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.* ($C_{29}H_{29}NO_4S$) 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.* ($C_{29}H_{31}NO_2S$·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_3Si) 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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(12) I. Baxter, L. T. Allan, and G. A. Swan, *J. Chem. Soc.*, 3154 (1955).

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.[2] The reaction for the synthesis of I follows.

$$RNHCSNH_2 + ArNHCN \xrightarrow[\text{gas}]{HCl} ArNHC(=NH)NHCSNH_2 \cdot HCl \quad (R)$$

I

Experimental Section

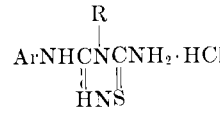
It has been found possible[2-4,9] to prepare many substituted amidinothioureas hydrochlorides (Table I) by the interaction of arylcyanamides with appropriate thioureas.

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

(1) P. K. Srivastava and M. Saleem, *J. Med. Chem.*, **12**, 196 (1969).
(2) C. P. Joshua, V. K. Verma, and K. S. Suresh, *Tetrahedron Lett.*, **19**, 663 (1961).
(3) C. P. Joshua, *J. Sci. Ind. Res.* (India), **21B**, 588 (1962).
(4) S. N. Pandeya, *Indian J. Chem.*, **1**, 525 (1963).
(5) D. Campbell, F. W. Landgrebe, and T. N. N. Morgan, *Lancet*, **246**, 630 (1944).
(6) E. J. Baumann, N. Metzger, and D. Marine, *Endocrinology*, **34**, 14 (1944).
(7) C. H. Li, *J. Amer. Chem. Soc.*, **67**, 1065 (1945).
(8) R. H. Williams, A. R. Weinglass, and G. A. Kay, *Am. J. Med. Sci.*, **207**, 701 (1944).
(9) P. K. Srivastava, *Indian J. Chem.*, **1**, 432 (1963).
(10) C. S. Pittman and E. L. Jones, *Endocrinology*, **73**, 403 (1963).
(11) R. Pitt-Rivers, V. Gabon, and N. S. Halmi, *ibid.*, **63**, 699 (1958).
(12) W. D. Alexander and J. Wolf, "Current Topics in Thyroid Research," Proceedings of the International Thyroid Conference, 5th, Rome, May 23-27, 1965, p 271.
(13) V. A. Gabon and R. Pitt-Rivers, *Endocrinology*, **64**, 835 (1959).
(14) R. Pitt-Rivers, *Ann. N. Y. Acad. Sci.*, **86**, 362 (1960).

TABLE I



No.	Ar	R	Formula[a]	Yield, %	Mp, °C
I	CH_2=$CHCH_2$	CH_2=$CHCH_2$	$C_8H_{14}N_4S\cdot HCl$	80	145–146
II	2,6-$(CH_3)_2C_6H_3$	*n*-Bu	$C_{14}H_{22}N_4S\cdot HCl$	75	139–140
III	*p*-$CH_3OC_6H_4$	*n*-Bu	$C_{13}H_{20}N_4OS\cdot HCl$	75	134–135
IV	*m*-$CH_3OC_6H_4$	*n*-Bu	$C_{13}H_{20}N_4OS\cdot HCl$	72	142–144
V	*p*-$CH_3C_6H_4$	*n*-Bu	$C_{13}H_{20}N_4S\cdot HCl$	77	129–130
VI	*p*-$C_2H_5OC_6H_4$	*n*-Bu	$C_{14}H_{28}N_4OS\cdot HCl$	70	159–160
VII	*p*-ClC_6H_4	*n*-Bu	$C_{12}H_{17}ClN_4S\cdot HCl$	78	144–146
VIII	*p*-$CH_3C_6H_4$	CH_3	$C_{10}H_{14}N_4S\cdot HCl$	76	158–160
IX	2,6-$(CH_3)_2C_6H_3$	CH_3	$C_{11}H_{16}N_4S\cdot HCl$	75	152–153
X	C_6H_5	CH_3	$C_9H_{12}N_4S\cdot HCl$	78	167–168

[a] All compounds were analyzed for N and S and the analytical results were within ±0.4% of the theoretical values.

TABLE II

ANTITHYROIDAL ACTION IN INTACT RATS

Compd[a] (mg)	Thyroid radioactivity, dpm ± std error: ^{125}I uptake	PB^{125}I	Inorg ^{125}I	Estd act. (thiouracil = 1.0)
Blank	272,189 ± 13,670	237,730 ± 12,340	25,017 ± 1238	
Thiouracil (0.500)	39,428 ± 9233[b]	30,679 ± 7645[b]	8,102 ± 1694[b]	1.0
I (0.913)	45,714 ± 6683[b]	38,247 ± 5857[b]	5,933 ± 899[b]	0.63
II (1.22)	41,152 ± 17,735[b]	34,984 ± 16,240[b]	4,837 ± 1341[b]	0.57
III (1.45)	24,764 ± 5672[b]	18,318 ± 4762[b]	5,155 ± 601[b]	1.01
IV (1.43)	64,265 ± 12,059[b]	52,448 ± 10,708[b]	9,852 ± 1251[b]	0.74
V (1.30)	22,967 ± 5011[b]	15,674 ± 4151[b]	6,253 ± 691[b]	1.31
VI (1.54)	29,005 ± 4056[b]	22,538 ± 3658[b]	5,408 ± 339[b]	0.91
VII (1.46)	65,647 ± 10,866[b]	52,935 ± 8888[b]	8,482 ± 1203[b]	0.62
VIII (1.01)	87,405 ± 25,535[b]	74,372 ± 21,921[b]	8,468 ± 2041[b]	0.42
IX (1.06)	74,005 ± 12,561[b]	62,403 ± 22,513[b]	8,324 ± 979[b]	0.54
X (1.19)	128,604 ± 33,855[c]	113,338 ± 31,297[c]	10,189 ± 1768[b]	0.33

[a] Concentration of test compounds equimolar to thiouracil. [b] $P < 0.001$. [c] $P < 0.01$.

(100–125 g) were maintained on a low-iodide diet for 3 days then divided into groups consisting of four rats in each group. The animals in each group received an intraperitoneal injection of 1 ml of either a blank (0.9% NaCl), thiouracil, or one of the test compounds. One hour later, 1 μCi of Na^{125}I (carrier free) was injected intraperitoneally. Three hours after the injection of ^{125}I, the animals were sacrificed and the thyroids were removed. The whole lobes were placed in ground-glass homogenizing tubes and counted in a Nuclear-Chicago well scintillation counter to determine total thyroidal uptake. The whole lobes were then homogenized in 1 ml of 0.05 *M* barbital buffer (pH 8.6) containing 1.0×10^{-5} *M* thiouracil. One milliliter of cold 20% trichloroacetic acid (TCA) was added and the homogenate was centrifuged. The precipitate was washed twice with 1.0 ml of cold 10% TCA. The original supernatant and the two washes were combined and the radioactivity was determined. The ^{125}I in this fraction indicated the concentration of inorganic ^{125}I or TCA-soluble ^{125}I. The washed precipitate was counted in the homogenizing tube. The radioactivity in this fraction indicated the PB^{125}I (protein-bound iodine) or the TCA-precipitable ^{125}I. The counts were all corrected for counting efficiency and are expressed as disintegrations per minute.

All compounds were dissolved in saline for injection. Thiouracil and IX were dissolved with heating to 55°; III was only partially dissolved in saline, EtOH, or NH_4OH, and therefore it was injected as a suspension in saline. All compounds (except III, IX, and X) were assayed at concentrations equimolar and ten times equimolar to 0.5 mg of thiouracil (3.9 μmoles) and the biological effect was almost the same at both doses. Table II summarizes the observations made with compounds I–X.

All the compounds have antithyroidal activity and appear to inhibit incorporation of I_2 in a manner similar to thiouracil. Compounds III, V, and possibly VI appear to be slightly more potent than thiouracil while IV and VII–X appear to be slightly less potent.

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Antiinflammatory Aryl Pyridyl Ketones

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In a routine screening evaluation for nonsteroidal antiinflammatory[2] agents, it was found that 2-benzoylpyridine (**1**) possessed a good level of activity in the carrageenan foot edema assay.[3] This finding prompted us to prepare a series of aryl pyridyl ketones for evaluation as potential antiinflammatory agents.

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(2) For a survey of recent developments in nonsteroidal antiinflammatory agents see T. Y. Shen in "Annual Reports in Medicinal Chemistry, 1967," C. K. Cain, Ed., Academic Press, New York, N. Y., pp 215–226.

(3) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).