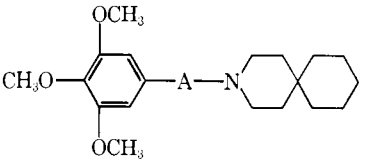
junction was conducted by Rice and coworkers.[2] Several of the *p*-fluoroaroylalkylazaspirane derivatives were found to possess CNS depressant, hypotensive, and antiinflammatory activity and were also found to be clinically effective tranquilizers at doses of 5–10 mg.[2f] N-[γ-(*p*-Fluorobenzoyl)propyl]-3-azaspiro[5.5]undecane possessed marked antipsychotic effect at low dosage, and its behavioral and toxicity effects were similar to those of haloperidol.[2f,3,4] In continuation of our previous work,[5] it was decided to synthesize a similar type of compounds having 3-azaspiro[5.5]undecane as a basic fragment. Accordingly, the compounds of the general formula I were synthesized and studied for their CNS activity.



I, A = CO, $COCH_2$, $COCH_2CH_2$, $COCH_2CH_2CH_2$

**Chemistry.**—N-(3,4,5-Trimethoxybenzoyl)-3-azaspiro[5.5]undecane (I, A = CO), N-(3,4,5-trimethoxyphenacyl)-3-azaspiro[5.5]undecane (I, A = $COCH_2$), and N-[γ-(3,4,5-trimethoxybenzoyl)propyl]-3-azaspiro[5.5]undecane (I, A = $COCH_2CH_2CH_2$) were synthesized by the condensation of 3-azaspiro[5.5]undecane with 3,4,5-trimethoxybenzoyl chloride, α-bromo-3,4,5-trimethoxyacetophenone, and γ-chloro-3,4,5-trimethoxybutyrophenone, respectively. N-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-3-azaspiro[5.5]undecane (I, A = $COCH_2CH_2$) resulted from the Mannich reaction on 3,4,5-trimethoxyacetophenone and 3-azaspiro[5.5]undecane hydrochloride.

All these compounds were tested for CNS activity in mice. The study of gross behavior and spontaneous motor activity revealed that none of the compounds in this series possessed any significant CNS depressant activity.

### Experimental Section[6]

**Intermediates.**—The requisite cyclohexane-1,1-diacetic acid,[7] cyclohexane-1,1-diacetic anhydride,[8] 3-azaspiro[5.5]undecane-2,4-dione,[2f] 3-azaspiro[5.5]undecane,[2f] 3,4,5-trimethoxybenzoyl chloride,[9] 3,4,5-trimethoxyacetophenone,[10] and α-bromo-3,4,5-trimethoxyacetophenone[11] were prepared by the literature methods. γ-Chloro-3,4,5-trimethoxybutyrophenone was obtained as described earlier.[5]

**N-(3,4,5-Trimethoxybenzoyl)-3-azaspiro[5.5]undecane (1).**—To a solution of 3.06 g (0.02 mole) of 3-azaspiro[5.5]undecane and 4.0 g (0.04 mole) of $Et_3N$ in 25 ml of anhydrous $CHCl_3$, was added slowly a solution of 4.6 g (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 25 ml of anhydrous $CHCl_3$. The reaction mixture was refluxed for 4 hr and then cooled, washed ($H_2O$), dried ($Na_2SO_4$), and concentrated. Traces of $CHCl_3$ and $Et_3N$ were removed *in vacuo*. The residue solidified when treated with hexane. The solid was then crystallized first from boiling hexane and then from EtOH, mp 122–123°. *Anal.* ($C_{20}H_{29}NO_4$) C, H, N.

**N-(3,4,5-Trimethoxyphenacyl)-3-azaspiro[5.5]undecane Hydrochloride (2).**—A solution of 3.18 g (0.011 mole) of α-bromo-3,4,5-trimethoxyacetophenone in 30 ml of EtOH was added slowly to a solution of 1.53 g (0.01 mole) of 3-azaspiro[5.5]-undecane and 2.0 g (0.02 mole) of $Et_3N$ in 30 ml of EtOH. The mixture was refluxed for 6 hr and then concentrated. $H_2O$ was added and the residue was extracted with $CHCl_3$. The extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting oil was taken up in anhydrous $Et_2O$ and added to 5 ml of 2-propanolic HCl (22%). This on dilution with ether gave a white solid which was filtered and recrystallized (EtOH), mp 256–258° dec. *Anal.* ($C_{21}H_{31}NO_4 \cdot HCl$) C, H, N.

**N-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-3-azaspiro[5.5]undecane Hydrochloride (3).**—To a solution of 3.8 g (0.02 mole) of 3-azaspiro[5.5]undecane hydrochloride in 60 ml of EtOH, were added 3 ml (~0.03 mole) of aqueous HCHO (37–41%) and a solution of 4.62 g (0.022 mole) of 3,4,5-trimethoxyacetophenone in 30 ml of EtOH. The reaction mixture was refluxed for 7 hr. Additional aqueous $CH_2O$ (3 ml) was added and reflux continued further for 7 hr. It was then concentrated to one-fourth of its volume and allowed to cool, when a white solid separated out which was filtered and crystallized from EtOAc–*i*-PrOH and then from *i*-PrOH, mp 210–212° dec. *Anal.* ($C_{22}H_{33}NO_4 \cdot HCl$) C, H, N.

**N-[γ-(3,4,5-Trimethoxybenzoyl)propyl]-3-azaspiro[5.5]undecane Hydrochloride (4).**—A mixture of 2.73 g (0.01 mole) of γ-chloro-3,4,5-trimethoxybutyrophenone and 3.06 g (0.02 mole) of 3-azaspiro[5.5]undecane was gently warmed so as to form a homogeneous mixture and left overnight at room temperature. The next day, it was heated at 100° for 4 hr. After cooling, water was added to it and extracted twice with 40 ml of $CHCl_3$. The extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residual oil was taken up in anhydrous $Et_2O$ and added to 5 ml of isopropanolic HCl (22%). The resultant white solid was filtered and recrystallized (EtOH), mp 172–174° dec. *Anal.* ($C_{23}H_{35}NO_4 \cdot HCl$) N.

**Acknowledgment.**—The authors wish to thank Mr. M. K. Jaokar for microanalyses and Dr. U. K. Sheth, Professor of Pharmacology, Seth G. S. Medical College, Bombay, for pharmacological screening. They are also grateful to Dr. N. K. Dutta, Director, Haffkine Institute, Bombay, for providing facilities to carry out the present work. One of us (R. B. P.) is greatly indebted to the Indian Council of Medical Research, New Delhi, for the award of a fellowship.

(2) (a) J. B. Clements and L. M. Rice, *J. Org. Chem.*, **24**, 1958 (1959); (b) L. M. Rice and C. H. Grogan, *ibid.*, **26**, 54 (1961); (c) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.*, **6**, 388 (1963); (d) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *ibid.*, **7**, 78 (1964); (e) L. M. Rice, M. E. Freed, and C. H. Grogan, *J. Org. Chem.*, **29**, 2637 (1964); (f) C. H. Grogan, C. F. Geschickter, M. E. Freed, and L. M. Rice, *J. Med. Chem.*, **8**, 62 (1965).

(3) G. M. Simpson, T. Farkas, and J. C. Saunders, *Psychopharmacologia*, **5**, 306 (1964).

(4) G. M. Simpson, J. H. Blair, and E. H. Cranswick, *Clin. Pharmacol. Therap.*, **5**, 310 (1964).

(5) R. B. Petigara, C. V. Deliwala, S. S. Mandrekar, and U. K. Sheth, *J. Med. Chem.*, **11**, 332 (1968).

(6) Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were taken in capillary tubes sealed at one end, with a partial immersion thermometer and are uncorrected.

(7) C. C. Van Wessem and E. L. Sakal (Warner-Lambert Pharmaceutical Co.), U. S. Patent 2,960,441 (Nov 15, 1960); *Chem. Abstr.*, **55**, 9308g (1961).

(8) N. V. Koninklijke Pharmaceutische Fabrieken Voorheen Brocades-Stheeman and Pharmacia, Belgian Patent 638,406 (April 9, 1964); *Chem. Abstr.*, **62**, 13151e (1965).

(9) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed, D. C. Heath and Co., Boston, Mass., 1941, p 381.

(10) J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953).

(11) W. J. Horton and G. Thompson, *ibid.*, **76**, 1909 (1954).

## Studies of Catecholamines. I. Sulfur Analogs of Norepinephrine

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In pursuit of our current interests in catecholamines we have prepared 2-amino-1-(3,4-dihydroxyphenyl)-ethanethiol (throughout the following referred to as

SCHEME I

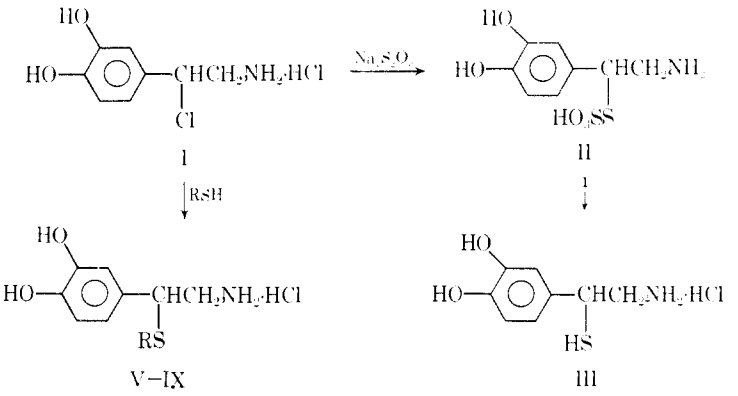
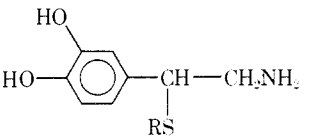


TABLE I

SULFUR ANALOGS OF NOREPINEPHRINE



| Compd | R | Method | Time of reaction, hr | Yield, % | Recrystn solvent | Mp, °C | Formula | Analyses |
|---|---|---|---|---|---|---|---|---|
| IIa | $SO_3H$ | | | | $H_2O$ | 144–145 | $C_8H_{11}NO_5S_2 \cdot H_2O$ | C, H, N, S, $H_2O$ |
| IIb | $SO_3H$ | | | 63 | $H_2O$ | 204–206 | $C_8H_{11}NO_5S_2 \cdot H_2O$ | C, H, N, S, $H_2O$ |
| II | $SO_3H$ | | | | MeOH–EtOH | 189–191 | $C_8H_9NO_5S_2$ | H, S; C[a] |
| III | H | | | 67 | | 184.5–186 | $C_8H_{11}NO_2S \cdot HCl$ | C, H, N, S |
| IV | $CH_3$ | | | 57 | AcOH | 181–182 | $C_9H_{13}NO_2S \cdot HCl$ | C, H, N, S, Cl |
| V | *n*-$C_3H_7$ | A | | 92 | *i*-PrOH | 157.5–158.5 | $C_{11}H_{17}NO_2S \cdot HCl$ | C, H, N, S |
| | | B | 1.25 | 78 | | | | |
| VI | *i*-$C_3H_7$ | B | 3 | 92 | AcOH and *i*-PrOH | 202–203.5 | $C_{11}H_{17}NO_2S \cdot HCl$ | C, H, N, S |
| | | A | | 87 | | | | |
| VII | *n*-$C_4H_9$ | B | 2 | 73 | Dioxane and AcOH | 164–165 | $C_{12}H_{19}NO_2S \cdot HCl$ | C, H, N, S, Cl |
| | | A | | 81 | | | | |
| VIII | *i*-$C_4H_9$ | A | | 90 | AcOH | 200–202 | $C_{12}H_{19}NO_2S \cdot HCl$ | C, H, N, Cl, S |
| IX | $C_6H_5CH_2$ | B | 1 | 79 | *i*-PrOH and EtOH | 191–192.5 | $C_{15}H_{17}NO_2S \cdot HCl$ | C, H, Cl, S |
| X | $CH_2COOH$ | A | 0.5 | 57 | $H_2O$ and 50% EtOH | 153–155 | $C_{10}H_{13}NO_4S \cdot H_2O$ | C, H, N, S, $H_2O$ |
| XI | $CH_2CH_2COOH$ | A | 0.5 | 23 | $H_2O$ | 218–219 | $C_{11}H_{15}NO_4S$ | C, H, N, S |

[a] C: calcd, 43.32; found, 42.79.

thionorepinephrine) and a number of S-alkylated analogs with the purpose of examining their pressor and antiinflammatory properties.

3′,4′-Di-O-alkyl- and -acylthionorepinephrine derivatives have been described by Bhat and Mc Carthy,[1] but as already pointed out by Bretschneider[2] the preparation of analogs of the epinephrine type with unprotected 3′,4′-hydroxyl groups was connected with great difficulties.

We have synthesized all compounds, without protecting the 3′,4′-hydroxyl groups, from the highly reactive β-chloro-β-(3,4-dihydroxyphenyl)ethylamine hydrochloride (I) (Scheme I). The methyl[3] and ethyl[4] ethers of norepinephrine are prepared by passing dry HCl into a mixture of the alcohol and norepinephrine base. In our hands attempts to prepare thioethers of norephinephrine failed when replacing the alcohol by a mercaptan. If, however, dioxane was used as solvent the thioethers could be prepared. This made us consider I as a possible intermediate. By passing dry HCl into a suspension of norepinephrine in dry dioxane, I could be isolated rather pure and characterized by means of ir. It was stable on storage under proper conditions. It could also be prepared by prolonged stirring of norepinephrine in $Et_2O$ saturated with HCl.[5] Apparently it is formed very smoothly, since an attempt to isolate norepinephrine hydrochloride in isopropyl alcohol afforded the corresponding isopropyl ether as the main product[5] (nmr) contrary to an earlier finding.[3] Crude I has previously been prepared by treating norepinephrine base with $SOCl_2$.[6]

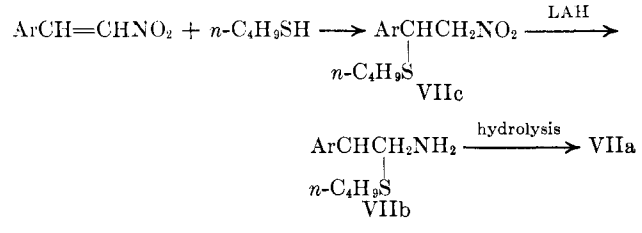
By adding I to a concentrated aqueous solution of $Na_2S_2O_3$, 2-amino-1-(3,4-dihydroxyphenyl)ethylthiosulfuric acid (II) precipitated as a hydrate. By hydrolyz-

(1) K. V. Bhat and W. C. Mc Carthy, *J. Pharm. Sci.*, **53**, 1545 (1964); **56**, 648 (1967).
(2) H. Bretschneider, *Monatsh.*, **81**, 372, 385 (1950).
(3) B. F. Tullar, *J. Am. Chem. Soc.*, **70**, 2067 (1948).
(4) I. Serlin and M. Goldenberg, *Biochem. J.*, **54**, 483 (1953).
(5) S. Rachlin, unpublished observations.
(6) R. A. Heacock, O. Hutzinger, and B. D. Scott, *Can. J. Chem.*, **43**, 2437 (1965).

ing II with concentrated HCl thionorepinephrine (III) was isolated. Because of a slow liberation of $H_2S$ from the rather unstable III purification is somewhat tedious. Sodium methylmercaptide reacted with I forming β-methylthio-β-(3,4-dihydroxyphenyl)ethylamine (IV) (Table I). Other analogous compounds were prepared either by reaction of I with a mercaptan (method A) or by passing dry HCl into a mixture of norepinephrine and the corresponding mercaptan in dry dioxane (method B).

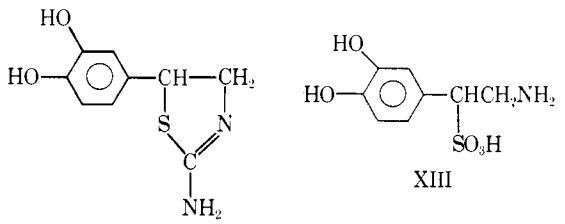
3′,4′-Di-O-alkyl- and -acylthionorepinephrine derivatives are usually prepared by addition of a mercaptan to β-nitrostyrenes and reduction of the nitro group[1,7] (Scheme II). This method yielded β-(*n*-butylthio)-β-(3,4-dihydroxyphenyl)ethylamine (VIIa), identical (ir and tlc) with VII prepared by method A or B.

SCHEME II




Compound I reacted with mercapto acids, such as mercaptoacetic acid and β-mercaptopropionic acid forming X and XI. By heating 2-amino-1-(3,4-dihydroxyphenyl)ethylmercaptoacetic acid (X) at 150° it was transformed into 6-(3′,4′-dihydroxyphenyl)-thiomorpholin-3-one (XIV).

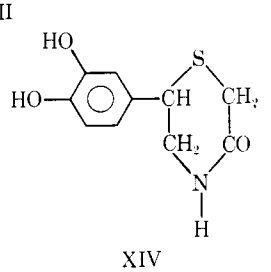
Compound I was also found to react with KSCN and $Na_2SO_3$ forming 2-amino-5-(3,4-dihydroxyphenyl)-2-thiazoline (XII) and 2-amino-1-(3,4-dihydroxyphenyl)ethylsulfonic acid (XIII), respectively. Compound XIII may also be prepared by the method of Schroeter and Higuchi.[8]




XII




XIII




XIV

**Biological Activity.**—The pressor activity (Table II) of the compounds was determined in cats anesthetized with chloralose or pentobarbital and pretreated with hexamethonium or chlorisondamine. In the case of compound V a rat anesthetized with pentobarbital and pretreated with chlorisondamine was used. In these preparations the compounds to be investigated were given in doses equipressor to standard doses of l-norepinephrine (usually 0.5 μg/kg).

TABLE II

PRESSOR ACTIVITIES

| Compd | Pressor act.[a] |
|---|---|
| II | 120 |
| III | 240 |
| IV | 240 |
| V | <8,000 |
| VI | <4,000 |
| VII | <2,000 |
| VIII | 40,000 |
| IX | 6,000 |
| X | 10,000 |
| XI | <20,000 |
| XIII | <10,000 |

[a] Amount equivalent to unit dose of *l*-norepinephrine.

The publication of antiinflammatory properties for a similar type of compounds[7] prompted us to test IV–VII and IX–XI for this effect. None of them revealed any activity, using the kaolin edema of the rat paw as described by Frey and Rohte.[9]

## Experimental Section[10]

**β-Chloro-β-(3,4-dihydroxyphenyl)ethylamine Hydrochloride (I).**—*dl*-Norepinephrine[11] base (205.0 g) was suspended in 2.0 l. of dry dioxane. With vigorous stirring and without cooling, dry HCl was passed into the suspension for 1 hr. The precipitate which formed was filtered off, washed with dioxane followed by $Et_2O$, and dried *in vacuo*. The yield of I was 238.0 g (82%); mp 190° dec; $\nu_{max}^{KBr}$ ($cm^{-1}$) 3200 (broad), 1615, 1510 (broad), 1447, 1358–1340, 1282, 1195, 1158, 1110, 1035 (broad), 930, 935, 855, 810, and 760. *Anal.* ($C_8H_{10}ClNO_2 \cdot HCl$) C, H, N; Cl: calcd, 31.66; found, 31.06.

**2-Amino-1-(3,4-dihydroxyphenyl)ethylthiosulfuric Acid (II).**—Compound I (10.0 g) was added in small portions over 5 min while stirring and cooling with ice to a solution of 11.0 g of $Na_2S_2O_3 \cdot 5H_2O$ in 15 ml of $H_2O$. The mixture was stirred at room temperature for about 15 min. The resulting precipitate was filtered off, washed with a little cold $H_2O$, and dried over $CaCl_2$ *in vacuo*. The yield of IIa was 8.0 g, mp 144–145° dec. Recrystallization from 15.0 ml of water afforded 5.8 g of IIb, mp 204–206° dec.

The hydrate exists in two forms: a lower melting form IIa and a higher melting form IIb. The proportion in which the forms are obtained depends on the concentration of the substance and crystallization temperature. Compound IIb (10.0 g) was dissolved in 30 ml of boiling $H_2O$. After cooling in ice IIa precipitated. It was filtered off and dried over $CaCl_2$ *in vacuo*. The yield of IIa was 7.2 g, mp 147–149° dec.

Anhydrous II was obtained from a solution of 1.0 g of IIa in 25 ml of dry MeOH by evaporation to about 10 ml and addition of dry EtOH. After cooling the precipitate was filtered off and dried over $P_2O_5$ *in vacuo;* yield 0.55 g, mp 189–191° dec.

**2-Amino-1-(3,4-dihydroxyphenyl)ethanethiol Hydrochloride (III).**—Compound IIb (5.0 g) was suspended in 15 ml of concentrated HCl. After 2.5 hr a clear solution resulted and 0.5 hr later a precipitate appeared. The mixture was stirred for an additional 20 hr at room temperature. The precipitate was collected by filtration and stirred with 20 ml of glacial AcOH. Upon filtration, washing with glacial AcOH and $Et_2O$, and finally

(7) T. I. Smith and Nephew Ltd., British Patent, 793,965 (April 23, 1958); *Chem. Abstr.*, **53**, 2156g (1959).

(8) L. S. Schroeter and T. Higuchi, *J. Pharm. Sci.*, **50**, 447 (1961).

(9) H. H. Frey and O. Rohte, *Arzneim.-Forsch.*, **15**, 92 (1965).

(10) Melting points are uncorrected. All compounds gave ir spectra in agreement with their assigned structures. Nmr spectra were obtained on a Varian A-60A instrument: s, singlet; t, triplet; dd, doublet of doublets; m, multiplet; b, broad. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(11) All preparations are based on racemic norepinephrine.

drying over $P_2O_5$ *in vacuo*, 2.6 g of III was obtained; nmr peaks ($D_2O$) (sodium 3-(trimethylsilyl)propanesulfonate (TSS) standard) δ 3.43 (dd, 2, $J$ = 7 and 8 Hz, $CH_2$), 4.17 (dd, 1, $J$ = 7 and 8 Hz, CH), 6.90 (m, 3, aromatic H).

**β-Methylthio-β-(3,4-dihydroxyphenyl)ethylamine Hydrochloride (IV).**—Into a solution of 1.8 g of Na in 50 ml of MeOH was passed 6.1 g of MeSH; then 9.0 g of I was added while stirring and cooling (Dry Ice–$Me_2CO$). The mixture was further stirred while cooling for about 3 hr, filtered, and concentrated *in vacuo* to dryness. Anhydrous $Et_2O$ was saturated with dry HCl and added to the reaction mixture. After repeated evaporation the mixture was treated with hot glacial AcOH, filtered, and cooled. The yield of IV was 6.2 g, mp 178–180°.

**Method A. General Procedure.**—To a suspension of 2.25 g of I in 10 ml of glacial AcOH, 3.0 ml of the appropriate mercaptan was added. The mixture was heated on a steam bath for about 10 min to complete solution. After cooling the precipitate was filtered and recrystallized (Table II).

**2-Amino-1-(3,4-dihydroxyphenyl)ethylmercaptoacetic Acid Hydrate (X). Method A.**—A mixture of 3.3 g of I and 5.0 ml of mercaptoacetic acid was heated on a steam bath for 0.5 hr. After cooling the unreacted mercaptoacetic acid was extracted with $Et_2O$; the residue thus obtained was dissolved in $H_2O$ and the pH was brought to about 5 with $NaHCO_3$. The precipitated solid was collected and washed with 96% EtOH and $Et_2O$: yield 2.2 g, mp 149–151°. Recrystallization from $H_2O$ and 50% EtOH gave 1.2 g, mp 153–155°.

**Method B. β-(*n*-Butylthio)-β-(3,4-dihydroxyphenyl)ethylamine Hydrochloride (VII).**—Norepinephrine (1.0 g) in 10 ml of dry dioxane and 10 ml of $n$-$C_4H_9SH$ were heated on a steam bath for 2 hr while passing dry HCl into the mixture. A small amount of insoluble material was removed by filtration and the filtrate was evaporated to dryness under vacuum. The residue was triturated with $Et_2O$ and EtOAc and the solid material was collected by filtration to give 1.6 g, mp 152–158°.

**2-*n*-Butylthio-2-(3,4-dibenzyloxyphenyl)-1-nitroethane (VIIc).**—Na (1.0 g) was dissolved in 25 ml of MeOH and 2.0 ml of $n$-$C_4H_9SH$ was added. 3,4-Dibenzyloxy-β-nitrostyrene[12] (7.2 g) in 10 ml of dioxane was added while stirring at 10° for 0.5 hr. After stirring for 2 hr at room temperature, the mixture was poured into $H_2O$ and made neutral with AcOH, and the separated oil was extracted with $Et_2O$. The dried extract was evaporated and the residue was extracted with petroleum ether (bp 60–80°). On cooling the extract deposited 4.5 g (50%) of crystals, mp 42.5–44°. Recrystallization from hexane gave mp 44–46°. *Anal.* ($C_{26}H_{29}NO_4S$) C, H, N, S.

**β-(*n*-Butylthio)-β-(3,4-dibenzyloxyphenyl)ethylamine Hydrochloride (VIIb).**—LAH (5.0 g) was suspended in 50 ml of dry $Et_2O$, and 4.5 g of VIIc was added. The reaction mixture was refluxed for 3 hr. $H_2O$ was slowly added, followed by NaOH solution. The $Et_2O$ layer was separated, dried ($Na_2SO_4$), and acidified with dry ethereal HCl. The yield of precipitated VIIb was 2.8 g (61%), mp 123–125°. Recrystallization from EtOAc gave a pure material, mp 128.5–130.5°. *Anal.* ($C_{26}H_{31}NO_2S$·HCl) C, H, Cl, S.

Compound VIIa was prepared by hydrolyzing 0.25 g of VIIb in a mixture of 10 ml of AcOH and 5 ml of concentrated HCl. The mixture was stirred for 4 hr at 60–70° and evaporated. The residue was stirred overnight with EtOAc to give 0.1 g, mp 147–149°; the ir spectrum was identical with that of VII; tlc on silica gel in *i*-PrOH–glacial AcOH–$H_2O$ (45:42:10), $R_f$ (VIIa and VII) 0.62, $R_f$ (VIIb) 0.76.

**2-Amino-5-(3,4-dihydroxyphenyl)-2-thiazoline (XII).**—Compound I (2.2 g) was added to 1.8 g of KSCN in 10 ml of $H_2O$. The solution was heated for 3 min and a precipitate was formed. The reaction mixture was heated for an additional 5 min, cooled, and filtered. After recrystallization from $H_2O$ and 96% EtOH the yield was 1.3 g (62%); mp 227–228°; nmr (DMSO-$d_6$, $Me_3Si$) δ 3.30 (dd, 1, $J$ = 10 and 11 Hz, 1 H in $CH_2$), 3.90 (t, 1, $J$ = 10 Hz, 1 H in $CH_2$), 4.80 (dd, 1, $J$ = 10 and 11 Hz, $CH$), 6.70 (m, 3, aromatic H), 7.95 (bs, 1, OH), 8.42 (bs, 1, OH), 8.82 (bs, 2, $NH_2$). *Anal.* ($C_9H_{10}N_2O_2S$) C, H, N, S.

**2-Amino-1-(3,4-dihydroxyphenyl)ethanesulfonic Acid (XIII).** A mixture of 8.5 g of norepinephrine, 5.2 g of $NaHSO_3$, 31.0 g of $Na_2SO_3$, and 50 ml of $H_2O$ was refluxed for 7 hr under $N_2$. After 15 min of reflux the pH was lowered to 6–7 with 4 *N* HCl. The mixture was evaporated *in vacuo* and extracted with EtOH. The EtOH was removed *in vacuo* and the product was recrystallized twice from $H_2O$; yield 5.0 g (43%) of XIII, mp >350°; nmr ($D_2O$, TSS standard) δ 3.60 (m, 2, $CH_2$), 4.25 (m, 1, CH), 6.95 (m, aromatic H). *Anal.* ($C_8H_{11}NO_5S$) C, H, N, S.

**6-(3,4-Dihydroxyphenyl)thiomorpholin-3-one (XIV).** Compound X (2.1 g) was heated at 150° for 2.5 hr. The product was recrystallized from $H_2O$ to give 1.1 g (61%) of XIV: mp 199–201°; nmr (DMSO-$d_6$, $Me_4Si$) δ 3.30 (s, 2, $SCH_2CO$), 3.45 (m, 2, $CH_2NH$), 4.21 (t, 1, $J$ = 7 Hz, CHS), 6.78 (m, 3, aromatic H), 7.85 (bt, 1, NH), 8.7 (bs, 2, OH). *Anal.* ($C_{10}H_{11}NO_3S$) C, H, N, S.

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## Synthesis of Some Antithyroid Compounds. II

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This paper deals with the preparation of some additional[1] alkyl- and aryl substituted amidinothioureas[2-4] as possible antithyroid compounds. The most highly active antithyroid substances contain thiourea moieties, NHCSNH, capable of being easily oxidized; the suggestion has been made that the interference with thyroxine synthesis is by a direct reaction between $I_2$ and SH (formed by enolization) to form a disulfide.[5-8] It was thought worthwhile to synthesize more amidinothioureas, due to their very facile oxidation into 1,2,4-thiadiazolidine derivatives.[9] The reaction for the synthesis of I follows.

$$BNHCSNH_2 + ArNHCN \xrightarrow[\text{gas}]{HCl} ArNHC(=NH)NHCSNH_2 \cdot HCl$$

I

### Experimental Section

It has been found possible[3,4,9] to prepare many substituted amidinothioureas hydrochlorides (Table I) by the interaction of arylcyanamides with appropriate thioureas.

Equimolecular quantities of arylcyanamides in dry $Et_2O$ solution and 1-alkylthioureas dissolved in $Me_2CO$ were mixed. Dry HCl was passed through the mixture for a few minutes. A colorless crystalline product separated which was filtered and washed thoroughly with warm $Me_2CO$ followed by $Et_2O$.

**Pharmacological Screening.**[10-14]—Male Sprague-Dawley rats

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