have found that the yield and the nature of the product obtained in sodium borohydride/palladium–charcoal reductions is greatly influenced by the choice of solvent and the rate of addition of the nitro compound to the reducing medium (16). This is also true in the reduction of VI. When dioxane was employed as solvent and the rate of addition of the



VI



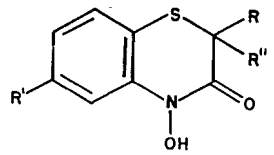
VII



nitro compound was extended to 1 h, a good yield of azoxy compound resulted. A more rapid reduction of VI using ethanol as solvent gave the same product (VII) in much poorer yield. Reduction of the ester (VI) with zinc and ammonium chloride also gave the same azoxy compound, again in poor yield. The structure of the azoxy compound was inferred from its elemental analysis, its color, and the fact that such compounds can be prepared by reducing nitro compounds with zinc and ammonium chloride. Corroboration was obtained from infrared studies. The infrared spectrum of the starting material (VI) showed typical strong absorption in the nitro group regions which was absent in the reduced compound (VII), having been replaced by a strong absorption peak at 1 474 cm^{-1}. This absorption may be attributed to the azoxy group for the reasons which follow. The infrared spectra of 4,4′-dichloroazobenzene, 4,4′-diphenylazobenzene, and 4-chloro-4′-phenylazobenzene were compared with 4,4′-dichloroazoxybenzene, 4,4′-diphenylazoxybenzene, and 4-chloro-4′-phenylazoxybenzene (mixture of isomers) respectively, in the 1 450 – 1 500 cm^{-1} region (17). In the case of each pair of azo and azoxy compounds, the azoxy compound possessed a strong additional absorption peak at 1 473 cm^{-1} (4,4′-dichloroazoxybenzene), 1 469 cm^{-1} (4,4′-diphenylazoxybenzene), and 1 475 cm^{-1} (4-chloro-4′-phenylazoxybenzene mixture). One of the two strong peaks at 1 255 and 1 270 cm^{-1} in the infrared spectrum of compound VII may also be attributed to N—O stretching of an azoxy group (18).

TABLE I

3,4-Dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine hydroxamic acids (V)



V

Compound	R	R′	R″	M.p.	Yield (%)	Calcd.				Found			
						C	H	N	S	C	H	N	S
V*a*	Me	H	H	149–150	43	55.37	4.65	7.17	16.42	55.30	4.47	7.12	16.24
V*b*	Et	H	H	104–106	41	57.39	5.30	6.70	15.32	56.77	5.44	6.60	15.26
V*e*	H	CF_3	H	137–139	87	43.38	2.43	5.62	12.78	43.48	2.62	5.48	12.67
V*f*	H	Br	H	169–170	42	36.94	2.33	5.39	12.33	37.00	2.33	5.39	12.33
V*g*	H	Me	H	105–107	21	55.37	4.65	7.17	16.42	55.36	4.61	7.18	16.35
V*h*	CH_2COOMe	H	H	122–124	71	52.16	4.40	5.53	12.61	52.08	4.57	5.42	12.72
V*i*	CH_2COOMe	CF_3	H	123–125	30	44.86	3.14	4.36	9.98	45.07	3.30	4.47	9.96
V*j*	CH_2COOMe	Br	H	165–167	83	39.77	3.03	4.22	9.65	39.43	2.92	4.36	9.66
V*k*	CH_2COOMe	Me	H	96–97	40	53.92	4.90	5.24	12.00	54.08	4.95	5.53	12.21
V*m*	Me	CF_3	H	126–128	83	45.63	3.06	5.32	12.18	45.77	3.22	5.11	12.45
V*n*	Me	Br	H	157–158	41	39.43	2.94	5.11	11.70	39.44	2.96	4.72	11.50
V*o*	Me	Me	H	135–137	73	57.39	5.30	6.69	15.32	57.25	5.31	7.24	15.45
V*p*	Me	CF_3	Me	100–101	72	47.65	3.64	5.05	11.56	47.58	3.66	5.15	11.77
V*q*	Me	Br	Me	116–118	93	41.68	3.50	4.86	11.13	41.90	3.76	5.15	10.96
V*i**	Me	H	H	186–188	89	47.57	3.99	6.16	14.11	47.32	4.13	6.39	14.15

*SO_2 replaces S in structure V.

One example of a substituted benzothiazine-1,1-dioxide was also prepared during this study. 3,4-Dihydro-4-hydroxy-2-methyl-3-oxo-2*H*-1,4-benzothiazine-1,1-dioxide (V*t*) was readily obtained by sodium borohydride/palladium–charcoal reduction of methyl 2-(*o*-nitrophenylsulfonyl)propionate (II*t*) which was, in turn, the product of oxidizing the related sulfide (II*u*) with potassium permanganate. Presumably the sulfones of the benzothiazines listed in Table I could be prepared in a similar manner.

Reduction by means of hydrazine hydrate and palladium–charcoal is also a suitable method of preparing cyclic hydroxamic acids (19) but when this method was applied to methyl (*o*-nitrophenylthio)acetate, no reduction occurred and the only product isolated was the hydrazide of the starting material. This preparative method was therefore not investigated further.

All the hydroxamic acids listed in Table I gave the expected violet color when ethanolic ferric chloride solution was added to an ethanolic solution of the acid. Addition of water to this solution usually resulted in the precipitation of a brown colored ferric chelate.

As previously mentioned, condensation of sodium *o*-nitrothiophenolate with diethyl bromomalonate gave no diethyl (*o*-nitrophenylthio)malonate (II*d*). Instead, a very good yield of bis(*o*-nitrophenyl) disulfide (III*a*) immediately resulted on the addition of the bromomalonate to an aqueous ethanolic solution of sodium *o*-nitrothiophenolate. The filtrate from this reaction, on concentration and standing, deposited a small amount of diethyl bis(*o*-nitrophenylthio)malonate (IV). Such a structure is suggested by elemental analysis, infrared spectrum, and the fact that the same compound is obtained when diethyl dibromomalonate is reacted with sodium *o*-nitrothiophenolate. The isolation of IV, however, is not due to the presence of diethyl dibromomalonate as an impurity in the monobromomalonate. When the dibromomalonate was condensed with sodium *o*-nitrothiophenolate in aqueous ethanol, a yield in excess of 80% of bis(*o*-nitrophenyl) disulfide was immediately formed and only a small quantity of IV was isolated. This reaction requires further investigation and will be the subject of a later communication. The formation of IV is reminiscent of the findings of Honkanen and Virtanen (20) who interacted sodium *o*-nitrophenolate and diethyl bromomalonate and obtained as a minor product of the reaction, a substance which was apparently diethyl bis(*o*-nitrophenoxy)malonate (IV, O replacing S).

A selection of the compounds of types I and II are at present being tested for antibacterial activity and for their action on selected enzymes. Preliminary results in the latter case are encouraging and will be reported elsewhere.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Equivalent weights were determined in aqueous ethanol by direct titration with standard alkali. Infrared spectra were recorded on a Beckmann I.R. 8 spectrophotometer except where stated otherwise, and microanalyses were carried out by Dr. F. Pascher and E. Pascher, Bonn, who determined the molecular weight values by measurement of vapor pressure. Palladium–charcoal refers to 10% palladium-on-charcoal. Ether solutions were dried over Na_2SO_4.

o-Nitrothiophenol

Using Claass' method (8) except that aqueous acetic acid was employed instead of mineral acid to finally liberate the phenol, apparently good yields of *o*-nitrothiophenol (20–24 g) are obtained from bis(*o*-nitrophenyl) disulfide (30 g). The green precipitate, m.p. 48–52°, is impure, however, only approximately half of it being soluble in light petroleum from which the thiophenol is obtained as yellow crystals, m.p. 59–60°, lit. (10) m.p. 61°.

Ethyl 2-(o-Nitrophenylthio)propionate (IIa)

Bis(*o*-nitrophenyl) disulfide (10 g) was converted to sodium *o*-nitrothiophenolate using Claass' method (9), and to the aqueous solution of the salt was added ethyl 2-bromopropionate (8.8 ml). The mixture was stirred until the red solution became much lighter in color, and the oil which separated was extracted into ether.

The dried ether solution was distilled, and the fraction boiling at 184–188° at 10–15 mm Hg (4.41 g) was collected. The oil solidified when triturated with a little methanol and gave ethyl 2-(*o*-nitrophenylthio)propionate (3.71 g) as yellow crystals, m.p. 47–48°.

Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.71; H, 5.13; N, 5.52; S, 12.55. Found: C, 51.82; H, 4.86; N, 5.67; S, 12.38.

Methyl (2,4-Dinitrophenylthio)acetate (IIc)

This was prepared by the method used for II*a*, from the disulfide (20 g) and methyl bromoacetate (10 ml). The compound was a yellow solid (11.2 g), m.p. 92–93°, lit. (12) m.p. 93–94°.

Ethyl 2-(o-Nitrophenylthio)butyrate (IIb)

o-Nitrothiophenol (3.88 g) was dissolved in a solution of sodium hydroxide (1 g) in water, (4 ml) and ethanol (80 ml). To the red solution was added ethyl 2-bromobutyrate (5.09 g). A precipitate of crude disulfide (III*a*, 0.71 g) was removed and the filtrate was evaporated to 20 ml, flooded with water, and extracted with ether. The washed and dried ether layer was distilled. The yellow oil, b.p. 200–205° at 23 mm Hg, (2.49 g) was ethyl 2-(*o*-nitrophenylthio)butyrate.

Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.51; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.21; H, 5.89; N, 4.96; S, 12.07.

(4-Trifluoromethyl-2-nitrophenylthio)acetic Acid (IIe)

Method (a)

Bis(4-trifluoromethyl-2-nitrophenyl) disulfide (25 g) was heated under reflux with ethanol (200 ml). To the refluxing solution was added successive small portions of a concentrated aqueous solution of sodium sulfide nonahydrate (11.7 g) and sodium hydroxide (6.7 g). The dark red solution of the mercaptide was diluted with water (500 ml), cooled, and filtered. To the filtrate was added a solution of chloracetic acid (16.7 g) and anhydrous sodium carbonate (10 g) in water (100 ml) and the whole was heated gently for 2 h. The cooled solution was then extracted with ether, and the aqueous layer was acidified with dilute hydrochloric acid and yielded an almost black solid (10.3 g), m.p. 90–95°. The crude product was purified by repeated dissolution in sodium bicarbonate solution, followed by reprecipitation with acetic acid and crystallization from benzene. This gave 3.22 g of yellow acid (II*e*), m.p. 158°, lit. (14) m.p. 154–155°.

Method (b)

The acid (II*e*) was obtained in 68% yield from 4-chloro-α,α,α-trifluoro-3-nitrotoluene and thioglycollic acid using the general method of preparing 2-(*o*-nitrophenylthio) acids, which is described below. Reflux time time was 5 h. Crystallization from benzene gave yellow crystals, m.p. 158°.

Anal. Calcd. for $C_9H_6F_3NO_4S$: C, 38.44; H, 2.15; N, 4.98; S, 11.40. Found: C, 38.48; H, 2.04; N, 5.17; S, 11.57.

General Method of Preparing 2-(o-Nitrophenylthio) Acids and Esters of Type II

The substituted *o*-nitrochloro or *o*-nitrobromobenzene (0.05 mole) and the α-mercaptoacid (0.05 mole) were refluxed for the stated time in 50% aqueous ethanol (100 ml), in which was suspended a slight excess of sodium bicarbonate (0.11 or 0.16 mole, for monobasic or dibasic acids respectively). The solution was then concentrated to approximately 50 ml, diluted with water, and extracted with ether. The ether layer was rejected. The *o*-nitrophenylthio acid was obtained in the stated yield from the aqueous solution by acidifying with dilute hydrochloric acid.

The acids listed in Table II were obtained by this method. All were yellow solids, except II*i* and II*p* which were pale brown in color, and all had characteristic infrared spectra (KBr discs) which showed the expected carbonyl, hydroxyl, and nitro group absorption peaks. The corresponding methyl esters were prepared in excellent yield by refluxing the acid (5 g) in methanol (50 ml) containing concentrated sulfuric acid (5 ml) for 18–24 h, and the products were isolated in the normal way. The esters were not analyzed before reduction but were characterized by infrared spectrum and m.p. only (see Table II).

Attempted Preparation of α-(2-Nitrophenylthio)isobutyric Acid (IIr)

o-Chloronitrobenzene (3.15 g), α-mercaptoisobutyric acid (2.48 g) and sodium bicarbonate (7.51 g) were refluxed in 50% aqueous ethanol (50 ml) for 48 h. The resulting pale yellow solution was diluted with water and extracted with ether. The ether layer was rejected. The aqueous solution was acidified and extracted with ether which was washed, dried, and evaporated to give an oily solid. Trituration with benzene gave a nitrogen-free cream solid (0.857 g), m.p. 195–197°. Lit. (21) m.p. of α,α'-dithiodiisobutyric acid is 196°.

Attempted Preparation of α-(4-Methyl-2-nitrophenylthio)isobutyric acid (IIs)

By a similar method to that reported immediately above, the interaction of 4-chloro-3-nitrotoluene (3.456 g) and α-mercaptoisobutyric acid (2.425 g) yielded α,α'-dithiodiisobutyric acid (0.905 g), the infrared spectrum and m.p. of which were identical to those of the compound reported above.

General Method of Preparing Cyclic Hydroxamic Acids by Reducing Esters of Type II with Sodium Borohydride and Palladium–Charcoal

Sodium borohydride (0.8 g) was dissolved in water (5 ml) or in some cases 2% aqueous sodium hydroxide (5 ml), and palladium–charcoal (0.1 g) suspended in water (3 ml) was carefully added. The suspension was

TABLE II

Substituted (*o*-nitrophenylthio)acetic acids (II)

Acid	Yield (%)	M.p.	S*	*t*† (h)	Calcd. C	Calcd. H	Calcd. Eq. wt.	Found C	Found H	Found Eq. wt.	Yield, form, and m.p. of methyl ester
(4-Bromo-2-nitrophenylthio)-acetic (II*f*)‡	63	216–218§	ae	4	—	—	—	—	—	—	91%, yellow solid, 109–110°
(4-Methyl-2-nitrophenylthio)-acetic (II*g*)	51	185–186‖	m	8	—	—	227.2	—	—	225	83%, yellow solid, 105–107°
α-(*o*-Nitrophenylthio)succinic (II*h*)¶	64	187–189	w	24	44.28	3.34	—	44.21	3.39	—	89%, orange oil
α-(4-Trifluoromethyl-2-nitrophenylthio)succinic (II*i*)	60	196–198	ae	24	38.94	2.38	169.6	39.23	2.38	172	92%, brown oil
α-(4-Bromo-2-nitrophenylthio)succinic (II*j*)	69	218–220	e	24	34.30	2.30	175.1	34.62	2.47	176	89%, yellow solid, 70–72°**
α-(4-Methyl-2-nitrophenylthio)succinic (II*k*)	35	215–218	e	24	46.31	3.86	142.6	46.32	3.86	144.5	70%, orange oil
α-(*o*-Nitrophenylthio)propionic (II*l*)	76	107–109	ae	18	47.56	3.99	227.3	47.71	4.12	224	83%, yellow solid, 54°
α-(4-Trifluoromethyl-2-nitrophenylthio)propionic (II*m*)	78	151–152	e	18	40.68	2.73	295.3	40.82	2.93	292	93%, yellow solid, 79–80°
α-(4-Bromo-2-nitrophenylthio)propionic (II*n*)	65	149–150	ae	18	35.31	2.35	305.9	35.56	2.53	310	95%, yellow solid, 62–64°
α-(4-Methyl-2-nitrophenylthio)propionic (II*o*)	47	141–142	ae	18	49.78	4.60	241.3	49.71	4.78	244	90%, yellow solid, 42–43°
α-(4-Trifluoromethyl-2-nitrophenylthio)isobutyric (II*p*)	86	125–126	w	20	42.72	3.26	309.3	42.88	3.34	308	84%, yellow solid, 58–60°
α-(4-Bromo-2-nitrophenylthio)isobutyric (II*q*)	71	137–139	w	18	37.52	3.15	320.2	37.55	3.04	320	62%, yellow solid, 44–46°

*S = Solvent of crystallization, where w = water, e = ethanol, ae = aqueous ethanol, and m = methanol.
†*t* = Reflux time.
‡Sodium salt precipitated during the reaction.
§Lit. (7) m.p. 216–217°.
‖Lit. (7) m.p. 182–183°.
¶Anal. Calcd.: N, 5.16; S, 11.82. Found: N, 5.27; S, 11.66.
**Calcd. for $C_{12}H_{12}NO_6SBr$: S, 8.48; Br, 21.13. Found: S, 8.35; Br, 20.97.

diluted with dioxane (10 ml) and nitrogen was passed through the mixture while the ester (2 g) in dioxane (10–20 ml) was added dropwise over a period of 30 min. The passage of nitrogen was continued for 15 min after the ester had been added. The mixture was then filtered, acidified with dilute hydrochloric acid, and diluted with water. In some cases the hydroxamic acid precipitated and was filtered off. In other cases, the solution was concentrated and extracted with ether. Extraction of the ether solution with sodium carbonate solution or sodium hydroxide solution, acidification of the aqueous layer with dilute hydrochloric acid, reextraction with ether, and evaporation of the ether gave the hydroxamic acid.

Using this general method of reduction, compounds II*a* and II*b*, the methyl esters of compounds II*e* to II*k*, and the methyl esters of compounds II*m* to II*q* gave rise respectively to 3,4-dihydro-4-hydroxy-2-methyl-3-oxo-2*H*-1,4-benzothiazine (V*a*), the corresponding 2-ethyl derivative (V*b*); 6-trifluoromethyl-3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine (V*e*), the corresponding 6-bromo derivative (V*f*), the corresponding 6-methyl derivative (V*g*); methyl 2-(3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazinyl)acetate (V*h*); methyl 2-(6-trifluoromethyl-3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazinyl)acetate (V*i*), the corresponding 6-bromo derivative (V*j*), the corresponding 6-methyl derivative (V*k*); 6-trifluoromethyl-3,4-dihydro-4-hydroxy-2-methyl-3-oxo-2*H*-1,4-benzothiazine (V*m*), the corresponding 6-bromo derivative (V*n*); 3,4-dihydro-4-hydroxy-2,6-dimethyl-3-oxo-2*H*-1,4-benzothiazine (V*o*); 6-trifluoromethyl-3,4-dihydro-4-hydroxy-2,2-dimethyl-3-oxo-2*H*-1,4-benzothiazine (V*p*) and the corresponding 6-bromo derivative (V*q*), in the yields stated (see Table I).

All the hydroxamic acids listed in Table I were white solids and, with the exception of compound V*t* for which ethyl acetate was employed, all were crystallized from ethanol or aqueous ethanol. A solution of each hydroxamic acid in ethanol turned deep violet on the addition of ethanolic ferric chloride solution. The infrared spectrum of each compound in KBr showed typical broad hydroxyl absorption in the 3 000 – 3 400 cm^{-1} region, the position of the peak varying from 3 090 to 3 280 cm^{-1}. Carbonyl absorption within the range 1 635 to 1 655 cm^{-1} was observed in all cases except compounds V*h*, V*i*, V*j*, and V*k* which had two carbonyl peaks, one in the 1 640 to 1 665 cm^{-1} region (hydroxamate carbonyl) and a second within the range 1 720 to 1 730 cm^{-1} (ester carbonyl).

Reduction of Methyl (4-Methyl-2-nitrophenylthio)acetate

This ester (2.408 g) was reduced by the general method. An ether extraction of the acidified filtrate yielded a yellow solid (1.562 g) which was dissolved in sodium carbonate solution (5%) and extracted with ether. The ether extract was rejected. The aqueous layer was again acidified (dilute hydrochloric acid) and (4-methyl-2-nitrophenylthio)acetic acid (II*g*) (0.948 g) was obtained (m.p. and infrared spectrum were identical to those of an authentic sample). The filtrate was extracted with ether which, on drying and evaporation, yielded 3,4-dihydro-4-hydroxy-6-methyl-3-oxo-2*H*-1,4-benzothiazine (V*g*) (0.229 g), m.p. 98–102°, raised to 105–107° on recrystallizing from ethanol.

In a repeat reduction, the ester (1.641 g) yielded II*g* (0.766 g) and V*g* (0.282 g).

Reduction of Methyl (2,4-Dinitrophenylthio)acetate

This acetate (2 g) was reduced by the general method except that methanol was used as solvent, and 2 g of sodium borohydride and 0.2 g of catalyst were employed in the reaction. The acidified filtrate was made slightly basic with ammonia solution, the excess ammonia was boiled off, and the resulting solution was diluted with water and extracted with ether. From the ether solution, a brown oil (0.25 g) was obtained on evaporation. It gave a violet color with alcoholic ferric chloride solution; it could also be diazotized and coupled with β-naphthol and thus gave an orange-red dye.

Methyl o-Mercaptobenzoate

o-Mercaptobenzoic acid (18.4 g) was refluxed for 15 h in methanol (150 ml) containing concentrated sulfuric acid (15 ml) and the ester was isolated as an oil in the usual way. The oil was distilled and the fraction boiling at 154° at 24 mm Hg (15.8 g) was collected and used in the following reaction. Lit. (22) b.p. 252°.

Methyl 2-(Nitrophenylthio)benzoate (VI)

Methyl *o*-mercaptobenzoate (4.21 g) was dissolved in a solution of sodium hydroxide (1 g) in water (2 ml) and methanol (50 ml). To the resulting red solution was added *o*-chloronitrobenzene (4.75 g) dissolved in methanol (20 ml). The mixture was allowed to stand for 4 days at room temperature then it was concentrated to half volume and flooded with water. A yellow precipitate (5.1 g, m.p. 89–93°) was obtained. After crystallizing from ethanol, the m.p. was 93°, lit. (23) m.p. 92–93°. Infrared spectrum (KBr disc): 1 725 (s) (C=O); 1 560 (s), 1 330 (s), 850 (m) (NO_2) cm^{-1}.

Reduction of Methyl 2-(o-Nitrophenylthio)benzoate

Method (a)

Methyl 2-(*o*-nitrophenylthio)benzoate (1.1 g) in dioxane (15 ml) was reduced by the general method described for the preparation of cyclic hydroxamic acids, except that the solution of the benzoate was added over a longer period (1 h) to the sodium borohydride (0.4 g) and palladium–charcoal (0.05 g) in aqueous dioxane. The filtrate was acidified with dilute hydrochloric acid, concentrated, flooded with water, and finally

extracted with ether. The ether extract was shaken with 5% sodium hydroxide solution, shaken with water, dried, and then evaporated to give a yellow neutral oil (1.01 g). This oil solidified when triturated with methanol and yielded, after recrystallization from ethanol, yellow crystals (0.71 g), m.p. 148–149° of 2,2′-bis((*o*-methoxycarbonyl)phenylthio)azoxybenzene (VII). Infrared spectrum (KBr disc): 1 710 (s) (C=O), 1 474 (s), 1 270 (s) or 1 255 (s) (azoxy) cm^{-1} (determined on a Perkin-Elmer model 21 spectrophotometer).

Anal. Calcd. for $C_{28}H_{22}N_2O_5S_2$: C, 63.38; H, 4.18; N, 5.28; S, 12.09; mol. wt. 530.6. Found: C, 63.12; H, 4.24; N, 5.23; S, 12.16; mol. wt. 511.

Method (b)

The ester (2 g) dissolved in a mixture of ethanol:methanol (3:1) (40 ml) was reduced as described in the general method for the preparation of cyclic hydroxamic acids, except that dioxane was replaced with the mixed solvent. The acidified filtrate yielded a viscous orange neutral oil (1.3 g) when treated as described in the experiment immediately above. On standing, followed by trituration with ethanol, the azoxybenzene (VII) was isolated from this oil as orange crystals (0.19 g), m.p. 145–149°.

Method (c)

A solution of ammonium chloride (2 g) in water (20 ml) was added to a solution of methyl 2-(*o*-nitrophenylthio)benzoate (2 g) in ethanol (50 ml). The mixture was stirred, zinc dust (2 g) was added in small portions over 15 min, and stirring was continued for a further 2 h at room temperature. The colorless filtrate was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was shaken successively with 5% sodium carbonate solution and water, dried, and evaporated to give a neutral viscous red oil (1.62 g) which, on standing, gave a yellow solid (0.15 g), m.p. 145–148°; the infrared spectrum of this solid was superimposable on that of the product obtained by methods (*a*) and (*b*).

Anal. Found: C, 63.79; H, 3.87; N, 4.90; S, 11.60.

Methyl α-(o-Nitrophenylthio)propionate (IIu)

Bis(*o*-nitrophenyl) disulfide (30 g) was converted to sodium *o*-nitrothiophenolate using Claass' method (9). The resulting red solution was filtered, and to the filtrate was added a solution of α-chloropropionic acid (18.8 ml) and anhydrous sodium carbonate (12 g) in water (100 ml). The solution was heated for 2 h, cooled, acidified, and extracted with ether. Re-extraction of the ether layer with sodium carbonate solution, followed by acidification (dilute hydrochloric acid) of the aqueous layer gave α-(*o*-nitrophenylthio)propionic acid (II*l*) (22.2 g) as a brown solid; m.p. 76–81°, raised to 106–108° on crystallization from aqueous ethanol. (Compare yield of II*l* by alternative method of preparation—see Table II). Fischer–Speier esterification of the acid gave an almost quantitative yield of the ester (II*u*) as an orange oil which quickly solidified. On crystallization from methanol, a yellow solid, m.p. 54°, was obtained which was not analyzed before oxidation.

Methyl α-(o-Nitrophenylsulfonyl)propionate (IIt)

The sulfide (II*u*) (3.25 g) was dissolved in glacial acetic acid (50 ml). To this solution, a 5% aqueous solution of potassium permanganate (90 ml) was added in small quantities, with stirring, over 1 h; stirring was then continued for an additional hour. Hydrogen peroxide solution was added dropwise to decolorize the solution and the pale brown sulfone crystals which had separated during the reaction (3.09 g, m.p. 77–81°) were filtered off. Crystallization from ethanol gave white rods, m.p. 87–88°.

Anal. Calcd. for $C_{10}H_{11}NO_6S$: C, 43.95; H, 4.06; N, 5.13; S, 11.73. Found: C, 43.79; H, 3.88; N, 5.09; S, 11.68.

3,4-Dihydro-4-hydroxy-2-methyl-3-oxo-2H-1,4-benzothiazine-1,1-dioxide (Vt)

This hydroxamic acid was prepared by reducing methyl α-(*o*-nitrophenylsulfonyl)propionate with sodium borohydride and palladium–charcoal, using the general method previously described. The yield, m.p., and analytical data are recorded in Table I.

Attempted Reduction of Methyl (o-Nitrophenylthio)acetate with Hydrazine Hydrate and Palladium–Charcoal

The ester (prepared in excellent yield by Fischer–Speier esterification of the corresponding acid, ref. 8) (1.923 g) was dissolved in methanol (25 ml), and palladium–charcoal (0.1 g) was added followed by hydrazine hydrate (2 ml). The mixture was refluxed for ½ h, a further 2 ml of hydrazine hydrate were added, and refluxing was continued for another ½ h. The solution was filtered and the filtrate was evaporated to dryness giving a brown oil which was dissolved in hot methanol. On cooling, yellow crystals of (*o*-nitrophenylthio)-acetic acid hydrazide separated (0.625 g), m.p. 164°. Infrared spectrum (KBr disc): 1 646 (s) (C=O); 1 536 (s), 1 342 (s), 856 (m) (NO_2) cm^{-1} when determined on a Perkin-Elmer model 21 spectrophotometer.

Anal. Calcd. for $C_8H_9N_3O_3S$: C, 42.28; H, 3.99. Found: C, 42.08; H, 3.97.

Treatment of o-Nitrothiophenol with Diethyl Bromomalonate

A solution of *o*-nitrothiophenol (3.89 g) was prepared as before (see II*b*). On the addition of diethyl bromomalonate (4.3 ml) with stirring, an immediate precipitate of bis(*o*-nitrophenyl) disulfide (2.703 g, m.p. 196°) resulted. The infrared spectrum was identical with that of an authentic sample. The red colored filtrate was cooled overnight and a second product, diethyl bis(*o*-nitrophenylthio)malonate (IV), separated (0.591 g, m.p. 98–101°). Crystallization from methanol gave yellow needles, m.p. 101–102°; the infrared spectrum displayed the expected bands at 1 775 (C=O); 1 555, 1 355, 855 (NO_2) cm^{-1}.

Anal. Calcd. for $C_{19}H_{18}N_2O_8S_2$: C, 48.92; H, 3.86; N, 6.01; S, 13.73; mol. wt. 466.5. Found: C, 48.72; H, 4.05; N, 5.84; S, 13.69; mol. wt. 464.

Treatment of o-Nitrothiophenol with Diethyl Dibromomalonate

Using the method described in the preparation immediately above, *o*-nitrothiophenol (3.88 g) and diethyl dibromomalonate (3.975 g) gave the disulfide (III*a*, 3.526 g, m.p. 192–196°), and from the concentrated and cooled filtrate, diethyl bis(*o*-nitrophenylthio)malonate (0.165 g) precipitated, m.p. 94–97°, raised to 101–102° on crystallizing from methanol.

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REFERENCES

1. R. T. Coutts and D. G. Wibberley. J. Chem. Soc. 4610 (1963).
2. R. T. Coutts, D. Noble, and D. G. Wibberley. J. Pharm. Pharmacol. **16**, 773 (1964).
3. R. T. Coutts. Can. Pharm. J. (Scientific Section), **97** (6), 32 (1964). See refs. 2–8 contained therein.
4. R. T. Coutts, W. N. Pitkethly, and D. G. Wibberley. J. Pharm. Sci. **54**, 792 (1965).
5. J. E. Reimann and R. U. Byerrum. Tetrahedron Letters, No. 4, 211 (1964).
6. J. Raeburn and A. Mackie. J. Chem. Soc. 787 (1952).
7. A. A. Cutler and A. Mackie. J. Chem. Soc. 3716 (1953).
8. M. Claass. Chem. Ber. **45**, 2424 (1912).
9. M. Claass. Chem. Ber. **45**, 747 (1912).
10. W. H. Mills and J. B. Whitworth. J. Chem. Soc. 2738 (1927).
11. W. T. Caldwell and A. N. Sayin. J. Am. Chem. Soc. **73**, 5125 (1951).
12. P. Friedlander, A. Chwala, and Z. Slubek. Monatsh. **28**, 247 (1907).
13. G. M. Badger, D. J. Clark, W. Davies, K. T. H. Farrer, and N. P. Kefford. J. Chem. Soc. 2624 (1957).
14. Y. E. Gerasimenko, S. M. Shein, G. G. Bakulina, A. P. Cherepivskaya, G. V. Semenyuk, and L. M. Yagupolskii. Zh. Obshch. Khim. **32**, 1870 (1962); Chem. Abstr. **58**, 2524*g* (1963).
15. T. Neilson, H. C. S. Wood, and A. G. Wylie. J. Chem. Soc. 371 (1962).
16. R. T. Coutts and K. W. Hindmarsh. Unpublished results.
17. R. A. Abramovitch and B. A. Davis. Unpublished results.
18. K. Nakanishi. Infrared absorption spectroscopy (practical). Holden-Day, Inc., San Francisco. 1962. p. 51.
19. R. T. Coutts, M. Hooper, and D. G. Wibberley. J. Chem. Soc. 5058 (1961).
20. E. Honkanen and A. I. Virtanen. Acta Chem. Scand. **14**, 1214 (1960).
21. Y. Iskander and Y. Riad. J. Chem. Soc. 2397 (1961).
22. L. Gattermann. Chem. Ber. **32**, 1136 (1899).
23. V. Hach and M. Protiva. Chem. Listy, **51**, 1909 (1957); Chem. Abstr. **52**, 4652*e* (1958).