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THE SYNTHESIS OF SOME *N*-[4-SUBSTITUTED PHENYL]-3-ACETOXYBENZTHIOAMIDES AND THEIR N^1, N^3-DISUBSTITUTED AMIDRAZONES

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Abstract: The synthesis of *N*-[4-substituted phenyl]-3-acetoxythiobenzamides **5** from corresponding carboxamides **4** is described. The reaction of **5** with hydrazine hydrate gave N^1, N^3-disubstituted amidrazones. They were characterized by their N^1-benzylidene derivatives **7**. The structures of these compounds were confirmed by IR-spectroscopy.

INTRODUCTION

The present work is a continuation of our current project on the synthesis and reactions of thiocarboxamides [1-4]. With the synthesis of 3-acetoxybenzthiocarboxamides described in this article we had two objectives in mind. Firstly, thioamides are intermediates in the synthesis of heterocyclic compounds [5,6]. Secondly, the thioamido group is also used as a carrier for an active moiety and thioamides can be converted into compounds, which on the basis of the literature [7] might have interesting biological activities. The fact that the phenolic hydroxyl group in hydroxybenzthiocarboxamides has a marked influence on bacteriostatic properties were demonstrated by the change in activity when shifting this group to the *o*-, *m*- and *p*-position. In monohalogen derivatives the influence of halogen position on the bacteriostatic activity is slightly noticeable [7]. It has been reported that several unsubstituted amidrazones can been prepared from heterocyclic acid thioamides such as isonicotinic [8] and picolinic acid thioamides [9], but that prolonged interaction gives rise to thiadiazoles.

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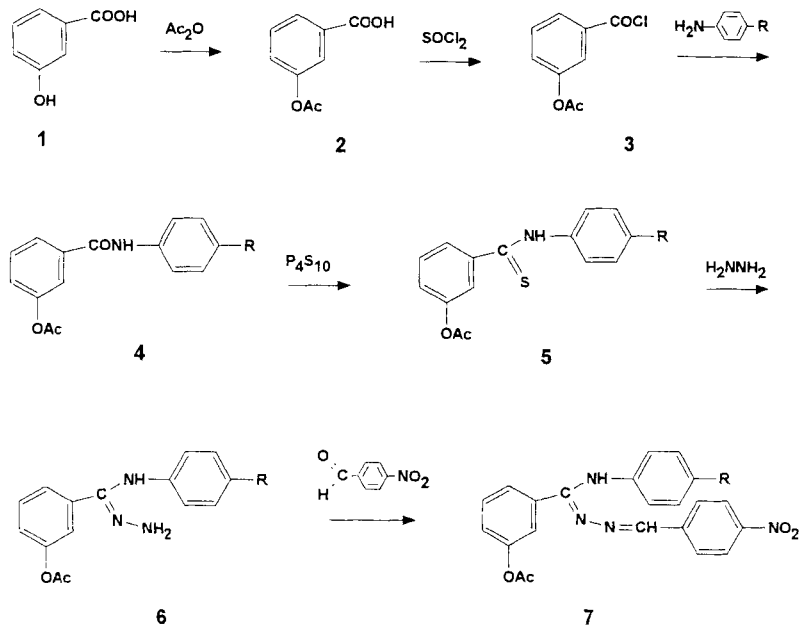
RESULTS AND DISCUSSION

3-Hydroxy benzoic acid **1** was used as a starting material for the synthesis. 3-Acetoxy benzoic acid **2** represents the common intermediate for the synthetic route involved in the preparation of amides and thioamides. The replacement of the C-3 hydroxy group of **1** by acetoxy was achieved by $\mathbf{Ac_2O}$ and the resulting ester **2** was converted to compound **3**.



Scheme 1

4 - 6	R
a	CH_3
b	OCH_3
c	F
d	Cl
e	Br
f	I

Table I

pro-duct	m.p. / solvent	yield	molecular formula	C %		H %		N %	
				calc.	found	calc.	found	calc.	found
4a	118 - 120°C EtOH	85%	$C_{16}H_{15}NO_3$	71,36	70,95	5,61	5,09	5,20	5,03
4b	138 - 140°C EtOH/H_2O 1:2	90%	$C_{16}H_{15}NO_4$	67,36	67,07	5,30	5,40	4,91	5,10
4c	144 - 146°C MeOH	95%	$C_{15}H_{12}FNO_3$	65,92	65,73	4,43	4,56	5,12	5,01
4d	169 - 170°C EtOH/H_2O 1:1	86,5%	$C_{15}H_{12}ClNO_3$	62,04	62,19	4,02	4,17	4,78	4,83
4e	179 - 180°C Me_2CO	88%	$C_{15}H_{12}BrNO_3$	53,90	54,09	3,61	3,97	4,19	4,32
4f	181 - 182°C Bz	75%	$C_{15}H_{12}INO_3$	47,26	46,86	3,17	3,25	3,67	4,01

The aminolysis of the resulting 3-acetoxybenzoyl chloride **3** with the appropriate primary aryl amine in anhydrous pyridine or dioxane, gave the corresponding 3-acetoxycarboxamides **4** in good yields (Table I). The methods employed for the synthesis of these compounds were generally analogues to those previously reported [1-4]. The reaction in the presence of pyridine was achieved in high yield in comparison to the results obtained in dioxane. It is a consequence of the acylation of pyridine prior to the acylation of amine, as well as the use of pyridine as an acceptor of hydrochloric acid. Investigation of this reaction [10] showed that amides can be successfully obtained via the corresponding complex formation of pyridine, 3-acetoxybenzoyl chloride and aryl amine. Pyridine is the solvent of choice for the acylation of the amine.

Compounds **5** were synthesized (see Scheme 1) by sulphurisation of the corresponding monosubstituted amides. The most useful reagent for the conversion of amides **4** to the amides **5** is phosphorus pentasulphide [1-4] in anhydrous pyridine. The thiobenzamides obtained as pale yellow solids after a convenient crystallization, are listed in Table II. IR and elemental analysis data confirm the assigned structures.

Thioamides react with hydrazines to give amidrazones among other products. Various derivatives have been prepared in this way by using *N*-monosubstituted thioamides as starting materials.

A series of N^3-substituted amidrazones has been prepared by the action of hydrazine hydrate on arylthiocarboxanilide but again higher temperatures and pro-

Table II

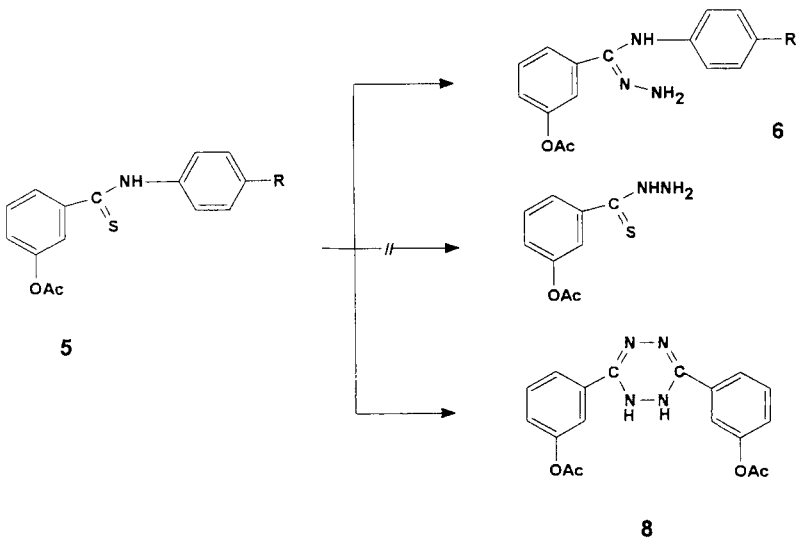
pro-duct	m.p. / solvent	yiel	molecular formula	C %		H %		N %	
				calc.	found	calc.	found	calc.	found
5a	124 - 126°C EtOH	90%	$C_{16}H_{15}NO_2S$	67,34	67,05	5,30	5,09	4,90	4,77
5b	138 - 140°C EtOH	85%	$C_{16}H_{15}NO_3S$	63,76	63,94	5,02	5,19	4,64	4,47
5c	126 - 127°C EtOH/H_2O 1:1	90%	$C_{15}H_{12}FNO_2S$	62,26	61,97	4,19	4,35	4,84	4,62
5d	148 - 150°C EtOH	85%	$C_{15}H_{12}ClNO_2S$	59,07	58,94	3,97	4,09	4,59	4,53
5e	162 - 163°C EtOH	70%	$C_{15}H_{12}BrNO_2S$	51,23	51,43	3,46	3,67	4,00	3,85
5f	155 - 157°C EtOH/H_2O 1:2	75%	$C_{15}H_{12}INO_2S$	45,35	45,65	3,05	3,25	3,52	3,25

Table III

pro-duct	m.p. / solvent	yiel	molecular formula	C %		H %		N %	
				calc.	found	calc.	found	calc.	found
6a	189 - 191°C EtOH	40%	$C_{16}H_{17}N_3O_2$	67,81	67,42	6,06	5,94	14,83	14,56
6b	181 - 182°C Me_2CO	45%	$C_{16}H_{17}N_3O_3$	64,19	63,98	5,74	5,65	14,03	13,95
6c	173 - 175°C EtOH	50%	$C_{15}H_{14}FN_3O_2$	62,70	62,61	4,92	5,34	14,63	14,39
6d	162 - 164°C Bz	52%	$C_{15}H_{14}ClN_3O_2$	59,30	59,73	4,65	4,36	13,83	13,52
6e	157 - 159°C MeOH	45%	$C_{15}H_{14}BrN_3O_2$	51,73	51,58	4,06	3,98	12,07	12,42
6f	148 - 150°C EtOH	40%	$C_{15}H_{14}IN_3O_2$	45,58	45,75	3,58	3,44	10,63	10,41

longed reaction-times were employed, secondary reaction products appeared e.g. dihydrotetrazines [11].

Although *N*-substituted amidrazones have frequently been the subject of chemical investigations very little is known about the preparations of disubstituted amidrazones **6** (Table III). When a little excess of hydrazine hydrate is added to a warmed concentrated suspension of **5**, and the reaction mixture is boiled for 60 minutes, amidrazones can be isolated in 40-60 % yield. Short heating time, as well as rapid isolation of the desired product is essential for obtaining good results. It



Scheme 2

was observed that an extension of the boiling period caused the yield to decrease to about 15 %. If the reaction mixture was allowed to stand overnight at room temperature very little amidrazone could be isolated. When an excess of hydrazine hydrate was used and on extended boiling a new compound was isolated. According to the analysis this compound has most probably the structure 3,6-di(3-acetoxy)-dihydrotetrazine **8** (Scheme 2).

The amidrazones reported in the present paper containing one free hydrazino-group were characterized by their *N*-benziliden derivatives 7. The addition occurred readily in pyridine at 50 °C and afforded up to 90-95 % yield of N^1,N^3-disubstituted amidrazone.

EXPERIMENTAL

The melting points were determined on a Kofler and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 580 Spectrophotometer in KBr. Elemental analyses of C and H were carried out with a Coleman Model 33 analyzer, and N was determined by the method of Dumas.

Purity of the compounds was checked by TLC on silica gel G plates using iodine vapors as visualizing agent.

Pyridine was redestilled, and the water-containing fore-run was rejected.

Esterification of the 3-hydroxy benzoic acid with acetic anhydride :

To a solution of 6,9 g (50 mmol) of **1** in 15 ml $\mathbf{Ac_2O}$ a catalytic amount of $\mathbf{H_2SO_4}$ was added and under stirring was heated on a steam bath for 30 min. The reaction mixture was then poured into water-ice (200 ml) and the separated solid collected by filtration, washed with $\mathbf{H_2O}$, dried and recrystallized from benzene, m.p. 130-131 °C .

*3-Acetoxy benzoyl chloride (**3**) :*

A solution of the acid **2** 5,4 g (30 mmol) in redistilled thionyl chloride (4 mol excess) was refluxed for 2 h. The unreacted thionyl chloride was removed by distillation under reduced pressure, and the acid chloride **3** obtained was dissolved in dry benzene or $\mathbf{Et_2O}$ and used as such for the next step.

N-[4-substituted phenyl]-3-acetoxybenzamides **(4a-f);**
General Procedure :

The acid chloride **3** (prepared from 5,4 g, 30 mmol of the acid **2**) in dry benzene (30 ml) was added dropwise with stirring to a cold solution of the 4-substituted amine in anhydrous pyridine at such a rate that the temperature did not rise above 5 °C. When reaction was complete, stirring was continued at that temperature for 1 h, then at room temperature for another 1 h. The mixture was poured into crushed ice. The solid formed was filtered off, washed with waterdried at room temperature and recrystallized from a suitable solvent.

Replacement of pyridine by dioxane results in decrease of the yield of **4** by ca 30% IR: 3400 cm^{-1} (νNH), 1650 cm^{-1} (Amide I), 1510 cm^{-1} (Amide II, δNH/νCN), 1330 cm^{-1} (Amide III,νCN/δNH), 1200-1250 cm^{-1} (ν as C-O-C), 1020-1060 cm^{-1} (ν s C-O-C), 835 cm^{-1} (*p*-disubst. aryl).

N-[4-substituted phenyl]-3-acetoxythiobenzamides **(5a-f);**
General procedures :

A mixture of 10 mmol of amides and 2,21 g (10 mmol) of phosphorus pentasulphide in 50 ml of anhydrous pyridine was heated to 95 °C for 1 h under stirring, cooled and poured into an excess of dil. **HCl**. The oil which separated was extracted with $\mathbf{CHCl_3}$ and the organic extracts were washed with a 5 % $\mathbf{Na_2CO_3}$ soln., then with water and dried over $\mathbf{Na_2SO_4}$.

Distillation of the solvent afforded the crude product, which was recrystallized from **EtOH** to give 70-90 % of **5**.

IR: 3300 cm^{-1} (νNH), 1510-1520 cm^{-1} (δNH/νCN), 1350 cm^{-1} (νCN/δNH), 1200 cm^{-1} (ν as C-O-C), 1020-1040 cm^{-1} (ν s C-O-C), 980 cm^{-1} (mainly νC=S).

N^3-[4-substituted phenyl]-3-acetoxybenzamidrazones **(6a-f)**;
General procedures :

A mixture of 10 mmol thoroughly ground thioamide **6** and 10 ml absolute ethanol was heated to boiling on a steam bath. Within about 3 minutes 10 mmol hydrazine hydrate (100 %) was added with stirring. Vigorous evolution of hydrogen sulphide occurred. After heating for 60 minutes a clear liquid resulted, which was cooled in an ice bath. The crystals were sucked off and recrystallised from absolute ethanol-ether.

These compounds are summarized in Table III.
IR: 3350 cm^{-1} (νNH), 3240 and 3180 cm^{-1} (ν as NH and ν as NH_2), 1650 cm^{-1} (νC=O,O-$COCH_3$), 1620 cm^{-1} (νC=N), 1600 cm^{-1} (νNH_2), 1510-1540 cm^{-1} (δNH/νCN), 1250 cm^{-1} (ν as C-O-C), 600-750 cm^{-1} (γNH, γNH_2)

Preparation of N^1-[4-nitro-benzylidene]-N^3-[4-substituted phenyl]-3-acetoxy-benzamidrazones (7) :

10 mmol of the amidrazone was dissolved in pyridine (10 ml) at 50 °C, after which the mixture was vigorously shaken with 10 mmol of 4-nitrobenzaldehyde. Upon cooling the compounds crystallized. Before analysis the compounds were recrystallised from solvents or mixture of solvents.

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