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}.

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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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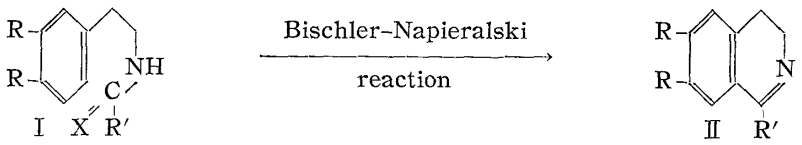
The cyclodehydration of N-phenethylamides to form 3,4-dihydroisoquinolines under the Bischler-Napieralski reaction conditions is well known.[1] Modifications involving the use of different condensing agents under various conditions with substituted or non substituted N-phenethylamides have been reported.[1] 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.

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1) W. M. Whaley, T. R. Govindachari : Org. Reactions, **6**, 74 (1951).
2) Part I. This Bulletin, **12**, 244 (1964).

Table I. Results of Cyclization of both N-Homoveratrylthioamides and Amides under Conditions of Bischler-Napieralski Reaction

R′	X	Reflux solvent	Period of reflux (hr.)	Base m.p. (°C)	Yield (%)	Picrate m.p. (°C)	Hydrochloride m.p. (°C)
CH_3	S	benzene	3	104~105	85.9	210~212	198~199.5
〃	O	〃	3	104~105[a]	95.8	210~212	198~199.5
C_6H_5	S	〃	2	120~122	81.3	193~194	212~213
〃	O	〃	2	120~122[b]	91.0	193~194	212~213
〃	S	toluene	2.5	120~122	85.9	193~194	212~213
$C_6H_5CH_2$	S	benzene	2	96~98[c]	82.1	176~178	175~176
〃	O	〃	2	96~98	87.5	176~178	175~176

a) N. Itoh and S. Sugasawa reported (Tetrahedron, **1**, 45 (1957)), m.p. 108~109° for the base, m.p. 210~212° for the picrate and m.p. 199~200° for the hydrochloride. A.M. Barbier and M.P. Rumpf reported (Bull. soc. chim. France, **1953**, 293), m.p. 106° for the base and m.p. 215° for the picrate.
b) H.J. Harwood and T.B. Johnson reported (J. Am. Chem. Soc., **56**, 468 (1934)), m.p. 120~121.5° for the base.
c) T.R. Govindachari and K. Nagarajin reported (Proc. Indian Acad. Sci., **42A**, 136 (1655), Chem. Abstr., **50**, 7804 (1956)) m.p. 176° for the picrate and m.p. 182° for the hydrochloride.

On the other hand, it has also been known that when methoxyl group is absent from *para*-position to the point of ring closure of N-phenethylamides, it is difficult to cyclize these compounds under the mild conditions of Bischler-Napieralski reaction. In case of thioamides, it was found that similar difficulties for cyclization occurred. Consequently, several stronger condensing agents and more drastic conditions were utilized; phosphorus pentoxide in tetralin and xylene, polyphosphoric acid and mixtures of phosphorus pentoxide and phosphoryl chloride were used for both thioamides as well as acid amides, and the 1-substituted isoquinoline derivatives were obtained in considerable yields as shown in Table II.

Table II. Results of Cyclization of N-Phenethylthioamides and Amides under Different Conditions for Individual Compounds

R′	X	Condensing agent	Reflux solvent	Period of reflux (hr.)	Yield of crude base (%)	Picrate m.p. (°C)	Yield of pure base due to picrate (%)	Hydrochloride m.p. (°C)
CH_3	S	P_2O_5	tetralin	0.5	76.6	189~191	57.7	194~196
〃	O	〃	〃	0.5	78.6	189~191[a]	63.1	194~196
〃	S	PPA	—	1.0	80.2	189~191	60.3	194~196
〃	O	〃	—	1.0	96.7	189~191[b]	82.3	194~196
C_6H_5	S	$POCl_3$-P_2O_5	xylene	3.0	96.2	174~176	82.5	237~238
〃	O	〃	〃	3.0	99.0	174~176[c]	92.7	237~238
$C_6H_5CH_2$	S	P_2O_5	〃	1.25	50.0	178~179	48.2	224~226
〃	O	〃	〃	1.25	87.0	178~179[d]	75.0	224~226

a) A. Pictet and F.W. Kay reported (Ber., **42**, 1973 (1909)), m.p. 188~190° for the picrate.
b) J.G. Cannon and G.L. Webster reported (J. Am. Pharm. Assoc., **47**, 3533 (1958)), m.p. 188~192° for the picrate.
c) E. Späth, F. Berger, and W. Kuntara reported (Ber., **63**, 134 (1930)), m.p. 173~174° for the picrate. W.M. Whaley and W.H. Hartung reported (J. Org. Chem., **14**, 650 (1949)), m.p. 178° for the picrate and m.p. 245~248° for the hydrochloride.
d) W.M. Whaley, *et al.* loc. cit. reported, m.p. 176~178° for the picrate and m.p. 227~229° for the hydrochloride. S. Sugasawa and R. Tachikawa reported (Tetrahedron, **53A**, 12328 (1959)), m.p. 173~175° for the picrate.

The data in Table II shows that the yields of the cyclized crude base from thioamides range from 50 to 96.2% and from 87 to 99% from the corresponding acid amides. As these bases are not solids, they were converted to their crystalline picrate for estimating the amount and the purity of these bases. The yields of picrate from thioamides were generally a little lower than those obtained from acid amides.

In all cases, the cyclized products from both N-homoveratryl as well as N-phenethylthioamides were identified by their elemental analysis, ultraviolet spectra, and

mixed melting points of the pure solid products of the former (II : R=OCH_3) and of picrate of the oily product of the latter (II : R=H), with authentic samples prepared from the corresponding acid amides.

We have reported before[2] that, the reaction of phosphorus pentasulfide on acid amides did not give the required thioamides but gave instead, the cyclized products. In order to ascertain whether phosphorus pentasulfide is an effective condensing agent in the Bischler-Napieralski reaction, further investigations involving the use of different solvents and higher temperature were performed. Thus, when N-homoveratrylthiobenzamide (I : R=OCH_3, R'=C_6H_5, X=S) was stirred under reflux with phosphorus pentasulfide in dimethylformamide, the required 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (II : R=OCH_3, R'=C_6H_5) was produced in 66% yield, when the same process was applied on N-homoveratrylbenzamide (I : R=OCH_3, R'=C_6H_5, X=O), the cyclized product was obtained in almost the same yield and thioamide was not detected in the latter case.

Since no previous reports on the use of phosphorus pentasulfide in the Bischler-Napieralski reaction are available, these results are good evidence of the possibility of using this reagent to obtain 6,7-dimethoxyisoquinoline from either N-homoveratrylthioamides or amides.

Application of this process on the corresponding N-phenethyl derivatives is under investigation.

Experimental

General Procedure for the Cyclization of N-Homoveratrylthioamides (I : R=OCH_3, R'=CH_3, C_6H_5 or $C_6H_5CH_2$, X=S)——Under anhydrous conditions, a solution of 1 g. (about 3.5 mmoles) of the required thioamide in 20 ml. of dry benzene was refluxed with 7 g. of $POCl_3$ for about 2~2.5 hr. The solution gradually darkened and HCl gas evolved. After cool, excess petr. ether was added and the mixture was left overnight or till separated into two layers. The petr. ether was decanted, and the yellowish residue washed well with fresh petr. ether, and treated with 30 ml. of 10% HCl acid solution when it gradually went into solution and H_2S gas evolved. A sticky mass was left adhering to the walls of the flask even after warming. The acid solution was then shaken with benzene and made strongly alkaline with 10% NaOH solution. The milky suspension so produced was extracted repeatedly with Et_2O, Et_2O extract was collected, washed thoroughly with H_2O, dried over anhyd. Na_2SO_4, filtered and Et_2O distilled off. A yellowish white crystalline residue was always left, which on recrystallization from the proper solvent, gave the required isoquinoline derivative in almost pure state.

The melting points of the cyclized pure bases as well as their picrates and hydrochlorides are listed in Table I.

Cyclization of N-Phenethylthioacetamide (I : R=H, R'=CH_3, X=S)——a) With P_2O_5 in tetralin as condensing agent : A solution of 1 g. (5.6 mmoles) of the thioamide in 30 ml. of anhyd. tetralin was heated to reflux with 5 g. of P_2O_5 for 15 min., another 5 g. of P_2O_5 was added, and the mixture was refluxed for 15 min. After cool, tetralin was decanted and the dark brown residue was treated with H_2O and 15% HCl solution under ice cooling. The acid mixture was steam distilled to remove traces of tetralin and the residual mixture in the distilling flask was made strongly alkaline with solid NaOH and steam distilled again. The distillate was extracted repeatedly with Et_2O, Et_2O extract was washed well with H_2O, dried over anhyd. Na_2SO_4, filtered and Et_2O distilled off to leave a yellow oil weighing 0.62 g. Yield of the crude base 76.6%. This was converted into picrate, total weight 1.2 g., yield of the pure base according to the picrate was 57.7%. Melting point and mixed melting point of picrate as well as hydrochloride with the corresponding authentic samples prepared from acid amide showed no depression (Table I). Picrate : *Anal.* Calcd. for $C_{16}H_{14}N_4O_7$: C, 51.28; H, 3.88; N, 15.06. Found: C, 51.34; H, 3.77; N, 14.97. UV : λ_{max}^{EtOH} 248 mμ (log ε 3.89), $\lambda_{max}^{EtOH+HCl}$ 275 mμ (log ε 3.97).

b) With polyphosphoric acid as a condensing agent : A mixture of 1 g. (5.6 mmoles) of N-phenethylthioacetamide and PPA (prepared from 17.5 g. of P_2O_5 and 10 ml. of 85% H_3PO_4) was heated at 230~240° (bath temperature) for 1 hr. H_2S gas evolved (detected by $(AcO)_2Pb$ paper). After cool, the whole mixture was thrown on crushed ice, the reaction flask rinsed with H_2O and the rinsing was added to the ice mixture. This was made distinctly alkaline by 20% NaOH solution and extracted repeatedly with benzene. The combined benzene extract was washed well with H_2O, dried over anhyd. Na_2SO_4, filtered, and benzene distilled off to leave a dark brown viscous oil weighing 650 mg. Yield of the crude base 80.2%. This was dissolved in EtOH, filtered from insoluble particles, and treated with saturated solution of picric acid in EtOH until no more precipitation occurred, filtered and dried. Yield,

1.26 g. Recrystallization from EtOH gave fine needles, m.p. 189~191°. Yield of pure base according to picrate is 60.3%.

Cyclization of N-Phenethylthiobenzamide (I : R=H, R'=C_6H_5, X=S)——A solution of 1 g. (4.15 mmoles) of the thioamide in 20 ml. of dry xylene was treated with 4 g. of P_2O_5 and 4 g. of $POCl_3$, and refluxed at 150~160° (bath temperature) for 3 hr. The mixture gradually darkened and HCl gas evolved. After cool, xylene was decanted and excess petr. ether was added to remove traces of $POCl_3$. The brown residue was then treated with H_2O under cooling to compensate the exothermic reaction, and this was followed by the addition of 10% HCl solution and slightly warmed to help dissolution. This acid solution was shaken with Et_2O when the latter acquired an orange color. Drying of this Et_2O extract and distillation gave a dark brown viscous substance which proved by IR to be different from thioamide as well as the cyclized product.

The acid layer was filtered and made alkaline with 10% NaOH solution when a brown oil separated, this oil was taken up in Et_2O, Et_2O extract was washed well with H_2O, dried over anhyd. Na_2SO_4, filtered, and the solvent was distilled off, a brown oil was left weighing 0.89 g. Yield of the crude base, 96.22%. All converted into picrate gave 1.5 g. or 0.712 g. of pure base. Yield, 82.5%. This picrate did not show any depression in melting point on admixture with authentic sample of picrate prepared from the acid amide. Picrate : *Anal.* Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.75; H, 3.90; N, 12.66. Found : C, 57.8; H, 3.70; N, 12.84. UV : λ_{max}^{EtOH} 256 mμ (log ε 4.04), $\lambda_{max}^{EtOH+HCl}$ 282 mμ (log ε 4.14).

Cyclization of N-Phenethyl-2-phenylthioacetamide (I : R=H, R'=$C_6H_5CH_2$, X=S)——A solution of 1 g. (4.0 mmoles) of the thioamide in 40 ml. of dry xylene was heated to 100°, 5 g. of P_2O_5 was added, and the mixture was refluxed for 15 min. Another 5g. of P_2O_5 was added and the mixture was again refluxed for 1 hr. The color gradually changed to brown and H_2S gas evolved. After cool, xylene was decanted the residue was treated with H_2O under cooling with ice, excess 10% HCl solution was added, and the mixture warmed on a water bath. This acid solution was shaken with Et_2O, filtered, made distinctly alkaline with 20% NaOH solution, and extracted repeatedly with Et_2O, the Et_2O extract was washed thoroughly with H_2O, dried over anhyd. Na_2SO_4, filtered and Et_2O was distilled off to leave a yellowish brown oil weighing 0.43 g. The yield of the crude product, 50%. All converted into picrate gave 0.85 g. or 0.42 g. of the pure base. Yield 48%. Mixed melting points of the picrate as well as the hydrochloride with authentic samples showed no depression. Picrate : *Anal.* Calcd. for $C_{22}H_{18}N_4O_7$: C, 58.74; H, 4.15; N, 12.44. Found : C, 58.66; H, 4.03; N, 12.44. UV : λ_{max}^{EtOH} 252 mμ (log ε 3.894), $\lambda_{max}^{EtOH+HCl}$ 276 mμ (log ε 3.96).

Cyclization of N-Homoveratrylthiobenzamide——(I : R=OCH_3, R'=C_6H_5, X=S) with P_2S_5 in dimethylformamide : A solution of 1 g. (3.5 mmoles) of the thioamide in 20 ml. of freshly distilled DMF was heated under stirring to 100°, then 6 g. of finely powdered P_2S_5 was added, and the volume of the mixture was completed to 40 ml. with DMF and refluxed for 1 hr. The dark brown mixture with viscous residue at the bottom of the flask was distilled under reduced pressure to remove DMF and the dark brown residue so obtained was treated with 40 ml. of 10% HCl solution when it dissolved completely (H_2S gas evolved). The solution was distilled again under reduced pressure to remove traces of DMF and H_2S, 60 ml. of H_2O was added, and the resulted solution was extracted with Et_2O to remove unreacted substances. This Et_2O on drying and distillation did not give the starting material. The acid solution was filtered, made distinctly alkaline with 10% NaOH solution, and extracted repeatedly with Et_2O. The Et_2O extract was washed thoroughly with H_2O, dried over anhyd. Na_2SO_4, filtered, and Et_2O was distilled off when a slightly reddish residue with prismatic crystals was left weighing 0.89 g. This on decolorization with charcoal in EtOH gave a slightly yellow crystals weighing 0.67 g., m.p. 113~115°. Recrystallization from benzene-hexane gave a large white square crystals m.p. 122~123°. This proved to be 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (II : R=OCH_3, R'=C_6H_5), by mixed m.p. with authentic sample of the pure base, picrate, and hydrochloride, as well as by IR and UV spectra.

Application of this Process on N-Homoveratrylbenzamide——(I : R=OCH_3, R'=C_6H_5, X=O), gave the cyclized 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (II : R=OCH_3, R'=C_6H_5) in 66% yield.

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Summary

Thioamides have been cyclized in good yield to the corresponding 1-substituted 3,4-dihydroisoquinoline under the normal Bischler-Napieralski reaction conditions which are generally used to cyclize acid amides. Phosphorus pentasulfide has been effectively used as a condensing agent in the Bischler-Napieralski reaction to get 1-substituted-3,4-dihydroquinoline from both thioamides as well as normal acid amides.

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