[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

RANEY NICKEL HYDROGENOLYSIS OF THIOAMIDES: A NEW AMINE SYNTHESIS

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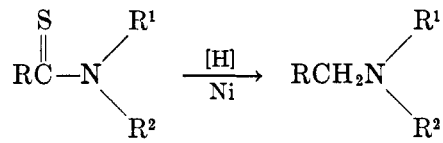
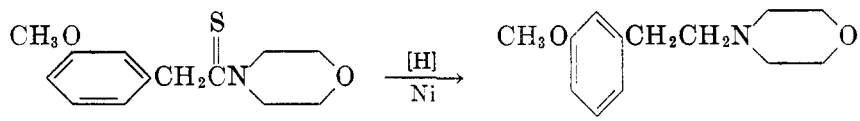
Recent extensions of the Kindler modification of the Willgerodt reaction (1, 2, 3) have made available a rather wide variety of thioamides by relatively simple procedures. It seemed probable to the present author that Raney nickel desulfurization of these and other thioamides should provide a new and useful synthesis of amines, *i.e.*,



Reduction of thioamides to amines has previously been effected by Kindler and coworkers (4) either electrolytically or by aluminum amalgam. The elegant application of Raney nickel in the absence of gaseous hydrogen to the hydrogenolysis of organic sulfur compounds has been extended during the past few years to include thioureas (5), mercaptans (5), sulfides (6), disulfides (6), sulfoxides (7), sulfones (8), thioacetals (9), and thiolesters (10). The method as it has been developed provides a valuable synthetic and degradative tool in organic chemistry. However, thioamides seem not to have been studied in this reaction.[1] The present paper, therefore, reports a study of the action of Raney nickel on a representative selection of thioamides.

Preliminary experiments were conducted with 3-methoxyphenylthioacetomorpholide (1) (I), using Raney nickel catalyst prepared by the recent method



I II

of Pavlic and Adkins (11), and it was found that this thioamide could be smoothly desulfurized to yield N-β-3-methoxyphenylethylmorpholine (II) in good yield. A further study of the reaction conditions showed that the optimum yield was obtained using considerably less nickel and shorter reaction periods than have been employed for previously studied desulfurizations. The results are summarized in Table I.

Finally, it was found that the conversion could be effected simply by shaking

[1] Since the completion of this work (1948), the reduction of a cyclic thioamide by means of Raney nickel has been reported (18). A brief report of the action of Raney nickel on certain other thioamides has also appeared (19).

a solution of the thioamide in 80% ethanol with Raney nickel at room temperature. A 47% yield of amine was obtained after one hour, thus indicating that the hydrogenolysis was somewhat slower under these conditions. As a preparative method, however, the use of a refluxing solvent was in general most convenient. Gaseous hydrogen at a pressure of 50 p.s.i. was of no advantage. The experience gained from this study was then applied to a variety of thioamides which were likewise readily converted to the corresponding amines. These results are presented in Table II.

It may be noted that the compounds selected show varied substitution on both the carbon and nitrogen of the thioamide linkage. Thioamides which are unsubstituted, monosubstituted, and disubstituted on nitrogen are included; the method, therefore, constitutes a new synthesis for primary, secondary, and tertiary amines. Several of the new amines may be more accessible by the new conversion than by known methods. In each case which has thus far been

TABLE I

HYDROGENOLYSIS OF 3-METHOXYPHENYLTHIOACETOMORPHOLIDE

GRAMS Ni / GRAM THIOAMIDE	REFLUX TIME, HOURS	YIELD OF AMINE, %
5.2	3.5[a]	52
5.6	1.0[a]	64
2.6	3.0[a]	68
3.1	1.0[a]	69
1.6	0.2[a]	46
1.6	.5[b]	44
2.6	.5[c]	50

[a] Solvent, 80% ethanol. [b] Solvent, 80% dioxane. [c] Solvent, 80% isopropanol.

studied the action of Raney nickel on a thioamide has produced a basic product. However, single runs with thioacetamide, thioformanilide, thioacetanilide, phenylthioacetanilide, and 3,4-dimethoxythiobenzamide have given crude products from which no solid derivative could be prepared.

In the course of the investigation two interesting side reactions were encountered. The first, a fission reaction, was first observed when phenylthioacetopiperidide (III) was treated with a large excess of Raney nickel during a relatively long reflux period. Under these conditions the normal product, N-β-phenylethylpiperidine (IV), was not isolated but instead N-ethylpiperidine (V) was formed.

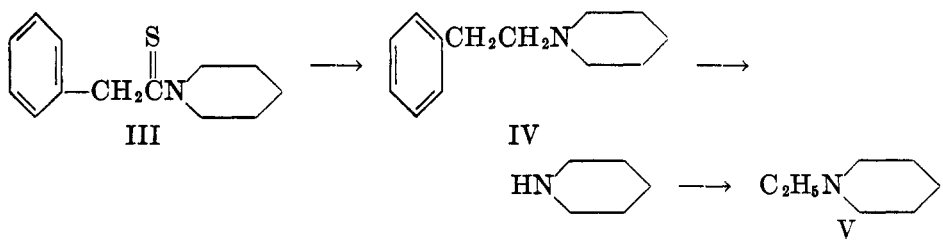


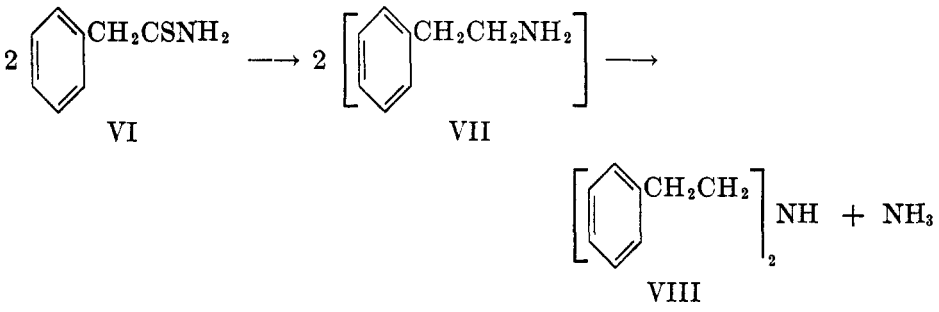
TABLE II

HYDROGENOLYSIS OF THIOAMIDES

THIOAMIDE REDUCED	G. Ni/G. THIOAMIDE	REFLUX TIME, HRS.	SOLVENT[a]	AMINE HCl'D OBTAINED	M.P., °C.	YIELD, %	ANALYSES			
							Calc'd		Found	
							C	H	C	H
3-$CH_3OC_6H_4CH_2CSNC_4H_8O$[b, f]	3.1	1.0	E	$C_{13}H_{20}ClNO_2$	210–212	69	60.57	7.82	60.80	7.88
$C_6H_5CH_2CSNC_5H_{10}$[c]	2.2	0.5	D	$C_{13}H_{20}ClN$	218–221[k]	63	69.16	8.93	68.85	8.65
$C_6H_5CH_2CSNHC_4H_9$	2.2	.5	D	$C_{12}H_{20}ClN$	252–253	49	67.43	9.43	67.46	9.54
4-$C_6H_{11}C_6H_4CH_2CSNC_4H_8O$[b, n]	2.5	.5	E	$C_{18}H_{28}ClNO$	267–269	57	69.77	9.11	69.77	9.28
$C_6H_5CH_2CSNHCH_2CH_2C_6H_5$	1.7	.5	E	$C_{16}H_{20}ClN$	259–261[l]	34	N, 5.35		N, 5.11	
2-$C_{10}H_7CH_2CSNC_4H_8O$[b, d, g]	2.3	.8	D	$C_{16}H_{20}ClNO$	264–266	68	69.18	7.26	68.88	7.22
2-$C_{10}H_7CH_2CSNC_5H_{10}$[c, d]	1.8	.5	D	$C_{23}H_{24}N_4O_7$ [i]	164–167	56	58.97	5.16	58.76	4.70
4-$C_6H_5C_6H_4CH_2CSNC_4H_8O$[b, h]	2.4	.8	E	$C_{18}H_{22}ClNO$	252–254	63	71.15	7.30	70.98	7.42
4-$C_6H_5C_6H_4CH_2CSNC_5H_{10}$[c, h]	2.1	.5	D	$C_{19}H_{24}ClN$	247–248	73	75.60	8.01	75.59	8.49
$C_6H_5CSNHC_6H_5$[j]	2.5	.3	D	$C_{13}H_{14}ClN$	205–206[l]	59	—	—	—	—
4-$CH_3OC_6H_4CH_2CH_2CSNC_4H_8O$[b]	1.9	.5	D	$C_{20}H_{24}N_4O_9$ [i]	165–168	65	51.72	5.21	51.68	5.33
$C_6H_5CH_2CSNHCH_2CH_2N(CH_3)_2$	1.7	.6	D	$C_{24}H_{26}N_8O_{14}$ [i]	184–186	55	44.31	4.03	44.63	4.38
$C_6H_5CH_2CSNHCH_2CH_2OH$	2.0	.6	D	$C_{10}H_{16}ClNO$	142–143	15	59.54	8.00	58.76	7.74
3-$C_5H_4NCH_2CSNC_4H_8O$[b, e, h]	3.5	2.0	E	$C_{11}H_{18}Cl_2N_2O$	260–261	40	49.82	6.84	49.65	6.76
$(C_6H_5)_2CHCSNH_2$	2.5	0.3	D	$C_{14}H_{16}ClN$	254–255[m]	10	71.94	6.90	71.64	6.75
$C_6H_5CSN(CH_3)_2$(4)	2.9	.5	E	$C_9H_{14}ClN$	172–176[l]	25	—	—	—	—
4,4′-(-$C_6H_4CH_2CSNC_4H_8O)_2$[b, h]	4.6	3.0	D	$C_{24}H_{34}Cl_2N_2O_2$	329–330 d.	72	63.57	7.56	62.02	7.35
3-$C_5H_4NCSN(C_2H_5)_2$[e]	3.4	0.7	E	$C_{10}H_{18}Cl_2N_2$	184–185	38	50.64	7.65	50.59	7.78

[a] E is 80% ethanol; D is 80% dioxane. [b] -NC_4H_8O is morpholide. [c] -NC_5H_{10} is piperidide. [d] -$C_{10}H_7$ is naphthyl. [e] -C_5H_4N is pyridyl. [f] Schwenk and Bloch, *J. Am. Chem. Soc.*, **64**, 3051 (1942). [g] Newman, *J. Org. Chem.*, **9**, 521 (1944). [h] Schwenk and Papa, *J. Org. Chem.*, **11**, 798 (1946). [i] Bernthsen, *Ber.*, **11**, 503 (1878). [j] Picrate. [k] Kohler and Bruce, *J. Am. Chem. Soc.*, **53**, 1994 (1931). [l] A mixed m.p. with an authentic sample showed no depression. [m] Freund and Immerwahr, *Ber.*, **23**, 2845 (1890) report m.p. 255°. [n] Thioamide kindly furnished by Dr. Q. F. Soper.

Apparently, the normal product (IV) is cleaved to yield piperidine which is ethylated in the presence of ethanol and Raney nickel to yield V. The alkylation doubtless takes place by condensation of the piperidine with traces of acetaldehyde which are always present under these conditions, and hydrogenolysis of the condensation product yields V. Hydrogenation of piperidine in ethanol in the presence of Raney nickel is, in fact, a good preparative method for making N-ethylpiperidine (12). This first side reaction is of no disadvantage because under less drastic conditions the normal product can be isolated in good yield as is shown in Table II. The second side reaction takes place with most of those thioamides which are unsubstituted on nitrogen. Thus, with phenylthioacetamide (VI) reduction by means of Raney nickel produces di-β-phenylethylamine (VIII) and ammonia rather than VII. Diphenylthioacetamide, however, yields



VI VII VIII

the normal primary amine (Table II). The results obtained in the study of these side reactions are summarized in Table III.

The thioamides used in this work were prepared by four different methods as follows:

A. Willgerodt-Kindler reaction
$RCOCH_3 + S + HNR^1R^2 \rightarrow RCH_2CSNR^1R^2$

B. $RCN + H_2S \rightarrow RCSNH_2$

C. $RCONR^1R^2 + P_2S_5 \rightarrow RCSNR^1R^2$

D. $RCSSR^1 + HNR^2R^3 \rightarrow RCSNR^2R^3$

The results obtained with methods A, B, and C parallel closely those in the literature. The condensation of amines with dithioesters (method D), moreover, was found to proceed with great facility but seems to have been somewhat neglected in the literature. In all, nine new thioamides were prepared, and method D was used to prepare several which have previously been prepared by one of the other methods.

EXPERIMENTAL

2-Naphthylthioacetopiperidide. A method similar to that used for 2-naphthylthioacetomorpholide (1) was employed. A mixture of 85.1 g. (0.5 mole) of aceto-2-naphthone, 25.6 g. (0.8 mole) of sulfur, and 125 ml. of piperidine was refluxed for six hours, poured into ethanol, and the oily product precipitated by adding water. It was washed several times with water by decantation. Addition of a little acetone caused the product to crystallize slowly, and the crude thioamide was then filtered and washed with ether; yield, 51 g. (38%). The product was recrystallized from a large volume of ether for analysis, m.p. 90–92°.

TABLE III

Side Reactions in Hydrogenolysis of Thioamides

Thioamide reduced	G. Ni/G. thioamide	Reflux time, hrs.	Solvent[a]	Product	Formula of hydrochloride	M.P., °C.	Yield, %	Analyses			
								Calc'd		Found	
								C	H	C	H
$C_6H_5CH_2CSNC_5H_{10}$	5.8	3.0	E	$C_2H_5NC_5H_{10}$	$C_7H_{16}ClN$	224–225	44	56.17	10.78	56.30	10.62
$C_6H_5CH_2CSN(C_2H_5)_2$	5.5	3.0	E	$(C_2H_5)_3N$	$C_6H_{16}ClN$	245–247[b]	66	52.35	11.72	51.82	11.45
$C_6H_5CH_2CSNH_2$	5.6	1.0	E	$(C_6H_5CH_2CH_2)_2NH$	$C_{16}H_{20}ClN$	259–261[b]	45	N, 5.35		N, 5.11	
$C_6H_5CH_2CSNH_2$	1.9	0.3	D	$(C_6H_5CH_2CH_2)_2NH$	$C_{16}H_{20}ClN$	259–261[b]	20	—		—	
n-$C_{13}H_{27}CSNH_2$[c]	2.7	.3	D	$(C_{14}H_{29})_2NH$	$C_{28}H_{60}ClN$	—[d]	40	Cl, 7.94		Cl, 7.94	

[a] As in Table II. [b] A mixed m.p. with an authentic sample showed no depression. [c] Ralston, Vanderwal, and McCorkle, *J. Org. Chem.*, **4**, 68 (1939); m.p. 91–93°. *Anal.* Calc'd for $C_{14}H_{29}NS$: S, 13.18. Found: S, 13.12. Ralston, *et. al.* report m.p. 87–88°. [d] Hydrochloride has no well defined m.p.

Anal. Calc'd for $C_{17}H_{19}NS$: S, 11.90. Found: S, 11.92.

4-Methoxyphenylthiopropiomorpholide. A solution of 82.1 g. (0.5 mole) of 4-methoxyphenylacetone and 25.6 g. (0.8 mole) of sulfur in 100 ml. of morpholine was refluxed for five hours. Excess morpholine was distilled *in vacuo*, and the residue was washed several times by decantation with water. A little ethanol was added, and after a few days the thioamide had crystallized; yield, 49 g. (37%). It was recrystallized from methanol, m.p. 94–95°.

Anal. Calc'd for $C_{14}H_{19}NO_2S$: S, 12.08. Found: S, 12.23.

Diphenylthioacetamide. Diphenylacetonitrile, 50 g., was placed in a steel hydrogenation bomb, and to it was added 550 ml. of a cold solution of absolute ethanol which had previously been saturated with hydrogen sulfide and ammonia until a thin slurry of ammonium bisulfide crystals resulted. The bomb was sealed and heated at 150–160° for three hours with shaking, after which the contents were removed and diluted with water. The thioamide was recrystallized from methanol; yield, 50%. An analytical sample melted at 153–154°.

Anal. Calc'd for $C_{14}H_{13}NS$: S, 14.10. Found: S, 14.25.

3,4-Dimethoxythiobenzamide. Veratronitrile (13), 50 g., was heated with 500 ml. of ammonium bisulfide solution as in the above example for two hours at 150°. The product crystallized on cooling and was washed with methanol; yield, 40 g. (67%). A sample was recrystallized from dilute ethanol, m.p. 193–194° (d.).

Anal. Calc'd for $C_9H_{11}NO_2S$: S, 16.25. Found: S, 16.39.

N-Butylphenylthioacetamide. *n*-Butylamine, 0.1 mole, was added slowly to 18.2 g. (0.1 mole) of methyl dithiophenylacetate (14). A vigorous reaction took place, and when it subsided, the condensation was completed by a brief warming on the steam-bath. The product crystallized on cooling, yield, 20 g. (96%). Recrystallized from ligroin (b.p. 60–70°), it separated in colorless needles, m.p. 67–68°.

Anal. Calc'd for $C_{12}H_{17}NS$: N, 6.76. Found: N, 6.54.

N,N-Diethylphenylthioacetamide. Diethylamine and methyl dithiophenylacetate (0.1 mole each) were mixed and refluxed for five hours. The product crystallized on standing and was recrystallized from benzene-petroleum ether, yield, 18 g. (87%); m.p. 59.5–60.0°.

Anal. Calc'd for $C_{12}H_{17}NS$: N, 6.76. Found: N, 6.35.

N-β-Phenylethylphenylthioacetamide. Methyl dithiophenylacetate, 0.1 mole, and β-phenylethylamine, 0.1 mole, were mixed. Heat was evolved, and methyl mercaptan distilled from the mixture. The reaction was completed by warming the liquid on a steam-bath for one-half hour. The product was cooled, petroleum ether was added, and the crystallized thioamide was washed with petroleum ether; yield, 98%; m.p. 69–71°. A sample was recrystallized from benzene-petroleum ether, m.p. 73.5–74.5°.

Anal. Calc'd for $C_{16}H_{17}NS$: S, 12.55. Found: S, 12.56.

Phenylthioacetopiperidide. This was prepared in an exactly similar fashion using piperidine; the reaction was exothermic. The thioamide was obtained in quantitative yield, m.p. 80–81°. King and McMillan report m.p. 77.5–78.5° (2).

Phenylthioacetanilide. Equimolecular quantities of aniline and methyl dithiophenylacetate were mixed, and when no exothermic reaction took place, the solution was refluxed for one hour. After the mixture had stood for two weeks, the product had crystallized. It was washed with benzene and petroleum ether; yield, 70%; m.p. 88–89°. Reissert and More report m.p. 88° (15).

Phenylthioacetamide. Methyl dithiophenylacetate, 0.1 mole, was added to a solution of dry ammonia in methanol. After about one-half hour the solvent was evaporated *in vacuo* whereupon the residue crystallized, yield, 14 g. (92%). Recrystallization from benzene-petroleum ether gave the pure thioamide, m.p. 96.0–96.5°. Bernthsen (16) found m.p. 97.5–98°.

N-(Dimethylaminoethyl)phenylthioacetamide. Equivalent quantities of the dithioester and dimethylaminoethylamine were mixed slowly, and the exothermic reaction was completed by warming on the steam-bath. The crude, oily product was used directly for the Raney nickel hydrogenolysis.

N-(Hydroxyethyl)phenylthioacetamide. In a similar way ethanolamine was condensed with methyl dithiophenylacetate and the crude product subjected to the desulfurization.

N,N-Diethylthionicotinamide. N,N-Diethylnicotinamide (Coramine) (17), 89 g., was thoroughly mixed with 55.6 g. of powdered phosphorus pentasulfide, and the reaction was initiated by warming slowly to 125°. At this point the conversion became exothermic, and the mixture had to be cooled. After the reaction had moderated the flask was kept at 125° for an additional 15 min. Powdered anhydrous sodium sulfide, 60.0 g., was then added and stirred in well. The hot mass was extracted by decantation with 1 l. of boiling toluene in three portions. The extracts were filtered and evaporated *in vacuo*, and the residue was distilled twice under reduced pressure, b.p. 195–196°/14 mm., yield, 62 g. (64%).

Anal. Calc'd for $C_{10}H_{14}N_2S$: S, 16.50. Found: S, 16.39.

The *hydrochloride* of the thioamide was prepared in ether and recrystallized from ethanol-ether, m.p. 165–170°.

Anal. Calc'd for $C_{10}H_{15}ClN_2S$: C, 52.05; H, 6.55.
Found: C, 52.61; H, 6.33.

Hydrogenolysis of the thioamides. The quantities of Raney nickel used, length of reflux time, and solvents employed are summarized in Table II. The general method was as follows: The thioamide (10 g.) was placed in a 500-ml. round-bottom flask with the wet catalyst, and 200 ml. of solvent was added. A slight exothermic reaction was often noted at this point. The mixture was then refluxed for the period noted in the Tables after which the flask was cooled. The catalyst was filtered and washed thoroughly with alcohol and a little water and dried to accurately determine the dry weight. The Raney nickel was usually pyrophoric even after the completion of the reaction, and it became quite hot during the air-drying operation.

The filtrate was concentrated *in vacuo*, the crude product was taken up in ether, and dilute hydrochloric acid was added to dissolve the amine. The acid extract was separated, made alkaline with potassium hydroxide, ether added, and the ether extract dried over solid potassium hydroxide. Dry hydrogen chloride was passed into the filtered ether solution, and the hydrochloride was purified by recrystallization. In most instances alcohol-ether was a satisfactory solvent. When the amine products obtained in the desulfurization were fairly volatile, *e.g.* triethylamine, N-ethylpiperidine, and benzyldimethylamine, the general procedure was modified by adding 10 ml. of concentrated hydrochloric acid *before* the removal of the solvent. Water was then added and the product worked up as before. In those cases in which oily or poorly crystalline hydrochlorides were obtained, picric acid in ethanol was used to prepare crystalline picrates. In the reduction of the dithiomorpholide of 4,4′-biphenyldiacetic acid twice the usual volume of solvent was employed because of the low solubility of the starting material.

Acknowledgment. The author wishes to express his appreciation to Dr. R. G. Jones for preparing several of the thioamides used and for helpful suggestions throughout the course of the work. The microanalyses were carried out by Mr. W. L. Brown and Mr. H. L. Hunter.

SUMMARY

1. Reductive desulfurization of thioamides in the presence of Raney nickel catalyst takes place smoothly in the absence of gaseous hydrogen to give good yields of the corresponding amines.

2. The formation of secondary rather than primary amines takes place with some thioamides which are unsubstituted on nitrogen.

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