from glacial acetic acid gave material melting sharply at 61–62°, but several additional recrystallizations from methanol gave the pure *cis* isomer, m.p. 74–74.5°. Carbon and hydrogen analysis of the material melting at 61–62° supported the conclusion that it was a mixture of *cis*- and *trans*-benzyl sulfones. A mixture of the *cis*- and *trans*-sulfones melted at 62–76°.

Isomerization of *cis*-2-Methylpentyl Benzyl Sulfone.—Treatment of either the pure *cis*-benzyl sulfone or the mixture of benzyl sulfones melting at 61–62° according to the method used to isomerize *cis*-2-methylcyclohexyl benzyl sulfone gave a 91% conversion to the *trans*-sulfone, m.p. 98–100°.

Attempts to isomerize the *cis*-thiol or *cis*-benzyl sulfide by this procedure were unsuccessful.

***cis*- and *trans*-2-Methylcyclohexyl Phenyl Sulfones.**—*cis*-2-Methylcyclohexylphenyl sulfide was prepared by heating a mixture of *cis*-2-methylcyclohexanethiol with iodobenzene and copper powder at 220° according to the procedure described by Cunneen.[4b] The sulfide also was prepared in 50% yield from 1-methylcyclohexene and thiophenol by heating on the steam-bath in the presence of *t*-butyl peroxide. Oxidation of each of these samples with 30% hydrogen peroxide in glacial acetic acid gave the same sulfone, m.p. 107–108° after recrystallization from methanol; Cunneen[4b] reports the melting point as 108°. Isomerization of the sulfone by the method described above gave an 85% yield of ***trans*-2-methylcyclohexyl phenyl sulfone** (m.p. 82–86°), which melted at 90–90.5° after recrystallization from methanol.

Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.40; H, 7.30.

A mixture of the *cis*- and *trans*-sulfones melted at 88–95°.

Addition of Thiolacetic Acid to 1-Hexene in Carbon Tetrachloride Solution.—Thiolacetic acid (28 g., 0.3 mole) was added slowly to a solution of 25 g. (0.3 mole) of 1-hexene in 461.5 g. (3 moles) of carbon tetrachloride under irradiation. The yield of *n*-hexyl thiolacetate, b.p. 88° (13 mm.), $n^{25}D$ 1.4591, was 83%; Wenzel and Reid[18] reported b.p. 205.8° (760 mm.), $n^{25}D$ 1.4591.

2-Mercaptomethyl-3,3-dimethylbicyclo[2,2,1]heptane.—Addition of 90 g. (1.2 moles) of thiolacetic acid to 136 g. (1 mole) of camphene in the usual manner gave 164 g. (77%) of 2-(S-thiolacetoxymethyl)-3,3-dimethylbicyclo[2,2,1]heptane, b.p. 93–95° (0.8–1.0 mm.); Behringer[4c] reports a boiling point of 147–148° (14 mm.). Alkaline hydrolysis gave 109 g. (83%) of 2-mercaptomethyl-3,3-dimethylbicyclo[2,2,1]heptane, b.p. 116° (20 mm.).

Anal. Calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65. Found: C, 70.68; H, 10.64.

The 2,4-dinitrophenyl sulfide[17] of this thiol melted at 126–126.5° after crystallization from alcohol.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: N, 8.33. Found: N, 8.33.

Isocamphane from the Desulfurization of 2-Mercaptomethyl-3,3-dimethylbicyclo[2,2,1]heptane.—Following the procedure of Papa, Schwenk and Ginsberg[19] a solution of 20 g. (0.117 mole) of thiol in 500 ml. of 10% aqueous sodium hydroxide and 40 ml. of alcohol was heated and stirred vigorously on a steam-bath for two hours, during which time 40 g. of Raney nickel alloy was added to the solution in small increments. The reaction mixture was heated an additional two hours and the product accumulating in the condenser during this time was washed back into the reaction flask with a little alcohol. The mixture was then steam distilled, and the distillate extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, and then distilled through a 3-plate Vigreux column to yield 3.5 g. (22%) of isocamphane, b.p. 163–164°, m.p. 54–56°. The reported physical constants[20] are b.p. 164.5° and m.p. 65–66° (the expected rearrangement product, camphane, boils at 160–161° and melts at 156–156.5°[20]).

The Addition of Thiolacetic Acid to β-Pinene.—The addition of 25.4 g. (0.33 mole) of freshly distilled thiolacetic acid to 45 g. (0.33 mole) of β-pinene gave 59 g. (84%) of thiolacetate, b.p. 91–92° (0.5 mm.), $n^{25}D$ 1.5090.

Anal. Calcd. for $C_{12}H_{20}OS$: C, 67.87; H, 9.49. Found: C, 68.00; H, 9.44.

Hydrolysis of 53 g. (0.25 mole) of the thiolester gave 40 g. (94%) of thiol, b.p. 124–125° (25 mm.), $n^{25}D$ 1.5100.

Anal. Calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65. Found: C, 70.86; H, 10.52.

Neither the thiolacetate nor the thiol showed a band in the 12.5 μ region of the spectra, which indicates the absence of a RR'C=CHR'' type of double bond.

Recrystallization of the 2,4-dinitrophenyl sulfide derivative of the thiol from alcohol gave two different products. The first crop of crystals (compound A) melted at 141–143°, and this melting point was not changed by recrystallization from hexane. The second crop of crystals (compound B) melted at 121–122°, and recrystallization from alcohol did not raise the melting point. A mixture of the derivatives melted at 118–130°.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: N, 8.33. Found: N, 8.40 (for A); N, 8.45 (for B).

Addition of Thiolacetic Acid to α-Pinene.—Addition of 22.8 g. (0.3 mole) of freshly distilled thiolacetic acid to 41 g. (0.3 mole) of α-pinene gave 43 g. (70%) of thiolacetate, b.p. 105° (3.2 mm.); Behringer[4c] reported the b.p. to be 135–137° (13 mm.). Hydrolysis of 42 g. of the thiolacetate gave 22 g. (64%) of thiol, b.p. 84° (7 mm.).

Anal. Calcd. for $C_{10}H_{18}S$: S, 70.52; H, 10.65. Found: C, 70.79; H, 11.07.

Crystallization of the 2,4-dinitrophenyl sulfide derivative[17] from alcohol gave two different products. The first crop (compound A') melted at 154–160°, and recrystallization from hexane gave material melting at 158.5–164°. The second crop (compound B') melted at 143–145°, and recrystallization from alcohol raised the melting point to 146–148°. A mixture of the two derivatives melted at 138–161°.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: N, 8.33. Found: N, 8.40 (for A'); N, 8.53 (for B').

Exhaustive attempts to purify the derivatives A, B, A' and B' were not made. It is probable that some or all might have higher melting points when purified further. A mixture of A (m.p. 141–143°) and B' (146–148°) melted at 115–130°.

EVANSTON, ILLINOIS

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[CONTRIBUTION FROM THE RESEARCH AND BIOLOGICAL LABORATORIES OF AYERST, MCKENNA & HARRISON LIMITED]

New Analeptics. 1-Benzhydryl-2-alkyl-2-thiopseudoureas[1]

BY STANLEY O. WINTHROP, STELLA SYBULSKI, GREGORY GAVIN AND GORDON A. GRANT

RECEIVED JANUARY 30, 1957

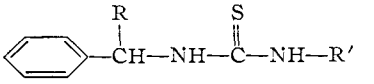
The synthesis of a series of S-alkylated benzhydrylthioureas is reported. The lower members have shown analeptic properties.

During a search for new spasmolytic agents, 1-benzhydryl-2-methyl-2-thiopseudourea hydroiodide (I) was prepared. When tested in animals this compound showed an interesting central stim-

(1) This paper was presented before the Division of Medicinal Chemistry, American Chemical Society, Miami, Florida, April, 1957.

TABLE I

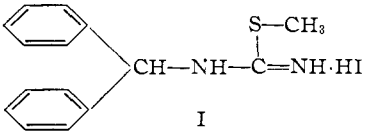
THIOUREAS,[b]



R	R′	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
2-ClC_6H_4[c]	H	172–173	99	$C_{14}H_{13}N_2SCl$					10.12	10.07	11.56	11.58
4-ClC_6H_4[d]	H	175–176	46	$C_{14}H_{13}N_2SCl$	60.74	60.89	4.73	4.67				
4-$CH_3OC_6H_4$[d]	H	178–179	52	$C_{15}H_{16}N_2SO$	66.15	65.97	5.92	5.83			11.77	12.03
C_6H_5[c]	CH_2CH_2OH	130–131	43	$C_{16}H_{18}N_2SO$	67.10	67.18	6.33	6.24	9.80	9.88	11.17	11.11
C_6H_5[a,c]	$CH_2CH_2N(C_2H_5)_2$	109–110	77	$C_{20}H_{27}N_3S$	70.34	70.52	7.97	7.94	12.30	12.01	9.39	9.57

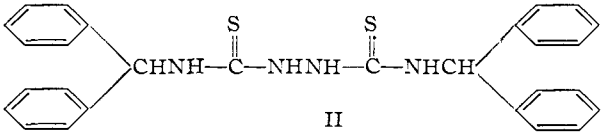
[a] Hydrochloride melts at 128–130°. Calcd. for $C_{20}H_{28}N_3SCl$: N, 11.12; S, 8.48; Cl, 9.39. Found: N, 11.22; S, 8.62; Cl, 9.02. [b] Other miscellaneous thioureas are included in the Experimental section of this paper. [c] Prepared from the appropriate benzhydryl isothiocyanate and amine. [d] Prepared from the appropriate benzhydrylamine hydrochloride and ammonium thiocyanate.

ulant activity. It appeared desirable therefore to prepare other compounds structurally related to I for pharmacological screening.



I

Schroeder[2] has described several methods for the preparation of thioureas. 1-Benzhydrylthiourea had previously been synthesized from benzhydryl isothiocyanate and ammonia.[3,4] It was found that 1-benzhydrylthioureas can also be conveniently prepared by fusing the benzhydrylamine hydrochloride and ammonium thiocyanate in the presence of an inert solvent. When benzhydryl isothiocyanate was allowed to react with a fivefold excess of hydrazine, a good yield of 4-benzhydrylthiosemicarbazide resulted. Equivalent amounts of these reactants, however, gave a new dithiobiurea (II) as the major product.



II

The 1-benzhydrylthioureas synthesized during the course of this investigation and not reported previously are listed in Table I. Other new miscellaneous thioureas are included in the Experimental section of this paper.

The thiopseudourea salts were prepared for the most part by refluxing an ethanol solution of the appropriate 1-benzhydrylthiourea and an alkyl halide. In the case of halides such as ethyl α-chloroacetate, α-chloroacetamide, α-chloroacetaldehyde and α-chloroacetone we were unable to isolate any thiopseudourea salt since these compounds so readily cyclized to thiazolidines. The cyclized compounds will be the subject of a later paper. When α-bromoacetic acid and 1-benzhydrylthiourea were brought together in an acetone–ether solution at room temperature, the desired thiopseudourea salt resulted. The same reactants gave a thiazolidine in ethanol. The thiopseudourea salts were stable, crystalline, high melting solids.

A thiopseudourea resulted when an aqueous methanolic solution of the thiopseudourea salt was treated with sodium carbonate. The 1-benzhydryl-2-alkyl-2-thiopseudoureas were easily isolated since they were considerably less soluble than their respective salts. In general, the thiopseudoureas were stable compounds. When 1-benzhydryl-2,3,3-trimethyl-2-thiopseudourea hydroiodide was treated with sodium carbonate in the usual manner for the preparation of a thiopseudourea, however, an appreciable amount of 1-benzhydryl-3,3-dimethylurea was obtained as a by-product. The characteristic odor of methyl mercaptan also was present.

Since the 1-benzhydryl-2-alkyl-2-thiopseudoureas appeared to be stable, it was of interest to investigate whether these compounds could be alkylated in the usual manner. There was also a question as to which of the two dissimilar nitrogens would be involved in the reaction. An acetone solution of 1-benzhydryl-2-methyl-2-thiopseudourea and methyl iodide was refluxed for 4 hr. Potassium carbonate was included to serve as the acid acceptor. The resulting product gave a hydroiodide which after purification was identical with 1-benzhydryl-2,3-dimethyl-2-thiopseudourea hydroiodide. This latter compound was prepared in an unambiguous manner from benzhydryl isothiocyanate by way of 1-benzhydryl-3-methyl-2-thiourea.

Pharmacological Acitivity.—Several of the 1-benzhydryl-2-alkyl-2-thiopseudourea salts were found to have central stimulant activity. The compounds were administered to rats and the degree of the stimulation recorded in activity cages.[5] The most active compound was the 1-benzhydryl-2-methyl-2-thiopseudourea hydroiodide. This activity decreased gradually with increasing size of the sulfur substituent. Substitution of a hydrogen atom from either nitrogen by a methyl group caused the activity to drop to about a tenth of its original level. Compounds with substituents on one of the phenyl rings had little or no activity. The other thiopseudourea salts were inactive when screened by this method.

This type of activity is not entirely unexpected in view of the report of some respiratory stimulation by 2-alkyl-2-thiopseudourea salts.[6] These ap-

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(3) H. L. Wheeler, *Am. Chem. J.*, **26**, 353 (1901).

(4) I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 403 (1952).

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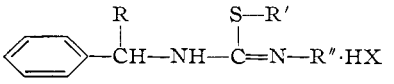
TABLE II

2-ALKYL-2-THIOPSEUDOUREA SALTS,[a]



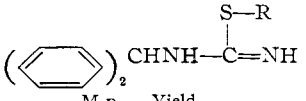
R	R	R″	X	Yield, %	M.p., °C.	Formula	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Halogen Calcd.	Halogen Found
C_6H_5	CH_3	H	I	92	178–180	$C_{15}H_{17}N_2SI$	7.29	7.17	8.33	8.39	33.07	33.13
C_6H_5	CH_2CH_3	H	I	73	145–147	$C_{16}H_{19}N_2SI$	7.04	7.04	8.05	8.17	31.88	32.38
C_6H_5	$CH_2CH_2CH_3$	H	I	74	150–151	$C_{17}H_{21}N_2SI$	6.79	6.86	7.78	8.21	30.81	30.79
C_6H_5	$CH(CH_3)_2$	H	I	63	185–186	$C_{17}H_{21}N_2SI$	6.79	6.77	7.78	7.95	30.81	30.68
C_6H_5	$CH_2CH_2CH_2CH_3$	H	I	75	160–161	$C_{18}H_{23}N_2SI$	6.57	6.67	7.52	7.78	29.74	29.67
C_6H_5	$CH_2C_6H_5$	H	Cl	77	168–172	$C_{21}H_{21}NSCl$	7.59	7.36	8.68	8.89	9.62	9.56
C_6H_5	CH_2CH_2OH	H	Br	71	179–182	$C_{16}H_{19}N_2SOBr$	7.63	7.63	8.73	8.78	21.76	21.88
C_6H_5	$CH_2CH_2CH_2OH$	H	Br	76	129–131	$C_{17}H_{21}N_2SOBr$	7.36	7.57	8.39	8.53		
C_6H_5	$CH_2CH_2OCH_2CH_3$	H	I	95	121–123	$C_{18}H_{23}N_2SOI$	6.33	6.48	7.25	7.36	28.69	28.10
C_6H_5	CH_2COOH	H	Br	97	162–163	$C_{16}H_{17}N_2SO_2Br$	7.36	7.32	8.42	8.53		
C_6H_5	$CH_2CH_2N(CH_3)_2 \cdot HI$	H	I	10	189–191	$C_{18}H_{22}N_2SI_2$	7.38	7.32	5.62	5.72	44.60	44.40
C_6H_5	$CH_2CH_2N(CH_2CH_3)_2 \cdot HCl$	H	Cl	50	176–178	$C_{20}H_{29}N_2SCl_2$	10.14	10.14	7.74	7.88	17.11	17.04
C_6H_5	$CH_2CH_2N(CH(CH_3)_2)_2 \cdot HCl$	H	Cl	74	205–208	$C_{22}H_{33}N_2SCl_2$	9.50	9.45	7.25	6.95	16.03	15.65
C_6H_5	CH_3	CH_3	I	97	172–173	$C_{16}H_{19}N_2SI$	7.03	6.98	8.05	8.34	31.86	31.64
C_6H_5	CH_3	CH_2CH_2OH	I	85	174–176	$C_{17}H_{21}N_2SOI$	6.54	6.75	7.48	7.67		
C_6H_5	CH_3	NH_2	I	79	172–173	$C_{15}H_{18}N_3SI$	10.52	10.64	8.03	8.10		
C_6H_5	CH_3	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	Cl	33	156–157	$C_{21}H_{31}N_3SCl_2$	9.81	9.62	7.48	7.68	16.55	16.55
2-ClC_6H_4	CH_3	H	I	90	165–167	$C_{15}H_{16}N_2SClI$	6.78	6.53	7.65	7.69		
4-ClC_6H_4	CH_3	H	I	67	134–136	$C_{15}H_{16}N_2SClI$	6.78	6.57	7.65	7.91		
4-$CH_3C_6H_4$	CH_3	H	I	63	133–134	$C_{16}H_{19}N_2SI$	7.03	7.36	8.06	8.28	31.85	31.81
4-$CH_3OC_6H_4$	CH_3	H	I	93	152–153	$C_{16}H_{19}N_2SOI$	6.76	6.98	7.74	8.06	30.63	30.57
4-ClC_6H_4	CH_2CH_2OH	H	Br	68	140–141	$C_{16}H_{18}N_2SOClBr$	6.97	7.08	7.97	8.09		
4-$CH_3C_6H_4$	CH_2CH_2OH	H	Br	69	108–110	$C_{17}H_{21}N_2SOBr$	7.35	7.33	8.39	8.50	20.90	20.81
4-$CH_3OC_6H_4$	CH_2CH_2OH	H	Br	60	119–120	$C_{17}H_{21}N_2SO_2Br$	7.05	6.94	8.09	7.67	20.10	20.12
H	CH_3	H	I	81	103–108	$C_9H_{13}N_2SI$	9.09	9.26	10.42	10.30		

[a] Other miscellaneous thiopseudourea salts are included in the Experimental section of this paper.

peared to be predominantly respiratory stimulants, however, which is not the case for the compounds in this present investigation.

TABLE III

1-BENZHYDRYL-2-ALKYL 2-THIOPSEUDOUREAS,



R	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	161–162	85	$C_{15}H_{16}N_2S$[a]	10.95	10.74
$CH_2CH_2CH_3$	75–77	89	$C_{17}H_{20}N_2S$	9.85	9.90
$CH_2CH_2CH_2CH_3$	77–79	98	$C_{18}H_{22}N_2S$	9.38	9.41
$CH_2C_6H_5$	94–97	55	$C_{21}H_{20}N_2S$	8.42	8.30
$CH_2CH_2CH_2OH$	107–108	64	$C_{17}H_{20}N_2SO$	9.33	9.33
$CH_2CH_2N(CH(CH_3)_2)_2$	Oil[b]	60	$C_{22}H_{31}N_3S$	11.37	11.48

[a] Calcd.: C, 70.25; H, 6.28; S, 12.52. Found: C, 70.34; H, 6.33; S, 12.59. [b] This compound could not be induced to crystallize. It was purified by repeated precipitations.

Acknowledgments.—The authors would like to thank Dr. C. I. Chappel of our laboratories for the pharmacological data, Mr. W. J. Turnbull for the analyses and Dr. Gilles Papineau-Couture and Mrs. J. Jachner for numerous infrared spectra.

Experimental[7]

Starting Materials.—*p*-Methylbenzophenone,[8] *p*-methoxybenzophenone,[8] *p*-chlorobenzhydrylamine,[8] benzhydrylamine,[8] benzhydryl chloride,[8] α,α-diphenylacetonitrile[9] and *o*-chlorobenzaldehyde[9] were available from commercial sources. The following were prepared but had been previously described in the literature: *o*-chlorobenzhydrol,[10] m.p. 64–66° (lit. m.p. 56–66°), *o*-chlorobenzhydryl chloride,[11] b.p. 150–155° at 2 mm., $n^{24}D$ 1.6020 (lit. b.p. 142–145° at 1.5 mm., $n^{21.5}D$ 1.6028); benzhydrylmethylamine hydrochloride,[11] m.p. 245–246° (lit. m.p. 238°); β,β-diphenylethylamine hydrochloride,[12] m.p. 256–257° (lit. m.p. 256°) *p*-methylbenzhydrylamine hydrochloride,[13] m.p. 256–260° (lit. m.p. 250°); *p*-methoxybenzhydrylamine hydrochloride,[14] m.p. 203° dec. (lit. m.p. 190° dec.); 1-benzylthiourea,[15] m.p. 160–162° (lit. m.p. 161–162°); 1-*p*-methylbenzhydrylthiourea,[16] m.p. 165–167° (lit. m.p. 162–163°); 1-benzhydryl-3-methyl-2-thiourea,[2] m.p. 156–157° (lit. m.p. 152–153°).

1-Benzhydrylthiourea.[3,4]—Benzhydrylamine hydrochloride, 780 g. (3.56 moles) and 800 g. (3.9 moles) of ammonium thiocyanate were refluxed in three liters of toluene for 4 hr. The solid was collected, washed with hot water and dried to yield 510 g. (60%) of product, m.p. 182–183°. Two recrystallizations from isopropyl alcohol raised the melting point to 186–187° (lit. m.p. 189°). Carrying out the reaction in refluxing xylene gave rise to benzhydryl thiocyanate which made purification of the product difficult.

1-Benzhydryl-2-methyl-2-thiopseudourea Hydroiodide.—1-Benzhydrylthiourea, 680 g. (2.83 moles), was dissolved in 12 liters of 1:1 acetone–ether, and 600 g. (4.15 moles) of methyl iodide was added. The reaction was considered complete after 1 hr. at room temperature. The solid was collected and dried to yield 800 g. (75%) of product melting at 175–178°. One recrystallization from isopropyl alcohol raised the melting point to 178–180° (see Table II).

1-Benzhydryl-2-methyl-2-thiopseudourea Hydrochloride.—1-Benzhydrylthiourea, 400 g. (1.67 moles), was dissolved in 2600 ml. of acetone, and 500 g. (10 moles) of methyl chloride was added. The solution was placed in a one-gallon pressure autoclave and heated at 80° for 16 hr. The product was then collected and dried to yield 376 g. (81%) melting at 192–195° dec. One recrystallization from ethanol–ether gave an analytical sample, m.p. 196–197° dec. This compound was also prepared by the addition of hydrogen chloride to an acetone solution of 1-benzhydryl-2-methyl-2-thiopseudourea. Calcd. for $C_{15}H_{17}N_2SCl$: C, 61.45; H, 5.85; N, 9.57; S, 10.94; Cl, 12.09. Found: C, 61.24; H, 5.65; N, 9.56; S, 10.74; Cl, 11.95.

1-Benzhydryl-2-methyl-2-thiopseudourea Methyl Bisulfate.—1-Benzhydrylthiourea, 12 g. (0.05 mole) and dimethyl sulfate, 3.15 g. (0.025 mole), were refluxed in 100 ml. of methanol for 3 hr. The methanol was then removed

(7) All melting points are uncorrected.

(8) Trubek Laboratories, East Rutherford, N. J.

(9) Eastman White Label.

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in vacuo leaving an oil residue which crystallized on triturating with ether to yield 11 g. of solid, m.p. 110–118°. Two recrystallizations from isopropyl alcohol raised the melting point to 130–132°. Calcd. for $C_{16}H_{20}N_2S_2O_4$: C, 52.25; H, 5.48; N, 7.89; S, 18.06. Found: C, 52.65; H, 5.65; N, 7.83; S, 17.83.

1-Benzhydryl-2-methyl-2-thiopseudourea.—1-Benzhydryl-2-methyl-2-thiopseudourea hydroiodide, 46 g. (0.12 mole), was dissolved in aqueous methanol, and 10% sodium carbonate solution was added in excess. The thiopseudourea was filtered off, washed with water and recrystallized from benzene to yield 17 g., m.p. 160–161°. A second recrystallization raised the melting point to 161–162° (see Table III).

1-Benzhydryl-2-methyl-2-thiopseudourea Salts.—The following salts were prepared by addition of the appropriate acid to an acetone–ether solution of 1-benzhydryl-2-methyl-2-thiopseudourea: hydrobromide: m.p. 198–199°. Calcd. for $C_{15}H_{17}N_2SBr$: N, 8.31; S, 9.51; Br, 23.70. Found: N, 8.56; S, 9.59; Br, 23.76. Hydrogen sulfate: m.p. 202–203°. Calcd. for $C_{15}H_{18}N_2S_2O_4$: N, 7.91; S, 18.10. Found: N, 7.99; S, 18.35. Acetate: m.p. 144–145°. Calcd. for $C_{17}H_{20}N_2SO_2$: N, 8.86; S, 10.13. Found: N, 9.14; S, 10.32. Maleate: m.p. 164–165°. Calcd. for $C_{19}H_{22}N_2SO_4$: N, 7.48; S, 8.56. Found: N, 7.46; S, 8.80.

1-Benzhydryl-2-carboxymethyl-2-thiopseudourea Hydrobromide.—1-Benzhydrylthiourea, 4.8 g. (0.02 mole) and α-bromoacetic acid, 4.16 g. (0.03 mole), were dissolved in 100 ml. of a 1:1 acetone–ether mixture. On five minutes standing at room temperature, a solid started to separate out of solution. After ten minutes the precipitation appeared complete and the product was filtered off and dried to yield 7.3 g., m.p. 162–163° (see Table II).

1-Benzhydryl-2-(β-diethylaminoethyl)-2-thiopseudourea Dihydrochloride.—1-Benzhydrylthiourea, 8.0 g. (0.033 mole) and β-diethylaminoethyl chloride hydrochloride, 5.7 g. (0.033 mole) were refluxed in 150 ml. of isopropyl alcohol for 48 hr. The isopropyl alcohol was then removed *in vacuo* and the residue crystallized from an isopropyl alcohol–ether mixture to yield 6.9 g. of product, m.p. 164.5–165.6°. Three recrystallizations from a mixture of isopropyl alcohol and ether raised the melting point to 176–178° (see Table II).

***o*-Chlorobenzlhydryl Isothiocyanate.**—*o*-Chlorobenzhydryl chloride, 92.5 g. (0.39 mole), and ammonium thiocyanate, 30 g. (0.39 mole), were refluxed in 75 ml. of benzene for five days. The solid material remaining was then collected and the benzene filtrate evaporated down *in vacuo* leaving a high boiling liquid residue. Vacuum distillation gave 46 g. (46%) of product boiling from 186–189° at 1.5 mm. Calcd. for $C_{14}H_{10}NSCl$: N, 5.39. Found: N, 5.60.

1-(*o*-Chlorobenzhydryl)-thiourea.—*o*-Chlorobenzhydryl isothiocyanate, 26 g. (0.1 mole), was dissolved in 500 ml. of an ethanol solution containing 37 ml. of concentrated ammonium hydroxide. The solution was brought to boiling and then allowed to stand at room temperature for 16 hr. Sufficient water was then added to ensure complete precipitation of the product which was collected, washed and dried to give a quantitative yield, 28 g. of crude product, m.p. 166–167°. Two recrystallizations from isopropyl alcohol raised the melting point to 172–173° (see Table I).

1,6-Dibenzhydryl-2,4-dithiobiurea.—Benzhydryl isothiocyanate, 34 g. (0.15 mole), was dissolved in 500 ml. of ethanol and 7.4 ml. of 85% aqueous hydrazine (0.20 mole) was added. An immediate reaction took place. The reaction was considered complete after 30 minutes. The ethanol was then removed *in vacuo* and the oil residue triturated with a little methanol to yield 22 g. of solid with m.p. 168–172°. Four recrystallizations from acetonitrile raised the melting point to 194–195° dec. Calcd. for $C_{28}H_{26}N_4S_2$: C, 69.75; H, 5.43; S, 13.28. Found: C, 69.55; H, 5.49; S, 13.14.

4-Benzhydrylthiosemicarbazide.[17]—The above procedure was repeated using a fivefold excess of hydrazine in order to increase the yield of product by keeping the formation of the dithiobiurea to a minimum. A solid came out of solution and was collected and dried to yield 32.3 g. (70%) of product, m.p. 150–152° dec. One recrystallization from acetonitrile did not raise the melting point (lit. m.p. 144°).

1-Benzhydryl-3,3-dimethyl-2-thiourea.—Benzhydryl isothiocyanate, 34 g. (0.15 mole), was dissolved in 500 ml. of ethanol, and 9.02 g. (0.2 mole) of dimethylamine (25% aqueous solution) was added. The solution was allowed to stand at room temperature for 70 hr. The ethanol was then removed *in vacuo* and the residue crystallized from isopropyl alcohol to yield 37.5 g. of product, m.p. 131–132°. One recrystallization from ethanol did not raise the melting point. Calcd. for $C_{16}H_{18}N_2S$: C, 71.06; H, 6.71; N, 10.36; S, 11.86. Found: C, 71.42; H, 6.94; N, 10.36; S, 12.11.

1-Benzhydryl-2,3,3-trimethyl-2-thiopseudourea Hydroiodide.—1-Benzhydryl-3,3-dimethyl-2-thiourea, 6.1 g. (0.023 mole), and 4.95 g. (0.035 mole) of methyl iodide were refluxed in 50 ml. of ethanol for 2 hr. On cooling and adding of ether, 8.3 g. of product, m.p. 148–150° dec., precipitated. One recrystallization from isopropyl alcohol did not raise the melting point. Calcd. for $C_{17}H_{21}N_2SI$: N, 6.80; S, 7.77; I, 30.78. Found: N, 6.97; S, 8.09; I, 30.78.

1-Benzhydryl-3,3-dimethyl-2-(α-acetonyl)-2-thiopseudourea Hydrochloride.—1-Benzhydryl-3,3-dimethyl-2-thiourea, 7.11 g. (0.03 mole) and α-chloroacetone, 4.2 g. (0.045 mole), were refluxed in 40 ml. of a 1:1 ether–acetone mixture for 2 hr. The acetone–ether was removed *in vacuo* and the residue crystallized from isopropyl alcohol to yield 6.8 g. of product, m.p. 133–144°. Two recrystallizations from an isopropyl–ether mixture followed by two recrystallizations from acetonitrile raised the melting point to 136–137°. Calcd. for $C_{19}H_{23}N_2SOCl$: N, 7.72; S, 8.84; Cl, 9.78. Found: N, 7.50; S, 8.78; Cl, 9.89.

1-Benzhydryl-2,3,3-trimethyl-2-thiopseudourea.—1-Benzhydryl-2,3,3-trimethyl-2-thiopseudourea hydroiodide, 21 g. (0.015 mole), was dissolved in 75 ml. of methanol, and 2.8 g. (0.052 mole) of sodium methoxide was added portionwise with cooling. On removal of about one-third of the methanol *in vacuo* at room temperature, a solid separated out, was filtered off and dried to yield 9 g. of product, m.p. 55–57°. An attempt at purification by recrystallizing from ethanol resulted in a poor recovery of material melting from 50 to 55° and the production of some methyl mercaptan whose presence was noticed by its characteristic odor. Calcd. for $C_{17}H_{20}N_2S$: C, 71.78; H, 7.08; N, 9.84; S, 11.30. Found: C, 72.19; H, 6.78; N, 9.92; S, 11.03.

On evaporating down the original methanol filtrate, additional 3.5 g. of material melting at 185–186° resulted. Two recrystallizations from ethanol raised the melting point to 194–195°. The infrared spectrum and analytical data indicated this compound was 1-benzhydryl-3,3-dimethylurea. Calcd. for $C_{16}H_{18}N_2O$: C, 75.50; H, 7.13; N, 11.02. Found: C, 76.15; H, 7.27; N, 11.05.

1-Benzhydryl-1-methyl-2-thiourea.—Benzhydrylmethylamine hydrochloride, 10 g. (0.043 mole), and ammonium thiocyanate, 3.6 g. (0.017 mole), were added to 100 ml. of xylene, and the reaction mixture was stirred and heated at 135° for 3 hr. On cooling, the solid material was collected, washed with hot water and dried to yield 3.1 g. of product, m.p. 186–189°. One recrystallization from isopropyl alcohol raised the melting point to 193–195°. Calcd. for $C_{15}H_{16}N_2S$: N, 10.92; S, 12.50. Found: N, 10.97; S, 12.42. The xylene filtrate was evaporated down to yield 5.6 g. of solid melting at 120–130° whose infrared spectrum suggested the benzhydrylmethylamine hydrothiocyanate salt.

1-Benzhydryl-1,2-dimethyl-2-thiopseudourea Hydroiodide.—The compound was prepared in the usual manner. It was recrystallized from an isopropyl alcohol-ether mixture to give an analytical sample melting at 175–176° dec. Calcd. for $C_{16}H_{19}N_2SI$: N, 7.03; S, 8.05; I, 31.86. Found: N, 6.81; S, 8.17; I, 31.92.

1-(β,β-Diphenylethyl)-thiourea.—β,β-Diphenylethylamine hydrochloride, 18.5 g. (0.079 mole), and ammonium thiocyanate, 6.7 g. (0.087 mole), were added to 350 ml. of xylene and stirred and heated at 135° for 6 hr. The xylene was then evaporated down *in vacuo* and the solid residue triturated with hot water, filtered and dried to yield 19.7 g. of product, m.p. 198–200°. One recrystallization from ethanol raised the melting point to 203–204°. Calcd. for $C_{15}H_{16}N_2S$: C, 70.30; H, 6.28; N, 10.92; S, 12.50. Found: C, 70.53; H, 6.42; N, 11.11; S, 12.65.

1-(β,β-Diphenylethyl)-2-methyl-2-thiopseudourea Hydroiodide.—The compound was prepared in the usual manner. Two recrystallizations from an isopropyl alcohol–ether mixture gave an analytical sample melting at 139–141°. Calcd. for $C_{16}H_{19}N_2SI$: N, 7.03; S, 8.05; I, 31.86. Found: N, 6.71; S, 8.06; I, 32.12.

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Alkylation of 1-Benzhydryl-2-methyl-2-thiopseudourea.—1-Benzhydryl-2-methyl-2-thiopseudourea, 7.68 g. (0.03 mole), and methyl iodide, 6.4 g. (0.045 mole), were refluxed in 100 ml. of acetone with 2 g. (0.015 mole) of potassium carbonate for 4 hr. Some inorganic material was filtered off and the acetone filtrate was evaporated down *in vacuo* at room temperature to leave a thick oil residue. The residue was taken up in chloroform and the chloroform solution filtered to remove more inorganic solids. The chloroform was then evaporated down *in vacuo* at room temperature and the residue taken up in a little isopropyl alcohol. Upon addition of dilute hydriodic acid to the isopropyl alcohol solution, 4.0 g. of a solid hydroiodide salt, m.p. 162–164°, precipitated. Two recrystallizations from an isopropyl alcohol–ether mixture gave a product, m.p. 173–174°, which was identical in every way with 1-benzhydryl-2,3-dimethyl-2-thiopseudourea hydroiodide.

MONTREAL, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Reactions with Mercaptans. IV. Reaction of Aromatic Thiols with 3(2H)-Thianaphthenone-1,1-dioxides and 2-Benzylidene-3(2H)-thianaphthenone-1-1-dioxide

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The condensation reaction of 3(2*H*)-thianaphthenone-1,1-dioxides (I) with aromatic aldehydes has been investigated, *e.g.*, 3(2*H*)-thianaphthenone-1,1-dioxide condenses with benzaldehyde to give 2-benzylidene-3(2*H*)-thianaphthenone-1,1-dioxide (IIa). The latter undergoes an addition reaction with thiophenol, yielding the thiol adduct believed to have structure VI. Aromatic thiols react with 3(2*H*)-thianaphthenone-1,1-dioxides, in the presence of anhydrous zinc chloride and hydrogen chloride, to yield the corresponding unsaturated sulfides VII which are readily oxidized to the sulfone derivatives VIII.

Aldehyde condensation products of 3(2*H*)-thianaphthenone-1,1-dioxide (Ia) have not previously been prepared, although Ia has been known since 1912.[1] Weston and Suter[2] were unable to condense benzaldehyde with Ia in an alkaline medium.

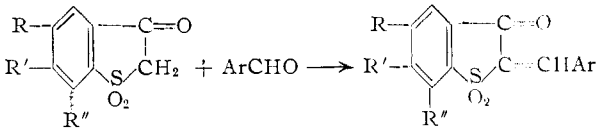
We obtained well-defined crystalline products by the reaction of benzaldehyde with Ia and by that of *p*-nitrobenzaldehyde with 7-methyl-3(2*H*)-thianaphthenone-1,1-dioxide (Id). The analytical data indicate that one molecule of aldehyde condenses with one molecule of the thianaphthenone-1,1-dioxide with the elimination of one molecule of water.

The structural assignments for these products are based on their participation in known reactions. When 2-benzylidene-3(2*H*)-thianaphthenone-1,1-dioxide (IIa) was treated with hydroxylamine hydrochloride, the corresponding oxime of 3(2*H*)-thianaphthenone-1,1-dioxide (IIIa)[3] was obtained.[4] The treatment of IIa with phenylhydrazine gave the hydrazone of 3(2*H*)-thianaphthenone-1,1-dioxide (IIIb).[5]

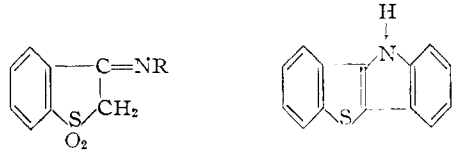
2-Benzylidene-3(2*H*)-thianaphthenone reacted with phenylhydrazine to give [10*H*]-thianaphtheno-[3,2-*b*]-indole (IV), *via* the Fischer indole ring closure of the resulting phenylhydrazone of 3(2*H*)-thianaphthenone.[5,6]

We have also studied the addition, *e.g.*, of benzenethiol, to the double bond at position 2 which is conjugated with the unsaturated group in 2-arylidene-3(2*H*)-thianaphthenone-1,1-dioxides.

IIa, like the 2-arylideneindan-1,3-diones,[7] undergoes addition reaction with thiophenol in absence of a catalyst to give a colorless adduct which can be represented by V or VI.

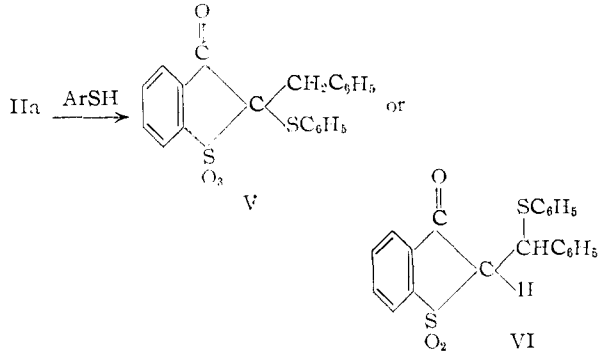


Ia, R = R′ = H
b, R = CH_3; R′ = R″ = H
c, R′ = CH_3; R = R″ = H
d, R″ = CH_3; R = R′ = H
e, R″ = Cl; R = R′ = H
IIa, R = R′ = R″ = H; Ar = C_6H_5
b, R = R′ = H, R″ = CH_3; Ar = $C_6H_4NO_2$-*p*



IIIa, R = OH
b, R = NHC_6H_5

IV



V

VI

In view of the well-established mechanism for the addition of thiols to analogous α,β-unsaturated

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