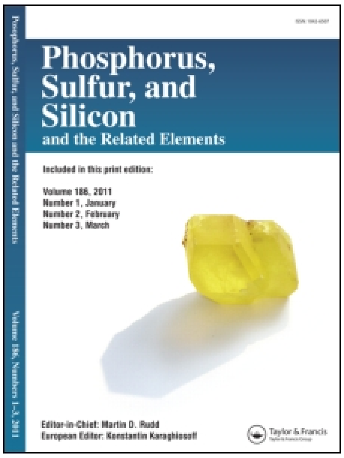

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Heterocyclic Sulfur Compounds-Cv 1,2-Dihmtdro-3,1,2,γ^5-Benzothiazaphosphinine-2,4-Dithiones—A New Synthetic Route to 2-Arylamino-Thiobenzamides and To 2-(2-Arylaminophenyl)-4,5-Dihydrothiazoles (Or Oxazoles)

Louis Legrand[a]; Noël Lozac'h[a]
[a] Laboratoire & Chimie des Composés Thioorganiques, ISMRA, Université de Caen, Caen Cedex, France

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HETEROCYCLIC SULFUR COMPOUNDS—CV 1,2-DIHYDRO-3,1,2λ^5-BENZOTHIAZAPHOSPHININE-2,4-DITHIONES—A NEW SYNTHETIC ROUTE TO 2-ARYLAMINO-THIOBENZAMIDES AND TO 2-(2-ARYLAMINOPHENYL)-4,5-DIHYDROTHIAZOLES (OR OXAZOLES)

LOUIS LEGRAND† and NOËL LOZAC'H

Laboratoire de Chimie des Composés Thioorganiques, ISMRA, Université de Caen, F-14032 Caen Cedex, France

(*Received May 29, 1985*)

2-Alkoxy-1-aryl-1,2-dihydro-3,1,2λ^5-benzothiazaphosphinine-2,4-dithiones react with a primary or secondary alkylamine and an alcohol giving a 2-arylamino-thiobenzamide and an *O,O*-dialkyl alkylammonium dithiophosphate. Ethane-1,2-diamine and propane-1,3-diamine, with the same reagents, give a 2,2′-bis-(arylamino)-*N,N′*-di(or tri)methylenebis(thiobenzamide) accompanied, respectively, by a 2-(2-arylaminophenyl)-4,5-dihydro-1*H*-imidazole or by a 2-(2-arylaminophenyl)-1,4,5,6-tetrahydropyrimidine.

In similar conditions, 2-aminoethanol leads to the expected thiobenzamide, often accompanied by a 2-(2-arylaminophenyl)-4,5-dihydrooxazole. With 2-amino-ethanethiol, a 2-(2-arylaminophenyl)-4,5-dihydrothiazole is obtained.

INTRODUCTION

Renewed interest has been shown for the synthesis of 2-amino-thiobenzamides because of the potential pharmacological properties of this type of compound.[1,2] Various methods have been described whose applicability depends, to a large extent, on the substituents of the amine and amide groups.

Reaction of 2-aminobenzonitrile with hydrogen sulfide, in the presence of ammonia[3] or of triethylamine[4] leads to a thioamide unsubstituted on the amide group.

Action of phosphorus pentasulfide, in boiling pyridine, on a 2-amino-benzamide has been used for preparing variously substituted thioamides.[1,2] In this synthesis, a phosphorus intermediate is formed for which the structure of a pyridinium 2,4-dithioxo-1,2,3,4-tetrahydro-1,3,2λ^5-benzodiazaphosphinine-2-thiolate has been suggested.[2] Hydrolysis of this salt yields the desired thioamide.

Some 2-amino-thiobenzamides have been prepared by reacting a primary amine with a 1*H*-3,1-benzothiazine-2,4-dithione.[2] However, according to the nature of the reagents, this may lead also, and sometimes exclusively, to a 1*H*,3*H*-quinazoline-2,4-dithione.

In previous papers, we have shown that 2-amino-thiobenzamides can be obtained by reacting 1,2-dihydro-3,1-benzothiazine-3-thiones with diverse amines: primary

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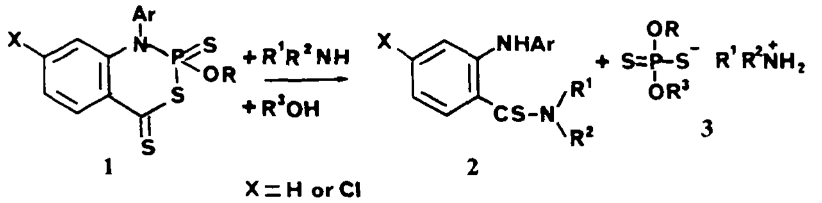
† Deceased the 18 November 1984. This paper is an homage to a valued Co-worker. N. L.

and secondary aliphatic amines,[5] arylamines.[6] In the case of ethane-1,2-diamine, the major product is a 2-(2-aminophenyl)-4,5-dihydro-1*H*-imidazole, resulting from a cyclisation of the thioamide.[7] Similarly, with propane-1,3-diamine, a 2-(2-aminophenyl)-1,4,5,6-tetrahydropyrimidine can be obtained.[8]

RESULTS

This paper describes a synthesis of 2-arylamino-thiobenzamides **2** starting from *N*-substituted anthranilic esters and using as intermediates the 2-alkoxy-1-aryl-1,2-dihydro-3,1,2λ^5-benzothiazaphosphinine-2,4-dithiones **1** whose preparation from anthranilic esters has been described in a previous paper.[9] Reaction of amines on compounds **1** is shown in Scheme 1.



SCHEME 1

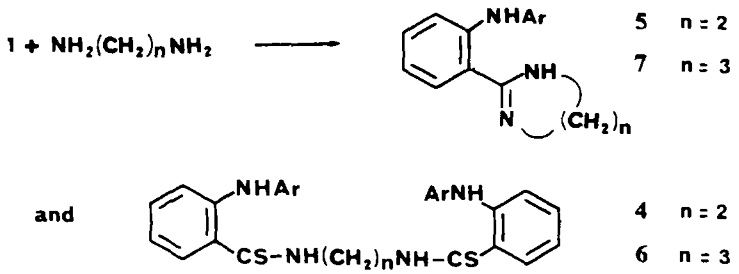
It has been possible to obtain samples of the dithiophosphates **3** in some cases, for instance with methylamine ($R^1{=}CH_3$, $R^2{=}H$) in the presence of methanol or ethanol ($R^3{=}CH_3$ or C_2H_5). It appears that this reaction constitutes a method for preparing *O,O*-dialkyl dithiophosphate anions containing two different alkyl groups.

Two compounds **1** have been reacted with ethane-1,2-diamine and in both cases two compounds have been obtained:

—a *N,N'*-ethylenebis(thiobenzamide) **4**;

—a 2-[2-(arylamino)phenyl]-4,5-dihydroimidazole **5**.

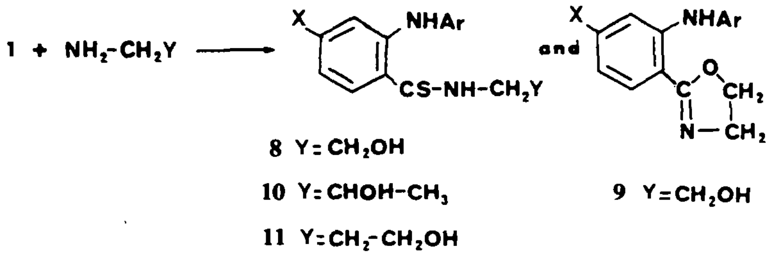
A similar reaction, performed with propane-1,3-diamine gave a mixture of 2,2'-bis(*p*-tolylamino)-*N,N'*-trimethylenebis(thiobenzamide) **6** and of 2-[2-(*p*-tolylamino)phenyl]-1,4,5,6-tetrahydropyrimidine **7**. These reactions are summarized in Scheme 2.



SCHEME 2

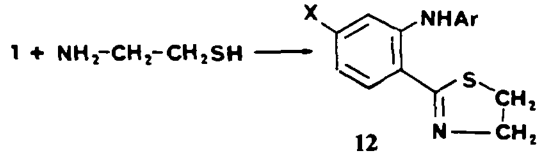
Compounds **4**, **5**, **6** and **7** had been previously obtained by reacting the same diamines with 1,2-dihydro-3,1-benzothiazine-3-thiones.[7,8]

2-Aminoethanol, 2-amino-1-propanol and 3-amino-1-propanol react as monoalkylamines on compounds **1**, leading to 2-arylamino-*N*-(hydroxyalkyl)-thiobenzamides **8**, **10** or **11**. When 2-aminoethanol is used, the thiobenzamide **8** is sometimes accompanied by a 2-(2-arylaminophenyl)-4,5-dihydrooxazole **9** (Scheme 3).



SCHEME 3

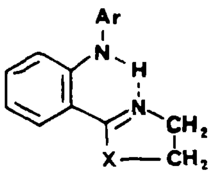
When the same reaction is performed with 2-mercaptoethanol, the expected 2-arylamino-*N*-(2-mercaptoethyl)-thiobenzamides are unstable and their cyclization products, 2-(2-arylaminophenyl)-4,5-dihydrothiazoles **12** are obtained (Scheme 4).



SCHEME 4

In ^{1}H-nmr of compounds **9**, the two CH_2 groups give a multiplet between 4.00 and 4.35 ppm while, for the sulfur analogues **12**, the two CH_2 groups give two well separated triplets, one near 3.30 ppm, the other near 4.50 ppm.

For compounds **9** and **12** it is also interesting to note that the signal due to the proton in position 6 of the phenyl group is significantly displaced towards low fields. It appears between 7.75 and 7.90 ppm for compounds **9**, between 7.40 and 7.70 ppm for compounds **12**. It is likely that this comes from the fact that the two rings are coplanar, possibly because of a chelation of the amino hydrogen atom as shown in Scheme 5.



SCHEME 5

EXPERIMENTAL

^{1}H-nmr spectra have been recorded on Varian A60-D or EM-360 spectrometers, using $CDCl_3$ as solvent and TMS as internal reference.

Reaction of primary and secondary alkylamines. The amine is slowly added to the phosphorus compound **1** dissolved in a benzene-methanol (1 : 1) or benzene-ethanol (1 : 1) boiling mixture. When the brown-red color of **1** has disappeared, the solvent is distilled under reduced pressure. The residue is extracted by benzene, which removes the thiobenzamide **2**. The latter is purified by chromatography on alumina, the elution being done with a mixture benzene-cyclohexane (1 : 5). The thiobenzamides thus obtained are indicated in Table I.

The oil remaining after benzene extraction contains an ammonium *O*,*O*-dialkyl dithiophosphate which sometimes can be recrystallized in a benzene-chloroform (1 : 1) mixture. The following salts have been isolated and characterized by nmr:

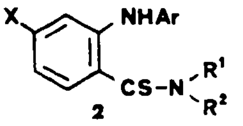
Methylammonium *O*,*O*-dimethyl dithiophosphate—Yield 80%—White crystals F = 89°C—nmr: 2.63(s): NCH_3; 3.63(d, $J_{POCH} = 14$ Hz): OCH_3; 7.8(m, $W_H = 22$ Hz): NH_3^+. $C_3H_{12}O_2NS_2P$—Calc'd: C, 19.03; H, 6.39; N, 7.40; P, 16.37. Found: C, 19.24; H, 6.35; N, 7.59; P, 16.37.

Methylammonium *O*-ethyl *O*-methyl dithiophosphate—Yield 75%—oil—nmr: 1.26(t, $J = 7.5$ Hz): CH_3—(CH_2); 2.80(s): NCH_3; 3.65(d, $J_{POCH} = 14$ Hz): OCH_3; 4.04 (2 q, $J_{POCH} = 10$ Hz, $J_{HCCH} = 7.5$ Hz): CH_2—(CH_3); 7.4(m, $W_H = 15$ Hz): NCH_3^+. $C_4H_{14}O_2NS_2P$—Calc'd: C, 23.63; H, 6.94; N, 6.89; P, 15.24. Found: C, 23.83; H, 6.91; N, 7.25; P, 15.33.

Methylammonium *O*,*O*-diethyl dithiophosphate—Yield 78%—White crystals F = 67°C—nmr: 1.31(t, $J = 7$ Hz): CH_3—(CH_2); 2.75(s): NCH_3; 4.05(2 q, $J_{POCH} = 9.5$ Hz, $J_{HCCH} = 7$ Hz): OCH_2—(CH_3); 7.1(m, $W_H = 25$ Hz): NH_3^+. $C_5H_{16}O_2NS_2P$—Calc'd: N, 6.45. Found: N, 6,93.

Reaction of ethane-1,2-diamine and of propane-1,3-diamine. The reaction is performed as for monoamines but the chromatography on alumina is slightly modified. Elution, begun with dichloromethane, gives first a bis(thiobenzamide) **4** or **6**, recrystallized in a benzene-cyclohexane(1 : 1) mixture. The phosphorus starting compounds **1** contained an ethoxy substituent. Other substituents are apparent from

TABLE IA



2

2-(Arylamino)thiobenzamides **2**

OR[a]	Ar	X	R^1	R^2	No	Yield%	F°C	Ref.
OCH_3	Phenyl	H	CH_3	H	**2Aa**	60	186	5
OCH_3	Phenyl	H	C_2H_5	H	**2Ab**	85	116	5
OC_2H_5	Phenyl	H	CH_3	CH_3	**2Ac**	92	94	5
OC_2H_5	Phenyl	H	C_2H_5	C_2H_5	**2Ad**	95	123	
OCH_3	Phenyl	Cl	CH_3	H	**2Ba**	83	123	5
OCH_3	Phenyl	Cl	CH_3	CH_3	**2Bc**	90	130	
OC_2H_5	4-Methylphenyl	H	CH_3	H	**2Ca**	95	133	5
OC_2H_5	4-Methylphenyl	H	C_2H_5	H	**2Cb**	87	95	5
OCH_3	4-Methylphenyl	H	CH_3	CH_3	**2Cc**	72	102	5
OCH_3	4-Methylphenyl	H	C_2H_5	C_2H_5	**2Cd**	40	129	
OCH_3	4-Methylphenyl	H	CH_2—$(CH_2)_3$—CH_2		**2Ce**	55	124	5
OCH_3	4-Methylphenyl	Cl	CH_3	H	**2Da**	80	104	5
OCH_3	4-Methylphenyl	Cl	C_2H_5	C_2H_5	**2Dd**	70	110	
OCH_3	4-Methoxyphenyl	H	CH_3	H	**2Ea**	90	134	5
OCH_3	4-Methoxyphenyl	H	C_2H_5	H	**2Eb**	90	98	
OCH_3	4-Methoxyphenyl	H	C_2H_5	C_2H_5	**2Ed**	60	94	
OCH_3	4-Methoxyphenyl	H	CH_2—$(CH_2)_3$—CH_2		**2Ee**	75	123	5

[a] Nature of the alkoxy in the starting material **1**.

TABLE IB

Analyses

No	Formula	Calculated C	H	N	S	Found C	H	N	S
2Aa	$C_{14}H_{14}N_2S$	69.38	5.82	11.56	—	69.45	6.09	11.44	—
2Ab	$C_{15}H_{16}N_2S$	70.27	6.29	10.93	—	70.17	6.27	10.82	—
2Ac	$C_{15}H_{16}N_2S$	70.27	6.29	10.93	12.51	70.45	6.40	10.94	12.75
2Ad	$C_{17}H_{20}N_2S$	71.79	7.09	9.85	—	71.54	7.25	9.89	—
2Ba	$C_{14}H_{13}N_2SCl$	60.74	4.73	10.12	11.59	60.87	4.91	10.17	11.61
2Ca	$C_{15}H_{16}N_2S$	70.27	6.29	10.93	—	70.34	6.25	10.92	—
2Cb	$C_{16}H_{18}N_2S$	71.07	6.71	10.36	11.86	71.12	6.86	10.32	11.75
2Cc	$C_{16}H_{18}N_2S$	71.07	6.71	10.36	11.86	70.88	6.72	10.50	11.67
2Cd	$C_{18}H_{22}N_2S$	72.43	7.43	9.39	10.74	72.18	7.45	9.59	10.73
2Ce	$C_{19}H_{22}N_2S$	73.54	7.14	9.03	10.31	73.69	7.12	9.05	10.15
2Da	$C_{15}H_{15}N_2SCl$	61.94	5.20	9.63	11.02	61.70	5.36	9.79	11.06
2Dd	$C_{18}H_{21}N_2SCl$	64.94	6.36	8.42	—	64.88	6.20	8.42	—
2Ea	$C_{15}H_{16}ON_2S$	66.14	5.92	10.28	—	66.24	5.80	10.13	—
2Eb	$C_{16}H_{18}ON_2S$	67.10	6.34	9.78	—	67.57	6.34	9.72	—
2Ed	$C_{18}H_{22}ON_2S$	68.75	7.05	8.91	—	68.53	7.19	8.89	—
2Ee	$C_{19}H_{22}ON_2S$	69.90	6.79	8.58	—	69.80	6.85	8.68	—

the products which are:

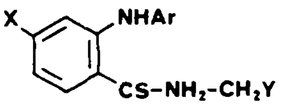
4A—2,2′-Bis(phenylamino)-*N*,*N*′-ethylenebis(thiobenzamide)—Yield 26%—F = 179°C. $C_{28}H_{26}N_4S_2$—Calc'd: C, 69.67; H, 5.43. Found: C, 69.79; H, 5.65.

4E—2,2′-Bis(4-methoxyphenylamino)-*N*,*N*′-ethylenebis(thiobenzamide)—Yield 40%—F = 179°C. $C_{30}H_{30}O_2N_4S_2$—Calc'd: C, 66.39; H, 5.57; N, 10.33; S, 11.81. Found: C, 66.31; H, 5.73; N, 10.38; S, 11.65.

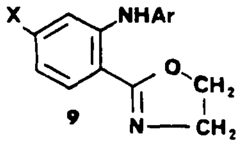
6C—2,2′-Bis(4-methylphenylamino)-*N*,*N*′-trimethylenebis(thiobenzamide)—Yield 66%—F = 173°C. $C_{31}H_{32}N_4S_2$—Calc'd: C, 70.96; H, 6.15; S, 12.21. Found: C, 71.31; H, 6.39; S, 12.33.

The elution, continued with ethyl acetate, gives afterwards the following compounds **5** or **7** which are recrystallized from a benzene-cyclohexane(1 : 1) mixture.

TABLE IIA



8; 10; 11



9

2-Arylamino-*N*-(hydroxyalkyl)-thiobenzamides **8**, **10**, **11**; 2-(2-Arylaminophenyl)-4,5-dihydrooxazoles **9**

OR[a]	Ar	X	Y	No	Yield%	F°C	No	Yield%	F°C
OC_2H_5	Phenyl	H	CH_2OH	**8A**	36	98	**9A**	22	72
OC_2H_5	4-Methylphenyl	H	CH_2OH	**8C**	80	oil	**9C**	10	93
OCH_3	4-Methoxyphenyl	Cl	CH_2OH	**8F**	38	130	**9F**	12	80
OC_2H_5	Phenyl	H	$CHOH\text{-}CH_3$	**10A**	90	110			
OCH_3	4-Methoxyphenyl	H	$CHOH\text{-}CH_3$	**10E**	71	130			
OC_2H_5	Phenyl	H	$CH_2\text{-}CH_2OH$	**11A**	55	85			
OC_2H_5	4-Methylphenyl	H	$CH_2\text{-}CH_2OH$	**11C**	52	75			
OC_2H_5	4-Methylphenyl	Cl	$CH_2\text{-}CH_2OH$	**11D**	52	102			
OC_2H_5	4-Methoxyphenyl	H	$CH_2\text{-}CH_2OH$	**11E**	35	72			
OCH_3	4-Methoxyphenyl	Cl	$CH_2\text{-}CH_2OH$	**11F**	58	91			

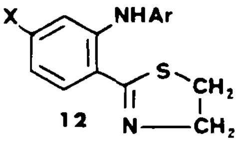
[a] Nature of the alkoxy in the starting material **1**

TABLE IIB

Analyses

No	Formula	Calculated				Found			
		C	H	N	S	C	H	N	S
8A	$C_{15}H_{16}ON_2S$	66.14	5.92	—	—	66.14	5.78	—	—
9A	$C_{15}H_{14}ON_2$	75.60	5.92	—	—	75.27	5.95	—	—
8C		oil: not analyzed							
9C	$C_{16}H_{16}ON_2$	—	—	11.10	—	—	—	11.14	—
8F	$C_{16}H_{17}O_2N_2SCl$	57.05	5.09	—	9.52	57.73	5.27	—	9.58
9F	$C_{16}H_{15}O_2N_2Cl$	63.47	4.99	9.26	—	63.45	4.95	9.39	—
10A	$C_{16}H_{18}ON_2S$	67.10	6.34	—	11.19	67.28	6.52	—	11.03
10E	$C_{17}H_{20}O_2N_2S$	64.52	6.37	8.85	—	65.03	6.27	8.88	—
11A	$C_{16}H_{18}ON_2S$	—	—	9.78	—	—	—	9.55	—
11C	$C_{17}H_{20}ON_2S$	67.97	6.71	9.33	—	67.80	6.62	9.15	—
11D	$C_{17}H_{19}ON_2SCl$	60.98	5.72	8.37	9.56	60.73	5.67	8.31	9.34
11E	$C_{17}N_{20}O_2N_2S$	64.53	—	—	10.13	64.54	—	—	10.26
11F	$C_{17}H_{19}O_2N_2SCl$	58.19	5.46	—	9.14	58.40	5.60	—	9.39

TABLE IIIA



12

2-(2-Arylaminophenyl)-4,5-dihydrothiazoles **12**

OR[a]	Ar	X	No	Yield%	F°C
OC_2H_5	Phenyl	H	**12A**	72	68
OCH_3	Phenyl	Cl	**12B**	75	87
OC_2H_5	4-Methylphenyl	H	**12C**	65	103
OCH_3	4-Methylphenyl	Cl	**12D**	70	95
OCH_3	4-Methoxyphenyl	H	**12E**	68	75
OCH_3	4-Methoxyphenyl	Cl	**12F**	85	124

[a] Nature of the alkoxy in the starting material **1**.

TABLE IIIB

Analyses

No	Formula	Calculated				Found			
		C	H	N	S	C	H	N	S
12A	$C_{15}H_{14}N_2S$	70.83	5.55	11.02	12.61	70.97	5.62	10.87	12.72
12B	$C_{15}H_{13}N_2SCl$	62.38	4.54	—	11.10	62.40	4.52	—	11.44
12C	$C_{16}H_{16}N_2S$	71.60	6.01	—	11.95	71.26	6.13	—	11.87
12D	$C_{16}H_{15}N_2SCl$	63.46	4.99	—	10.59	63.36	4.90	—	10.38
12E	$C_{16}H_{16}ON_2S$	67.57	5.67	—	11.27	67.54	5.74	—	11.04
12F	$C_{16}H_{15}ON_2SCl$	60.27	4.74	8.79	—	60.23	4.78	8.98	—

5A—2-(2-Phenylaminophenyl)-4,5-dihydro-1*H*-imidazole—Yield 10%—F = 88°C.[7] $C_{15}H_{15}N_3$—Calc'd: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.78; H, 6.34; N, 17.64.

5E—2-[2-(4-Methoxyphenylamino)phenyl]-4,5-dihydro-1*H*-imidazole—Yield 15%—F = 113°C.[7] $C_{16}H_{17}ON_3$—Calc'd: C, 71.89; H, 6.41; N, 15.72. Found: C, 71.94; H, 6.51; N, 15.69.

7C—2-[2-(4-Methylphenylamino)phenyl]-1,4,5,6-tetrahydropyrimidine—Yield 5%—F = 143°C.[8] $C_{17}H_{19}N_3$—Calc'd: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.97; H, 7.18; N, 15.75.

Reaction of amino-alcohols. 2-Aminoethanol, 1-amino-2-propanol or 3-amino-1-propanol are reacted with compounds **1** according to the procedure already indicated, apart from the fact that the reaction solvent is benzene. The reaction product is purified by chromatography on alumina, elution being begun with dichloromethane. When the reagent is 2-aminoethanol, a first fraction is obtained, containing a 2-(2-arylaminophenyl)-4,5-dihydrooxazole **9**, white crystals which are recrystallized in ethanol.

Elution, continued with a mixture dichloromethane-ethyl acetate(1 : 1), gives, according to the nature of the amino-alcohol used, a 2-arylamino-*N*-(2-hydroxyethyl)thiobenzamide **8**, a 2-arylamino-*N*-(2-hydroxypropyl)-thiobenzamide **10** or a 2-arylamino-*N*-(3-hydroxypropyl)thiobenzamide **11**.

Compounds **9**, **10**, **11** and **12** which have been obtained are indicated in Table II.

Reaction of 2-aminoethanethiol. 2-Aminoethanethiol is progressively added to the phosphorus compound **1** dissolved in a benzene-ethanol(1 : 1) boiling mixture until the brown-red color has disappeared. The solvent is distilled and the residue extracted by dichloromethane. The solution is chromatographed on alumina, elution being done with dichloromethane. The 2-(2-arylaminophenyl)-4,5-dihydrothiazole **12** thus obtained is crystallized in ethanol. Compounds **12** obtained in this way are indicated in Table III.

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