Canadian Journal of Chemistry

Issued by THE NATIONAL RESEARCH COUNCIL OF CANADA

VOLUME 44 AUGUST 1, 1966 NUMBER 15

ORGANIC SULFUR COMPOUNDS

II. CATALYZED SODIUM BOROHYDRIDE REDUCTIONS OF SELECTED α-(*o*-NITROPHENYLTHIO) ACIDS[1]

R. T. COUTTS, D. L. BARTON, AND ELIZABETH M. SMITH

College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan

Received February 28, 1966

ABSTRACT

The products obtained when α-(*o*-nitrophenylthio) acids are reduced by means of sodium borohydride and palladium–charcoal depend on (*a*) the reaction temperature, (*b*) the solvent, (*c*) the length of time in which the α-(*o*-nitrophenylthio) acid is in contact with the reducing agent, and (*d*) the nature of the substituents on the α-(*o*-nitrophenylthio) acid. By varying these conditions, benzothiazine hydroxamic acids (i.e. substituted 3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazines), the corresponding lactams (3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines), and derivatives of 2-carboxymethylthioazobenzene can be prepared.

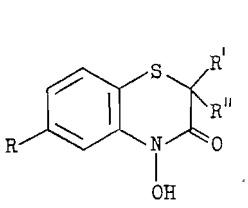
In two cases, additional products were obtained. When (*o*-nitrophenylthio)acetic acid was catalytically reduced for 30 min in dioxane, 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-1,1-dioxide (VI*c*) was an unexpected product, and when α-(4-trifluoromethyl-2-nitrophenylthio)-isobutyric acid was left for a prolonged time in contact with sodium borohydride and palladium–charcoal, a derivative of hydrazobenzene, namely, 2-carboxy(α,α-dimethyl)methylthio-5-trifluoromethylhydrazobenzene (V), was one of the three identified products.

When reduced by means of sodium borohydride and palladium–charcoal, certain aromatic nitro compounds which possess an ester group in a position suitably orientated with respect to the *o*-nitrophenyl group are converted into cyclic hydroxamic acids (1–3); the nitro group is reduced to a hydroxylamino group which then cyclizes with the ester function. When two nitro acids were reduced by similar means, however, complete reduction to the corresponding amines occurred, and in both cases, lactamisation resulted on acidification (1).

We have recently reported (3) that 2*H*-1,4-benzothiazine hydroxamic acids (I) are readily obtained by reducing suitably substituted (*o*-nitrophenylthio)acetates by means of sodium borohydride and palladium–charcoal. On the supposition that reduction of the corresponding acids would yield the related lactams (III), which could be expected to possess anthelmintic properties (4, 5), substituted (*o*-nitrophenylthio)acetic acids were reduced with sodium borohydride and palladium–charcoal. The resulting products depended on (*a*) time, (*b*) solvent, (*c*) nature of the substituents, and (*d*) temperature.

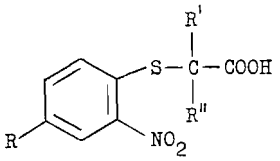
When α-(4-trifluoromethyl-2-nitrophenylthio)propionic acid (II*f*) was reduced in dioxane or methanol over a period of 30 min with excess sodium borohydride in the presence of palladium–charcoal, the corresponding amino compound was not formed (6). The isolation of 6-trifluoromethyl-3,4-dihydro-4-hydroxy-2-methyl-3-oxo-2*H*-1,4-benzothiazine (I*f*) in good yield, on acidification of the filtrate, indicated that reduction had proceeded only as far as the hydroxylamino stage. This reaction is a general one. A total

[1]*For part I in this series, see ref. 3.*



I

	R	R′	R″
a	Br	H	H
b	Cl	H	H
c	Cl	Me	H
d	Br	Me	H
e	CF_3	H	H
f	CF_3	Me	H

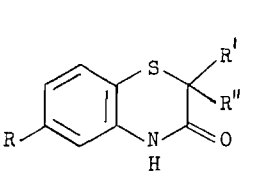


II

	R	R′	R″
g	CF_3	CH_2COOH	H
h	Me	Me	H
i	H	CH_2COOH	H
j	H	Me	H
k	Me	H	H
l	Br	Me	Me
m	CF_3	Me	Me

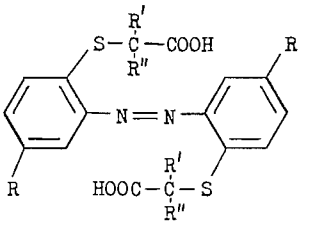
of 13 acids having the general formula II (i.e. II*a*–II*m*) were reduced by this method. In every case, the corresponding hydroxamic acid (I*a*–I*m*) was obtained, usually in good yield, regardless of whether methanol or dioxane was used as solvent (Table I).

A different result was obtained, however, when simple derivatives of (*o*-nitrophenylthio)acetic acid were left in contact with sodium borohydride and palladium–charcoal for extended periods of time. Reduction of (4-trifluoromethyl-2-nitrophenylthio)acetic acid (II*e*) in aqueous dioxane by this method gave initially an almost colorless solution which slowly darkened when left to stand at room temperature. After an interval of 72 h the solution was orange-red in color; at this stage the catalyst was removed and the filtrate acidified. No hydroxamic acid was obtained. Chromatographic analysis of the product showed that it was a mixture containing 6-trifluoromethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (III*a*), 2-carboxymethylthio-5-trifluoromethylazobenzene (IV*a*), and other unidentified material. In the same way, prolonged reductions of α-(4-bromo-2-nitrophenylthio)propionic acid (II*d*), α-(4-trifluoromethyl-2-nitrophenylthio)propionic acid (II*f*), α-(4-methyl-2-nitrophenylthio)propionic acid (II*h*), α-(*o*-nitrophenylthio)propionic acid (II*j*), and α-(4-bromo-2-nitrophenylthio)isobutyric acid (II*l*) with sodium borohydride and palladium–charcoal gave derivatives of 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (III*b*–III*f*, respectively), and azo compounds (IV*b*–IV*f*, respectively). Yields were generally poor, and other unidentified products were also obtained. A similar prolonged reduction of α-(4-trifluoromethyl-2-nitrophenylthio)isobutyric acid (II*m*) again failed to give hydroxamic acid. In this case, the solution had darkened appreciably after the reagents had been in contact for only 24 h. At this stage, the solution was filtered and acidified. Three identifiable products were isolated, two of which were the expected 2-carboxy-(α,α-dimethyl)methylthio-5-trifluoromethylazobenzene (IV*g*) and 6-trifluoromethyl-3,4-dihydro-2,2-dimethyl-3-oxo-2*H*-1,4-benzothiazine (III*g*). The third product has been deduced to be the hydrazo compound (V). Such a structure is compatible with elemental analysis and with equivalent and molecular weight determinations. Evidence from infrared studies also suggests this molecular structure. The infrared spectra of IV*g* and V are similar, except for absorption peaks attributable to the NH group, which occur only in compound V. The infrared spectra of azobenzene and hydrazobenzene were recorded for comparison purposes. As expected, they also showed many similarities, with differences mainly in the regions where NH absorption occurs.



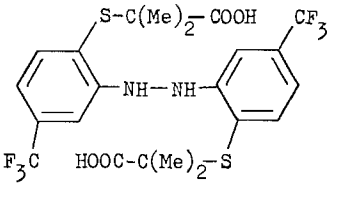
III

	R	R′	R″
a	CF_3	H	H
b	Br	Me	H
c	CF_3	Me	H



IV

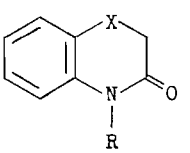
	R	R′	R″
d	Me	Me	H
e	H	Me	H
f	Br	Me	Me
g	CF_3	Me	Me



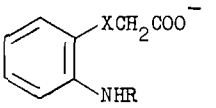
V

In addition to the expected hydroxyl and carbonyl absorption, it was noticeable that the infrared spectra of all the azo compounds (IV*a*–IV*g*) in potassium bromide had an absorption band of weak to medium intensity in the range 1 418 – 1 444 cm^{-1}. Such a band may be ascribed to the azo group (7). The mechanism involved in the formation of the azo and hydrazo compounds from the hydroxylamino intermediates is being investigated at present.

The products obtained from the reduction of (*o*-nitrophenylthio)acetic acid were also dependent on the rate of reduction and on the nature of the solvent used. A fast reduction (30 min) in dioxane gave 3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine (VI*a*) as the major product, though some of the corresponding lactam 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (VI*b*) was also formed. In addition to these products, an unexpected third product, namely, 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-1,1-dioxide (VI*c*), was isolated from the reaction mixture. One explanation for the formation of VI*c* is a concurrent oxidation and reduction of the intermediate VII*a* to yield VII*b* and VII*c*, which cyclize on acidification. A prolonged reduction of (*o*-nitrophenylthio)acetic acid in dioxane gave the lactam in very good yield, and rather surprisingly, no azo compound was obtained. The lactam (VI*b*) was also the only product isolated when the same acid was reduced over a 15 min period in methanol. A similar result was obtained when *o*-chloro-*α*-(*o*-nitrophenylthio)cinnamic acid (VIII) was reduced with an excess of sodium borohydride and palladium–charcoal. A fast reduction in dioxane yielded the hydroxamic acid (IX*a*) as the major product; some lactam (IX*b*) was also isolated. The lactam was the only product obtained when the fast reduction was repeated with methanol as solvent or when the reduction in dioxane was prolonged.

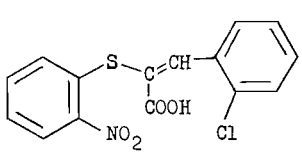


VI

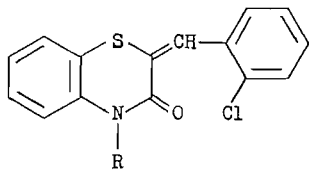


VII

a R = OH, X = S *b* R = H, X = S *c* R = H, $X = SO_2$

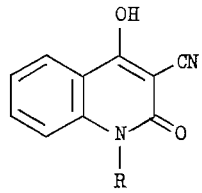


VIII



IX

a R = OH
b R = H



X

a R = OH
b R = H

This is not the first instance of solvent influencing the nature of the product obtained when sodium borohydride and palladium–charcoal are employed to reduce nitro compounds. We have previously reported (1) that the reduction of methyl (*o*-nitrobenzoyl)-cyanoacetate in sodium hydroxide solution gave 3-cyano-1,2-dihydro-1,4-dihydroxy-2-oxoquinoline (X*a*) in excellent yield. We have since found[2] that, when the solvent is changed to methanol, the hydroxamic acid does not form. The product is then the lactam (X*b*).

When α-(4-trifluoromethyl-2-nitrophenylthio)propionic acid (II*f*) was reduced in dioxane with sodium borohydride and palladium–charcoal over a period of 15 min at room temperature and left at 0° for 72 h before filtering and acidifying, the reaction mixture did not darken appreciably. On acidification, the hydroxamic acid (I*f*) was obtained as the major product, even though an excess of sodium borohydride was employed in the reaction. The corresponding lactam (III*c*) was the minor product of this reaction.

The results of this study should be compared with those of Neilson *et al.* (6), who showed that aromatic nitro compounds were smoothly reduced to amines with sodium borohydride and palladium–charcoal. These authors were unable to isolate any intermediate compounds in the reduction and they presented evidence that by-products of the azobenzene, azoxybenzene, or hydrazobenzene type were not formed and subsequently reduced to the amine.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Unicam SP200 spectrophotometer. Palladium–charcoal refers to 10% palladium on charcoal.

Preparation of α-(o-Nitrophenylthio) Acids (IIa–IIm)

With the exception of compounds II*b* and II*c*, the preparations of the acids used in this study were reported in part I (3).

(4-Chloro-2-nitrophenylthio)acetic acid (II*b*) was obtained in 96% yield by the previously described (3) general method for preparing 2-(*o*-nitrophenylthio) acids. It was a yellow solid, m.p. 209°, when recrystallized from methanol (lit. (8) m.p. 209–210°).

α-(4-Chloro-2-nitrophenylthio)propionic acid (II*c*) was prepared by the method described for II*b*. The title compound was obtained as a yellow solid (95% yield), m.p. 134–135°, when recrystallized from methanol. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 300 (m) (OH); 1 700 (s) (C=O); 1 525 (s), 1 340 (s), and 832 (m) (NO_2) cm^{-1}.

Anal. Calcd. for $C_9H_8ClNO_4S$: C, 41.30; H, 3.07. Found: C, 41.63; H, 3.05.

Fast Reductions of α-(o-Nitrophenylthio) Acids (IIa–IIm)

The method of reduction was similar to the one previously used for the reduction of the corresponding esters (3). Palladium–charcoal (0.2 g), suspended in water (10 ml), was added carefully to a solution of sodium borohydride (1 g) in water or 2% sodium hydroxide solution (10 ml) (see Table I). The suspension was diluted with dioxane or methanol (20 ml), and nitrogen was passed through the mixture while a solution of the acid (1 g) in dioxane or methanol (20–40 ml) was added dropwise over a period of 15 min. The reaction was

[2]*R. T. Coutts and S. J. Storey, unpublished results.*

allowed to continue for a further 15 min in an atmosphere of nitrogen; then the catalyst was removed by filtration and the hydroxamic acid was isolated from the filtrate by the methods reported earlier (3).

The yields of hydroxamic acids are recorded in Table I. Four hydroxamic acids (I*b*, I*c*, I*g*, and I*i*) have not been reported previously. Apart from these four compounds, all the hydroxamic acids listed in Table I had properties identical with those already reported (3) for these compounds.

6-Chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (I*b*) was a colorless compound, m.p. 179–180°, when recrystallized from ethanol. Infrared spectrum (KBr disk): 3 180 (m) (OH); 1 675 (s) and 1 628 (m) (free and hydrogen-bonded C=O) cm^{-1}.

Anal. Calcd. for $C_8H_6ClNO_2S$: C, 44.55; H, 2.80; N, 6.50. Found: C, 44.15; H, 2.78; N, 6.67.

6-Chloro-3,4-dihydro-4-hydroxy-2-methyl-3-oxo-2H-1,4-benzothiazine (I*c*) was a pale, tan-colored solid, m.p. 160–161°, when recrystallized from ethanol. Infrared spectrum (KBr disk): 3 120 (m) (OH); 1 675 (s) and 1 638 (s) (free and hydrogen-bonded C=O) cm^{-1}.

Anal. Calcd. for $C_9H_8ClNO_2S$: C, 47.06; H, 3.51; N, 6.10. Found: C, 47.27; H, 3.27; N, 6.43.

2-Carboxymethyl-6-trifluoromethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (I*g*) was a pale-yellow solid, m.p. 178–180°, when recrystallized from aqueous ethanol. Infrared spectrum (KBr disk): broad absorption 2 800 – 3 600 (m) with maximum at 3 300 (OH); 1 700 (s) (acid C=O); 1 642 (s) (hydroxamate C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_8F_3NO_4S$: C, 43.00; H, 2.63; N, 4.56. Found: C, 43.13; H, 2.70; N, 4.47.

2-Carboxymethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (I*i*) was a very pale yellow solid, m.p. 186–188°, when recrystallized from aqueous ethanol. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 400 with maximum at 3 300 (s) (OH); 1 698 (s) (acid C=O); 1 645 (s) (hydroxamate C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.86. Found: C, 50.56; H, 3.70; N, 5.48.

TABLE I

2*H*-1,4-Benzothiazine hydroxamic acids (I) obtained by reducing (*o*-nitrophenylthio) acids (II) with sodium borohydride and palladium–charcoal

Compound	Solvent*	Yield (%)	Compound	Solvent*	Yield (%)
I*a*	d	68	I*f*	m	79
I*b*	d	68	I*g*	d + s	95
I*c*	d	54	I*h*	d	68
I*d*	d	49	I*i*	d	59
I*e*	d	85	I*j*	d	76
I*e*	d + s	84	I*k*	d	30
I*e*	m	94	I*l*	d + s	91
I*f*	d	87	I*m*	d	89

*d = dioxane; d + s = dioxane + 2% sodium hydroxide; m = methanol.

Preparation of o-Chloro-α-(o-nitrophenylthio)cinnamic Acid (VIII)

The title compound was prepared by the reported (9) method. It was a yellow solid, m.p. 213–215°, when recrystallized from methanol (lit. (9) m.p. 215–217°).

Reduction of o-Chloro-α-(o-nitrophenylthio)cinnamic Acid

Method a

A fast reduction of the title compound (1.007 g) was carried out in dioxane by the previously described general method for the reduction of α-(*o*-nitrophenylthio) acids. The filtrate was acidified with concentrated hydrochloric acid, and 2-(*o*-chlorobenzylidene)-3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine (IX*a*) was precipitated as a yellow solid (0.506 g), m.p. 140–143°, which gave a violet color when treated with ethanolic ferric chloride solution. Two recrystallizations from methanol raised the melting point to 143–144°. Infrared spectrum (KBr disk): broad absorption 2 500 – 3 400 with maximum at 3 220 (m) (OH); 1 665 (m) and 1 624 (s) (free and hydrogen-bonded hydroxamate C=O) cm^{-1}.

Anal. Calcd. for $C_{15}H_{10}ClNO_2S$: C, 59.30; H, 3.32; N, 4.67. Found: C, 59.40; H, 3.29; N, 4.76.

The aqueous acidic filtrate remaining after removal of the above hydroxamic acid was completely extracted with ether, and then the combined ether extracts were re-extracted with 10% sodium carbonate solution. Evaporation of the ether solution gave 2-(*o*-chlorobenzylidene)-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (IX*b*) (0.27 g) as a yellow solid, m.p. 229–230°, after recrystallization from methanol (lit. (9) m.p. 225–227°).

Anal. Calcd. for $C_{15}H_{10}ClNOS$: C, 62.60; H, 3.50; N, 4.87. Found: C, 62.99; H, 3.58; N, 4.89.

The sodium carbonate extract was acidified with concentrated hydrochloric acid and extracted with ether. Removal of the ether gave a brown oil (0.1282 g) which was rejected.

Method b

The title compound (1.003 g) was reduced as described in method *a*, except that methanol was used as solvent. The filtrate was acidified with concentrated hydrochloric acid, and when the solution was cooled,

2-(*o*-chlorobenzylidene)-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (IX*b*) (0.346 g) separated as a pale-yellow solid, m.p. 229–230° after recrystallization from methanol. A further yield of IX*b* (0.360 g) was obtained by means of ether extraction of the aqueous acidic filtrate as described in method *a*.

Method c

The title compound (3.04 g) in dioxane (150 ml) was added in small portions over a period of ½ h to a suspension of palladium–charcoal (0.5 g) in 50% aqueous dioxane (50 ml), in which was dissolved sodium borohydride (2.5 g). Nitrogen was passed through the mixture during the addition of the solution of the title compound. The mixture was left for 72 h; then the solution was filtered and the filtrate acidified with concentrated hydrochloric acid. 2-(*o*-Chlorobenzylidene)-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (0.928 g) precipitated as a yellow solid, m.p. 214–217°, raised to 228–230° when recrystallized from methanol. The infrared spectrum was identical with that of an authentic sample. A further yield of IX*b* (0.896 g) was obtained from an ether extraction of the aqueous acidic filtrate as described in method *a*.

Reduction of (o-Nitrophenylthio)acetic Acid

This compound was reduced by methods which were essentially the same as those described under the reduction of *o*-chloro-α-(*o*-nitrophenylthio)cinnamic acid.

(*o*-Nitrophenylthio)acetic acid (1.06 g) in dioxane (50 ml) was reduced as described in method *a*, the solution filtered, and the filtrate acidified. A white solid (0.157 g), m.p. 187–189°, separated. Two recrystallizations from methanol gave 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-1,1-dioxide as a colorless solid, m.p. 208–209° (lit. (10) m.p. 207–208°). Infrared spectrum (KBr disk): broad absorption 2 800 – 3 400 with maxima at 3 090 (m) and 3 210 (m) (lactam NH); 1 682 (s) (C=O) cm^{-1}.

Anal. Calcd. for $C_8H_7NO_3S$: C, 48.72; H, 3.58; N, 7.10; S, 16.26. Found: C, 49.02; H, 3.28; N, 6.92; S, 16.00.

The acidic filtrate remaining after removal of the above product was extracted with ether; then the ether solution was re-extracted with 10% sodium carbonate solution. Evaporation of the ether solution gave 3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine (0.482 g), m.p. 179–180°, when recrystallized from methanol (lit. (11) m.p. 179°). The sodium carbonate solution was acidified and extracted with ether. Removal of the ether gave 3,4-dihydro-4-hydroxy-3-oxo-2*H*-1,4-benzothiazine (0.482 g) as colorless crystals, m.p. 149–150°, when recrystallized from methanol (lit. (1) m.p. 151–152°). The infrared spectra of both compounds were identical with those of authentic samples, and only the latter compound, m.p. 149–150°, gave a violet color when alcoholic ferric chloride solution was added.

This reduction by method *a* has been repeated a number of times. On two occasions, no product separated when the initial filtrate was acidified. The acidic solution was then extracted with ether and the ether-soluble material separated into neutral and acidic products. The neutral material was shown to contain 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (VI*b*) and the corresponding dioxide (VI*c*) by subjecting the mixture to chromatography on Whatman No. 1 paper with methanol–water (1:4) as solvent and locating the spots by means of ultraviolet light. The R_f values for VI*b* and VI*c* are 0.61 and 0.45, respectively.

When the title compound (1.02 g) was reduced by method *b*, a total yield of 0.581 g of 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine was obtained and no hydroxamic acid was isolated.

When the title compound (3.032 g) was reduced by method *c*, a total yield of 1.990 g of 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine was isolated.

Prolonged Reductions of α-(o-Nitrophenylthio) Acids

General Method

The α-(*o*-nitrophenylthio) acid (3 g) was dissolved in dioxane (minimum volume) and the resulting solution was added in small portions over a period of 15 min to an aqueous dioxane solution of sodium borohydride (3 g) in which was suspended palladium–charcoal (0.6 g). Nitrogen was passed through the mixture while the solution of the α-(*o*-nitrophenylthio) acid was added and for a further 15 min. The reaction mixture was then left exposed to the atmosphere at room temperature for 72 h, during which time the almost colorless solution turned dark red in color. The solution was then filtered and the filtrate was acidified with concentrated hydrochloric acid. This gave a dark-colored solid. The solid and the filtrate which remained after its removal were treated as described in individual examples.

Prolonged Reduction of (4-Trifluoromethyl-2-nitrophenylthio)acetic Acid (IIe)

The title compound (2.906 g) was reduced by the general method, and a pale-brown precipitate (2.118 g), m.p. 211–218°, was obtained. A portion (0.522 g) was recrystallized from ethanol and gave 2-carboxymethylthio-5-trifluoromethylazobenzene (IV*a*) (0.155 g) as an orange solid, m.p. 252–253°. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 300 with maxima at 3 050 (m) and 2 900 (m) (OH); 1 700 (s) (C=O); 1 426 (m) (azo) cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}F_6N_2O_4S_2$: C, 43.37; H, 2.43; N, 5.62; S, 12.87. Found: C, 43.68; H, 2.64; N, 5.57; S, 12.83.

A second portion (0.404 g) of the product, m.p. 211–218°, was chromatographed on alumina (8 cm × 1 cm). Elution with benzene gave 6-trifluoromethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine (III*a*) (0.077 g) as a white solid, m.p. 186–187°. Infrared spectrum (KBr disk): broad absorption 2 700 – 3 350 with maxima at 3 190 (m) and 3 095 (m) (lactam NH); 1 672 (s) (C=O) cm^{-1}.

Anal. Calcd. for $C_9H_6F_3NOS$: C, 46.35; H, 2.59; N, 6.01. Found: C, 46.76; H, 2.71; N, 5.57.

The solvent was then changed to methanol, which eluted unidentified material (0.105 g, m.p. 265–285°). Finally a mixture of methanol – 5% sodium hydroxide solution (19:1) was used as eluant. A dark-red solution was obtained which was concentrated to a small volume, diluted with water, acidified with hydrochloric acid, and extracted with ether. Evaporation of the ether solution gave a further quantity of 2-carboxymethylthio-5-trifluoromethylazobenzene (IV*a*) (0.134 g), m.p. 243–251°, raised to 251–253° when recrystallized from methanol–benzene. The infrared spectrum was superimposable on that of the earlier fraction of IV*a* obtained as described above.

Prolonged Reduction of α-(4-Methyl-2-nitrophenylthio)propionic Acid (IIh)

The title compound (2.995 g) was reduced by the general method, and an orange-brown solid (1.092 g), m.p. 170–180°, was obtained. Three recrystallizations from methanol gave 2-carboxy(α-methyl)methylthio-5-methylazobenzene (IV*d*) as a pale-orange solid, m.p. 205–208°. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 300 with maximum at 2 940 (m) (OH); 1 698 (s) (C=O); 1 442 (w) (azo) cm^{-1}.

Anal. Calcd. for $C_{20}H_{22}N_2O_4S_2$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.63; H, 5.20; N, 6.63.

The filtrate remaining after removal of the above solid, m.p. 170–180°, was extracted with ether. The product obtained on evaporation of the ether was dissolved in methanol and chromatographed on alumina (8 cm × 1 cm). Eluate (100 ml) was collected and evaporated. The resulting product was dissolved in ether (ca. 100 ml) and extracted with 10% sodium bicarbonate solution (3 × 50 ml). Evaporation of the washed and dried ether solution gave 3,4-dihydro-2,6-dimethyl-3-oxo-2*H*-1,4-benzothiazine (III*d*) as a pale-brown solid (0.541 g), m.p. 146–152°, raised to 158–159° when recrystallized from aqueous methanol. Infrared spectrum (KBr disk): broad absorption 2 800 – 3 400 with maxima at 3 225 (w) and 3 110 (w) (lactam NH); 1 660 (s) (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 62.14; H, 5.75; N, 7.25; S, 16.59. Found: C, 62.09; H, 6.28; N, 6.90; S, 16.06.

Acidification of the aqueous sodium bicarbonate extract gave an ether-soluble brown oil (0.277 g) which was rejected. A similar oil (0.179 g) was obtained when the eluant for the column was changed to methanol – 5% sodium hydroxide (19:1). It was also rejected.

Prolonged Reduction of α-(4-Trifluoromethyl-2-nitrophenylthio)propionic Acid (IIf)

Method a.—After the title compound (3.018 g) was reduced by the general method, acidification of the filtrate gave no precipitate, and so the solution was concentrated and extracted with ether. The product remaining after removal of the ether was chromatographed on alumina (8 cm × 1 cm) with methanol as eluant. Eluate (100 ml) was collected and evaporated to give product A, which was treated as described below. The eluant was then changed to methanol – 5% aqueous sodium hydroxide solution (19:1), and 100 ml was collected. The solvent was removed and the resulting product (product B) was treated as described below.

Product A was dissolved in ether (100 ml) and the ether solution was extracted with 10% sodium bicarbonate solution. Evaporation of the washed and dried ether solution gave 6-trifluoromethyl-3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzothiazine (III*c*) (0.502 g), m.p. 166–167°, as a pale-brown solid after two recrystallizations from aqueous methanol. Infrared spectrum (KBr disk): broad absorption 2 800 – 3 400 with maxima at 3 180 (w) and 3 080 (w) (lactam NH); 1 660 (s) (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_8F_3NOS$: C, 48.58; H, 3.26; N, 5.67. Found: C, 48.20; H, 3.29; N, 5.15.

Acidification of the aqueous sodium bicarbonate extract with concentrated hydrochloric acid gave 2-carboxy(α-methyl)methylthio-5-trifluoromethylazobenzene (IV*c*) (0.980 g) as an orange solid, m.p. 243–245°, after two recrystallizations from methanol. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 700 with maximum at 2 950 (m) (OH); 1 704 (s) (C=O); 1 432 (m) (azo) cm^{-1}.

Anal. Calcd. for $C_{20}H_{16}F_6N_2O_4S_2$: C, 45.62; H, 3.06; N, 5.32; S, 12.18. Found: C, 45.38; H, 3.31; N, 5.65; S, 12.19.

A solution of product B in water was acidified with concentrated hydrochloric acid, and a further 0.355 g of IV*c* was obtained, m.p. 227–230°, raised to 242–244° when recrystallized from methanol. The infrared spectra of this and the previous product were identical.

Method b.—The title compound (3.012 g) in dioxane (100 ml) was reduced by the general method, except that the reaction mixture was left at 0 °C for the 72 h period. The yellow filtrate was acidified and extracted with ether; the ether solution was re-extracted with 10% sodium carbonate solution. Evaporation of the resulting ether solution left an orange-brown oil which, on trituration with methanol, gave 6-trifluoromethyl-3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzothiazine (0.156 g), m.p. 158–161°, raised to 165–167° when recrystallized from methanol.

The sodium carbonate solution was acidified with concentrated hydrochloric acid, and then extracted with ether. The ether solution, on evaporation, gave 6-trifluoromethyl-3,4-dihydro-4-hydroxy-2-methyl-3-oxo-2*H*-1,4-benzothiazine (I*f*) (1.438 g) as a pale-yellow solid, m.p. 105–109°. Recrystallization from methanol raised the melting point to 124–126° (lit. (3) m.p. 126–128°). The infrared spectrum was identical with that of an authentic sample of the hydroxamic acid.

Prolonged Reduction of α-(o-Nitrophenylthio)propionic Acid (IIj)

The method used to reduce the title compound (3.034 g) was similar to that described for the reduction of α-(4-trifluoromethyl-2-nitrophenylthio)propionic acid (method *a*). With methanol as eluant, acidic and

neutral products were isolated. The acidic material, 2-carboxy(α-methyl)methylthioazobenzene (IV*e*) (0.902 g), was obtained initially as a red oil which solidified (m.p. 138–142°) when triturated with methanol. Recrystallization from aqueous methanol gave an orange solid, m.p. 151–152°. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 300 with maximum at 2 920 (m) (OH); 1 700 (shoulder) (s) and 1 688 (s) (C=O); 1 422 (w) (azo) cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_4S_2$: C, 55.36; H, 4.65; N, 7.17. Found: C, 55.72; H, 4.37; N, 7.58.

The neutral material, 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzothiazine (III*e*) (0.508 g), was obtained as an orange solid, m.p. 117–120°. Recrystallization from aqueous methanol gave a pale-brown solid, m.p. 126–128°. Infrared spectrum (KBr disk): broad absorption 2 700 – 3 400 with maxima at 3 215 (w) and 3 080 (w) (lactam NH); 1 662 (s) (C=O) cm^{-1}.

Anal. Calcd. for C_9H_9NOS: N, 7.82. Found: N, 7.79.

With methanol – 5% sodium hydroxide (19:1) as eluant, a red acidic oil (0.205 g) was obtained which was not investigated further.

*Prolonged Reduction of α-(4-Bromo-2-nitrophenylthio)propionic Acid (II*d*)*

This compound (3.052 g) was reduced by the general method, and the subsequent treatment was similar to that described for the prolonged reduction of α-(4-methyl-2-nitrophenylthio)propionic acid. 5-Bromo-2-carboxy(α-methyl)methylthioazobenzene (IV*b*) (1.707 g) was obtained initially as a red-brown solid, m.p. 167–170°. Two recrystallizations gave an orange solid, m.p. 235–236°. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 700 with maxima at 2 990 (m) and 3 080 (m) (OH); 1 702 (s) (C=O); 1 424 (w) (azo) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}Br_2N_2O_4S_2$: C, 39.43; H, 2.94; N, 5.11; S, 11.70. Found: C, 39.21; H, 2.86; N, 5.10; S, 11.90.

The neutral product was initially obtained as an orange oily solid which was triturated with methanol. In this way, 6-bromo-3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzothiazine (III*b*) (0.696 g) was obtained as a colorless solid, m.p. 188–190°, raised to 192–193° when recrystallized from methanol. Infrared spectrum (KBr disk): broad absorption 2 500 – 3 400 with maxima at 2 980 (m), 3 110 (m), and 3 210 (m) (lactam NH); 1 674 (s) (C=O) cm^{-1}.

Anal. Calcd. for C_9H_8BrNOS: C, 41.87; H, 3.12; N, 5.43. Found: C, 42.18; H, 3.20; N, 5.17.

*Prolonged Reduction of α-(4-Bromo-2-nitrophenylthio)isobutyric Acid (II*l*)*

The title compound (2.89 g) was reduced by the general method. The acidified filtrate was extracted with ether, and the combined ether extracts were re-extracted with 2% sodium hydroxide solution. The dried ether solution, on evaporation, gave 6-bromo-3,4-dihydro-2,2-dimethyl-3-oxo-2*H*-1,4-benzothiazine (III*f*) (0.564 g) as a cream-colored solid, m.p. 178–181°. Recrystallization from benzene gave a colorless solid, m.p. 188–189°. Infrared spectrum (KBr disk): broad absorption 2 700 – 3 350 with maxima at 3 000 (m), 3 130 (m), and 3 230 (m) (lactam NH); 1 670 (s) (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}BrNOS$: C, 44.13; H, 3.70; N, 5.15. Found: C, 44.34; H, 3.66; N, 5.20.

The aqueous alkaline extract was acidified and extracted with ether. The dark-red ether extract was dried and evaporated to give a purple solid (1.740 g) which was triturated with methanol, in which a portion (0.820 g) was insoluble. This insoluble portion was recrystallized from methanol to give 5-bromo-2-carboxy-(α,α-dimethyl)methylthioazobenzene (IV*f*) as purple prisms, m.p. 220–222°. Infrared spectrum (KBr disk): broad absorption 2 400 – 3 300 with maxima at 2 970 (m) and 3 075 (m) (OH); 1 688 (s) (C=O); 1 418 (w) (azo) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}Br_2N_2O_4S_2$: C, 41.68; H, 3.50; N, 4.86; S, 11.13. Found: C, 41.32; H, 3.52; N, 4.82; S, 11.43.

The portion of the purple solid which dissolved when triturated with methanol was not investigated further.

*Prolonged Reduction of α-(4-Trifluoromethyl-2-nitrophenylthio)isobutyric Acid (II*m*)*

The title compound (3.026 g) was reduced by the general method, except that the reaction was allowed to continue for only 24 h, at which time the solution was dark orange in color. The filtrate was acidified with concentrated hydrochloric acid and extracted with ether. The combined ether extracts were dried and evaporated to give a dark-red solid (2.457 g), m.p. 110–121°. A portion (1.40 g) of this solid was chromatographed on alumina (8 cm × 1 cm) with methanol as solvent. Suitable volumes of eluate were collected and evaporated, and the following fractions were collected.

Fraction No.	Weight	Color	Melting point
1	0.089 g	Colorless	139–142°
2	0.364 g	Colorless	135–139°
3	0.376 g	Pink	158–163°
4	0.077 g	Pink	157–160°
5	0.009 g	Cream	136–139°
6	0.065 g	Pink	135–149°

The eluant was changed to methanol – 5% sodium hydroxide (19:1), and the following fractions were isolated after evaporation and acidification.

Fraction No.	Weight	Color	Melting point
7	0.252 g	Pink	151–160°
8	0.061 g	Pink	179–200°

Fractions 1 and 2 were combined and recrystallized from aqueous ethanol to give 6-trifluoromethyl-3,4-dihydro-2,2-dimethyl-3-oxo-2*H*-1,4-benzothiazine (III*g*) as a cream-colored solid, m.p. 144–145°. Infrared spectrum (KBr disk): broad absorption 2 800 – 3 400 with maxima at 3 095 (m) and 3 200 (m) (lactam NH); 1 665 (s) (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}F_3NOS$: C, 50.57; H, 3.86; N, 5.36. Found: C, 50.80; H, 3.79; N, 5.29.

Fractions 3, 4, and 6 were mixtures and not investigated further at this time. Fraction 7 was recrystallized from aqueous ethanol to give 2-carboxy(α,α-dimethyl)methylthio-5-trifluoromethylhydrazobenzene (V) as a pale-pink solid, m.p. 166–168°. To enable direct comparison with the infrared spectrum of IV*g* (see later), the infrared spectrum of V (KBr disk) is given in detail (main peaks only): broad absorption 2 350 – 3 500 with maxima at 3 340 (w), 2 980 (m), 1 686 (shoulder) (s), 1 678 (s) 1 610 (m), 1 585 (m), 1 520 (m), 1 452 (s), 1 424 (s), 1 376 (w), 1 336 (s), 1 276 (s), 1 172 (s), 1 138 (s), 1 128 (s), 1 090 (s), 936 (m), 904 (m), 892 (m), 836 (m), 830 (m), 724 (w), and 678 (w) cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}F_6N_2O_4S_2$: C, 47.48; H, 3.98; N, 5.03; S, 11.52; mol. wt. 556.5; equiv. wt. 278.3. Found: C, 47.55; H, 3.97; N, 4.92; S, 11.66; mol. wt. (vapor pressure) 552; equiv. wt. (direct titration with barium hydroxide in aqueous methanol) 282 ± 12.

Fraction 8 recrystallized from aqueous methanol as a red solid, m.p. 211–213°. It was 2-carboxy(α,α-dimethyl)methylthio-5-trifluoromethylazobenzene (IV*g*). Infrared spectrum (KBr disk): broad absorption 2 300 – 3 500 with maxima at 2 950 (m), 1 692 (s), 1 600 (w), 1 470 (m), 1 444 (w), 1 416 (m), 1 406 (m), 1 376 (w), 1 332 (s), 1 294 (s), 1 186 (s), 1 136 (shoulder) (s), 1 126 (s), 1 088 (s), 954 (m), 924 (shoulder) (s), 918 (s), 850 (s), 826 (w), 736 (w), and 682 (w) cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}F_6N_2O_4S_2$: C, 47.65; H, 3.64; N, 5.05; S, 11.56; mol. wt. 554.5. Found: C, 47.96; H, 3.67; N, 4.91; S, 11.98; mol. wt. (vapor pressure) 548.

ACKNOWLEDGMENT

The financial assistance of the National Research Council of Canada is greatly appreciated.

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 (1965).
3. R. T. Coutts, H. W. Peel, and E. M. Smith. Can. J. Chem. **43**, 3221 (1965).
4. A. Mackie and J. Raeburn. J. Chem. Soc. 787 (1952).
5. A. Mackie and A. A. Cutler. J. Chem. Soc. 3716 (1953).
6. T. Neilson, H. C. S. Wood, and A. G. Wylie. J. Chem. Soc. 371 (1962).
7. R. J. W. LeFevre and R. L. Werner. Australian J. Chem. **10**, 26 (1957).
8. A. Roe and J. W. McGeehee. J. Am. Chem. Soc. **70**, 1662 (1948).
9. V. Baliah and T. Rangarajan. J. Chem. Soc. 4703 (1960).
10. M. Claass. Chem. Ber. **45**, 747 (1912).
11. M. A. T. Rogers and W. A. Sexton. J. Chem. Soc. 1619 (1947).