[Chem. Pharm. Bull. 12 (2) 244～249]

UDC 547.53'298.4.07 : 543.422.4

34. Shun-ichi Yamada, Abdul-Mohsen M. E. Omar, and Tohru Hino : Studies on Thioamides. I. Synthesis of N-(2-Arylethyl)-thioamides and their Infrared Absorption Spectra.*[1]

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For many years the chemistry of thioamides has been widely investigated to prepare not only biologically active compounds but also intermediates in many organic syntheses. The present authors attempted to synthesize the several N-(2-arylethyl)-thioamides (Ⅳa～f) as shown in Table I, in order to test their direct cyclization to the corresponding 3,4-dihydroisoquinolines by a Bischler-Napieralski type reaction or other methods.[1)]

Among several methods for the general synthesis of thioamides, the conversion of acid amide to the corresponding thioamide with phosphorus pentasulfide[2)] would be a method of first choice for our present purpose, because it usually requires only a simple procedure and gives a satisfactory yield of thioamide. When N-(3,4-dimethoxyphenethyl)-2-phenylacetamide (I) was heated with an excess amount of phosphorus pentasulfide in boiling toluene or xylene for one hour, the yield of the thioamide (Ⅳc) was, however, unexpectedly poor, partly due to the formation of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (Ⅱ) as illustrated in Chart 1.[1)]

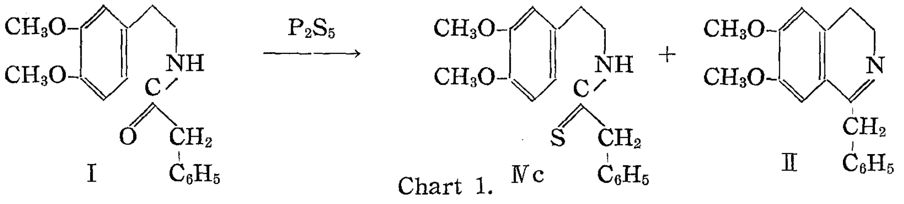


Chart 1.

Therefore, the attempt to use phosphorus pentasulfide on the N-(2-arylethyl)-substituted acid amides (I-type) was abandoned in favor of the use of the method which consists of the reaction of the 2-arylethylamines (Ⅲ) with the dithioesters (Ⅴ or Ⅵ)[3,4)] as depicted in Chart 2. As shown in Table I, both methods, A and B, did not give any

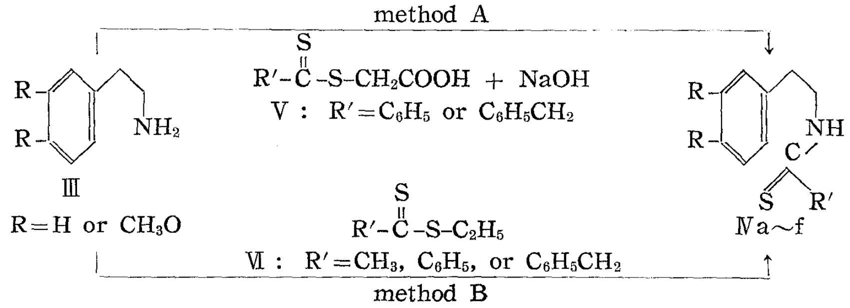


Chart 2.

[*1] Abstracted from the thesis submitted by Abdul-Mohsen M. E. Omar, in partial fulfilment of the requirement for the Master Degree at the University of Tokyo.

[*2] Hongo, Tokyo (山田俊一, アブドールーモハッセン・エム．イー．オマール, 日野 亨).

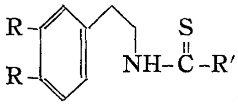
1) S. Yamada, A.-Mohsen M. E. Omar : This Bulletin, **12**, 249 (1964) and forthcoming papers.

2) R. Willstätter, T. Wirth : Ber., **42**, 1908 (1909); H. Rivier, J. Zeltner : Helv. Chim. Acta, **20**, 691 (1937); E. S. Gatewood, T. B. Johnson : J. Am. Chem. Soc., **48**, 2900 (1926); E. Klingsberg, D. Papa: *Ibid.*, **73**, 4988 (1951).

3) A. Kjaer : Acta Chem. Scand., **4**, 1347 (1950); *Idem* : *Ibid.*, **6**, 327 (1952).

4) C. S. Marvel, P. DeRadztzky, J. J. Brader : J. Am. Chem. Soc., **77**, 5997 (1955).

TABLE I. General Formula :



Ⅳ

Compound No.	R	R′	Yield (%) Method A	B	m.p. (°C)	Recrystn. solvent	Mol. formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ⅳa	CH_3O	CH_3	—	93	100～102	benzene	$C_{12}H_{17}O_2NS$	60.42	7.16	5.85	60.12	7.21	6.11
Ⅳb	〃	C_6H_5	45	98	117～119	benzene-hexane	$C_{17}H_{19}O_2NS$	67.76	6.36	4.65	67.71	6.73	4.37
Ⅳc	〃	$C_6H_5CH_2$	92	95	117	benzene	$C_{18}H_{21}O_2NS$	68.55	6.71	4.44	68.95	6.34	4.29
Ⅳd	H	CH_3	—	87	48～50	petr. ether	$C_{10}H_{13}NS$	67.02	7.31	7.82	66.92	7.33	7.65
Ⅳe	〃	C_6H_5	86	86	92～94	benzene-hexane	$C_{15}H_{15}NS$	74.66	6.27	5.81	74.72	6.15	5.75
Ⅳf	〃	$C_6H_5CH_2$	90	95～99	71～73[a]	〃	$C_{16}H_{17}NS$	75.27	6.71	5.49	75.10	6.49	5.44

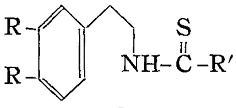
[a] E.C. Kornfeld (J. Org. Chem., **16**, 131 (1951)) reported m.p. 73.5～74.5°.

significant difference to the yield of the thioamides (Ⅳa～f). The dithioesters (Ⅴ and Ⅵ) used in this reaction were prepared by the known methods,[3～5] of which we now prefer to use the Marvel's method,[4] starting from nitrile, mercaptan and hydrogen chloride, because of the good yield of the dithioesters. The results are given in Table Ⅲ.

The infrared spectra of thioamides have not yet been well investigated in details as those of acid amides, although many authors have reported their results on the frequency of the thiocarbonyl absorption bands.[6～10] There is still some uncertainty as to the assignment of the bands which might be characteristic for the thiocarbonyl group. Lozac[7] assigned a band in the region of 1207～1225 cm^{-1} to the C=S stretching vibration in thioketones, while Jones and his co-workers[8] assigned it at 1125 cm^{-1} in dithioresorcylic acid, at 1408 cm^{-1} in thiourea and at 1334 cm^{-1} in thiocarbanilide.

TABLE Ⅱ.

The Regions in which Absorption Bands are Present in the Thioamides (Ⅳa～f) whereas either Absent or Relatively Weak in the Corresponding Acid Amides

 No.	R	R′	Frequencies in cm^{-1}
Ⅳa	CH_3O	CH_3	1392 (s),[a] 1343 (s), 1330 (sh), 868 (s)
Ⅳb	〃	C_6H_5	1388 (s), 1340 (vs) (slightly broad), 1100 (m), 948 (m), 898 (m)
Ⅳc	〃	$C_6H_5CH_2$	1416～1405 (vs), 1350～1332 (m), 1112 (s)
Ⅳd	H	CH_3	1402 (sh), 1390 (vs), 1340 (vs), 1335 (sh), 1147 (vs) (broad), 1085 (vs), 960 (s), 912 (m), 860 (s)
Ⅳe	〃	C_6H_5	1389 (s), 1345～1350 (vs), 1100 (m), 942 (s)
Ⅳf	〃	$C_6H_5CH_2$	1416～1405 (vs) (broad), 1352 (s), 1338 (s,sh), 1114 (vs), 1008 (m), 1002 (sh), 955 (w)

[a] Abbreviation: m=medium s=strong sh=shoulder vs=very strong w=weak

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5) J. Houben : Ber., **39**, 3219 (1906); *Idem* : *Ibid.*, **43**, 2481 (1910).
6) R. Mecke, Jr., R. Mecke, Sen. : Ber., **89**, 343 (1956); R. Mecke, R. Mecke, A. Lüttringhaus : *Ibid.*, **90**, 975 (1957).
7) N. Lozac : Bull. soc. chim. France, **1957**, 1221.
8) J.I. Jones, W. Kynaston, J.L. Hales : J. Chem. Soc., **1957**, 614.
9) E. Spinner : J. Org. Chem., **23**, 2037 (1958).
10) L.J. Bellamy, P.E. Rogasch : J. Chem. Soc., **1960**, 2218.

Marvel, *et al.*[4] also assigned it at 1170~1195 cm^{-1} in dithioesters and at 1110~1165 cm^{-1} in thioamides. Spinnre,[9] on the other hand, in a comparative study of the spectra of thioamides with the corresponding acid amides, assigned a band in the region between 1110~1115 cm^{-1} to the C=S stretching vibration in thioamides because it was comparatively weak in the oxygen analogues. Bellamy,[10] in an investigation of the solvent effect on the position of the C=S absorption bands, assigned it at 1119 cm^{-1} in ethyl dithioacetate, at 1000~950 cm^{-1} in thioamides and at 1207~1224 cm^{-1} in thioketones.

To find the characteristic absorption bands of thioamides, the present authors compared the infrared absorption spectra of the thioamides (Ⅳa~f) in chloroform solution

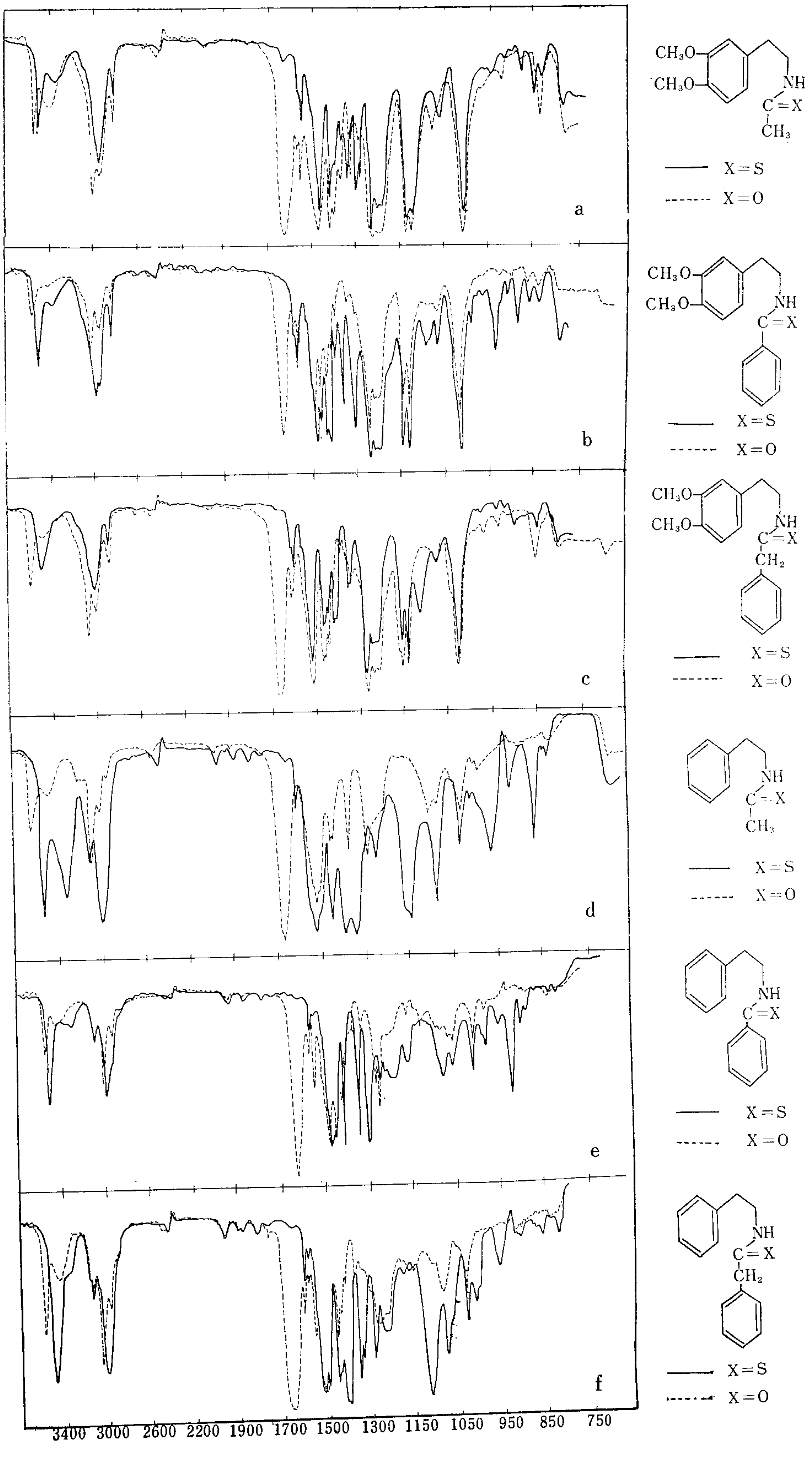

Fig. 2.

with those of the corresponding acid amides which were prepared by the conventional Schotten-Baumann reaction. The illustrative and summarized results are respectively shown in Fig. 1 and Table Ⅱ.

In addition to the bands listed in Table Ⅱ, there is observed in all thioamides, except for Ⅳa and Ⅳc, a band at about 1450 cm^{-1} with much more strong intensity than in the corresponding acid amides. The free and associated N-H stretching vibrational bands in the thioamides shift to lower wave numbers by about 100 cm^{-1} than those of the corresponding acid amides, as observed in Fig. 1.

To summarize Table Ⅱ further, the following bands seem to be the most characteristic for the C=S group in the N-phenethylthioamides (Ⅳd, Ⅳe, and Ⅳf):[*3]

i) 1389~1416 cm^{-1} : (s)[*4] (broad in Ⅳf).
ii) 1330~1352 cm^{-1} : (s) (two peaks).
iii) 1100~1150 cm^{-1} : (s) (broad, but relatively weak in Ⅳe).
iv) 942~960 cm^{-1} : (m)~(s) (relatively weak in Ⅳf).

In the N-(3,4-dimethoxyphenethyl)thioamides (Ⅳa, Ⅳb, and Ⅳc), the comparison method met with some difficulties due to the presence of methoxy groups. In the thioacetamide (Ⅳa), no characteristic absorption band is observed in the region between 1000~1150 cm^{-1}, in which all other compounds (Ⅳb and Ⅳc) have characteristic absorption bands as shown by the simple comparison method. The strong absorption band which appears at 1142~1157 cm^{-1} in both the thioamides (Ⅳa, Ⅳb, and Ⅳc) and the corresponding acid amides is naturally due to methoxy group. However, it would not be difficult to suppose that the characteristic absorption band in the former compounds is overlapped with that of methoxy group. Thus, the characteristic bands for the N-(3,4-dimethoxyphenethyl)thioamides (Ⅳa, Ⅳb, and Ⅳc) are as follows :

i) 1388~1416 cm^{-1} : (broad or two peaks in Ⅳc).
ii) 1330~1350 cm^{-1} : (two peaks, but broad in Ⅳb).
iii) 1100~1150 cm^{-1}.

Although it seems to be difficult to choose either of these regions as the most characteristic frequency of the C=S stretching vibration, the following regions would be the most characteristic for the bands in both the N-phenethyl- and N-(3,4-dimethoxyphenethyl) thioamides (Ⅳa~f) :

i) 1388~1416 cm^{-1} : A single band in all derivatives except for the 2-phenylthioacetamides (Ⅳc and Ⅳf) which give two bands in this region.
ii) 1330~1352 cm^{-1} : Two bands except for N-(3,4-dimethoxyphenethyl) thiobenzamide (Ⅳb) which shows a single band.
iii) 1100~1150 cm^{-1}.

Furthermore, a band appears in the region between 1508~1520 cm^{-1} in both the N-phenethyl- and N-(3,4-dimethoxyphenethyl)thioamides as well as the corresponding acid amides. This band corresponds to the amide (Ⅱ) band in the latter.

The recent study of the infrared absorption spectra on various types of thio-compounds by Rao and his co-workers[11)] revealed that the C=S absorption bands appear in different positions depending on the nature of the adjacent groups : In compounds in which the thiocarbonyl group is attached to elements other than nitrogen, the C=S frequency falls within a range of 1125±100 cm^{-1}, while in such compounds in which it is attached to one or two nitrogen atoms, strong vibrational coupling effects are possible

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[*3] The following bands are characteristic for every individual derivative :
i) At 1085 and 860 cm^{-1} for N-phenethylthioacetamide (Ⅳd).
ii) At 1077 cm^{-1} for N-phenethylthiobenzamide (Ⅳe).
iii) At 1075 cm^{-1} for N-phenethyl-2-phenylthioacetamide (Ⅳf).

[*4] For abbreviations : see those in Table Ⅱ.

11) C. N. R. Rao, R. VenKataraghavan : Spectrochim. Acta, **18**, 541 (1962).

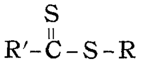
and the C=S vibration is not localized. In the latter case, they refered to three regions, namely, 1395~1570, 1260~1420, and 940~1140 cm^{-1} which were assigned to the -N-C=S (I, II, and III) band respectively.

Though our conclusion mentioned above was obtained from only a limited type of compounds, the characteristic absorption bands of the C=S group respectively fall within more narrow regions than those of Rao. The existence of a fourth band at 1510~1520 cm^{-1} in all of our thioamides rendered it difficult to judge correspondence of these four regions to those of Rao's -N-C=S (I, II, and III) band.

Experimental[*5]

Preparation of Dithioesters (V and VI)——Most of the dithioesters were prepared according to the direction of literature.[3~5] For ethyl dithiobenzoate and ethyl 2-phenyldithioacetate, the Marvel's procedure[4] was applied to benzonitrile and benzyl cyanide respectively. The results are listed in Table III.

TABLE III. General Formula :



$R'-\overset{\overset{S}{\|}}{C}-S-R$

R′	R	Procedure	Appearance	b.p. (°C/mm. Hg) or m.p. (°C) Observed	b.p. (°C/mm. Hg) or m.p. (°C) Reported	Yield (%)	Piperidine derivative m.p. (°C)
$C_6H_5CH_2$	CH_3	ref. 5)	orange liquid	131~135/4.5~5	149/12[5] 122~125/3[a]	27	79~80[c]
〃	CH_2COOH	ref. 3)	golden yellow plates	79.5~80	78~79[3]	35	—
C_6H_5	〃	〃	crimson red needles	123~124	127~128[3]	31	—
$C_6H_5CH_2$	C_2H_5	ref. 4)	orange yellow liquid	125~130/4	140~144/45[b]	73	79~80.5
C_6H_5	〃	〃	crimson red liquid	149~152/13	122~125/72[b]	60	—
CH_3	〃	〃	yellow liquid	48~52/15	42~43/11[4]	63	55~56[d]

a) J.W. Course, R.G. Jones, Q.F. Soper, C.W. Whitehead, O.K. Behrens : J. Am. Chem. Soc., **70**, 2837 (1948).
b) Y. Sakurada : Mem. Coll. Sci. Kyoto, **10**, 79 (1926).
c) E.C. Kornfeld (ref. *a*) in Table I) reported m.p. 77.5~78.5°.
d) W.F. Russel (J. Chem. Soc., **1954**, 1910) reported m.p. 60~61°; Marvel, *et al.* (ref. 4)) reported m.p. 55~56°.

Preparation of Thioamides (IVa~f)——The two general procedures applied are as follows :

Method A[3]——To a solution of the required dithioester in an equivalent amount of *N* NaOH was added an equimolecular amount of the required amine under cooling. Shortly an exothermic reaction occurred to separate a viscous mass, which gradually solidified. The solid was taken up in benzene or other appropriate solvent, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to dryness. The crude thioamide thus obtained was purified by recrystallization from the proper solvent.

Method B[4]——The required amine was added dropwise to an equimolecular amount of the required dithioester under N_2 stream while cooling in an ice-bath. Shortly mercaptan smelled and the product became almost a solid. The mixture was allowed to cool in an ice-bath for 15 min., then heated in a boiling water bath over a period of 13~30 min. The mixture was finally heated *in vacuo* for the same period of time as above in order to remove a trace of mercaptan. The crude thioamide thus obtained was purified by recrystallization (in the most cases) or distillation (in the case of N-phenethylthioacetamide (IVd)).

The yields and physical constants of the thioamides prepared by both methods are given in Table I.

Measurement of Infrared Absorption Spectra——The IR absorption spectra of the thioamides (IVa~f) and the corresponding acid amides were measured in $CHCl_3$ solution with a Nihon Bunko model DS-301 spectrophotometer. The cell thickness was 0.1 mm.

The authors express their gratitude to the members of the Central Analysis Room of this Faculty for the measurement of IR spectra and microanalytical data.

[*5] All melting and boiling points are not corrected.

Summary

Several N-(2-arylethyl)-substituted thioamides (Ⅳa～Ⅳf) were synthesized from the dithioesters (Ⅴ or Ⅵ) and the 2-arylethylamines in good yield, in order to test direct cyclization of the thioamides to the corresponding 3,4-dihydroisoquinolines by a Bischler-Napieralski type reaction The comparative study of the infrared absorption spectra of the thioamides with those of the corresponding acid amides shows that the most characteristic absorption bands of the C=S group in the thioamides (Ⅳa～Ⅳf) fall within four regions, namely, 1508～1520, 1388～1416, 1330～1352, and 1100～1150 cm^{-1}.

(Received October 10, 1963)

[Chem. Pharm. Bull. 12 (2) 249 ～ 252]

UDC 547.53′298.4.07

35. Shun-ichi Yamada and Abdul-Mohsen M. E. Omar : Studies on Thioamides. II. Application of Thioamides in Bischler-Napieralski Reaction.

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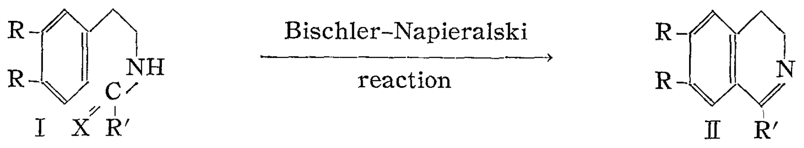
The cyclodehydration of N-phenethylamides to form 3,4-dihydroisoquinolines under the Bischler-Napieralski reaction conditions is well known.[1] Modifications involving the use of different condensing agents under various conditions with substituted or non substituted N-phenethylamides have been reported.[1] However, nothing is mentioned on the use of thioamides as starting materials in the Bischler-Napieralski reaction and no attempt was made to effect their cyclization.

The present authors have been much interested in the reactivities of thioamides. First, a good method was established for their preparation[2] and, in the present investigation, their cyclization was carried out under the same reaction conditions as for the corresponding acid amides to obtain 3,4-dihydroisoquinoline derivatives, as in the following general equation :



I

Ⅱ

$R=OCH_3$ or H
$R'=CH_3$, C_6H_5 or $C_6H_5CH_2$
$X=S$ or O

Cyclization of all N-homoveratrylthioamides drivatives (I : $R=OCH_3$) proceeded easily by using phosphoryl chloride in dry benzene and the products were found to be identical with the 3,4-dihydroisoquinoline derivatives prepared from the corresponding acid amides. When benzene was substituted with toluene for N-homoveratrylthiobenzamide (I : $R=OCH_3$, $R'=C_6H_5$, $X=S$), the yield of the cyclized product increased slightly. Results and the comparing yields with acid amides are summarized in Table I.

[*1] Hongo, Tokyo (山田俊一, アブドールーモハッセン・エム.イー.オマール).

[1] W. M. Whaley, T. R. Govindachari : Org. Reactions, **6**, 74 (1951).

[2] Part I. This Bulletin, **12**, 244 (1964).