ACTA CHEMICA SCANDINAVICA 4 (1950) 1347–1350

Thiobenzoylation of Esters and Amides of α-Amino Acids

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In connection with an investigation in this laboratory some thiobenzoylated esters and amides of α-amino acids were required. The literature on thioacylation has recently been reviewed [1], and it appears that salts or esters of thion- or dithioacids have proved useful as thioacylating agents. Dithiobenzoic acid, however, does not react with glycine or leucine [2], nor does thiobenzoyl chloride appear to be of much value in the thiobenzoylation of amino acids [3]. Holmberg [4] prepared carboxymethyl dithiobenzoate and demonstrated the easy formation of thiobenzamide and -hydrazide upon mild treatment of the dithioacid with ammonia or hydrazine respectively. The same author [5] later extended this observation to amino acids and described in addition the successful preparation of ethyl thiobenzamidoacetate by this method, whereas thiobenzoyl-L-asparagine was not isolated, although its presence in the reaction mixture was established. Using Holmberg's procedure, Elliott [6] recently reported the preparation of DL-N-thiobenzoyl-serine methyl ester.

Holmberg investigated different methods of preparing dithiobenzoic acid, required as an intermediate in the synthesis of carboxymethyl dithiobenzoate, and concludes that the highest yield (ca. 50 %) of the latter compound is obtained when benzotrichloride is used as a starting material. The alternative route from bromobenzene and carbon disulphide was found much inferior, the yield of the final product being only 17 %. In this laboratory, however, satisfactory yields were consistently obtained by the latter method, using slightly modified conditions. It is believed that this procedure, described in some detail in the experimental section, represents the most convenient one for preparing thiobenzoylthioglycollic acid in larger quantities.

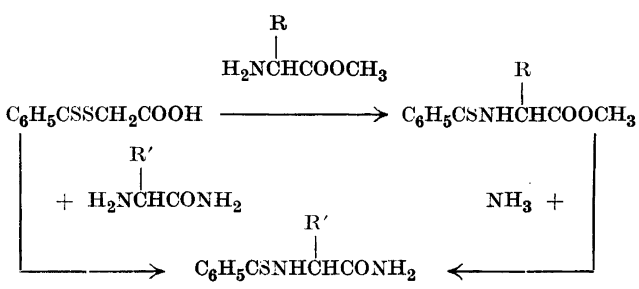
The thioacylations, as represented in the following scheme, were performed in neutral aqueous solutions at room temperature.

Tabel 1. Esters and amides

$C_6H_5CSNHCHCOR'$ (R)

R	R′	Yield, %	M. p., °C.	Formula	Car Calcd.
H	OCH_3	68[a]	73-4	$C_{10}H_{11}O_2NS$	57.38
CH_3[b]	OCH_3	78[a]	100-1	$C_{11}H_{13}O_2NS$	59.16
H	NH_2	89[c]	136-7[d]	$C_9H_{10}ON_2S$	55.63
CH_3[b]	NH_2	82[e]	204.5	$C_{10}H_{12}ON_2S$	57.65
C_6H_5[b]	NH_2	87[c]	160-1	$C_{15}H_{14}ON_2S$	66.67
p-OHC_6H_4OH[f]	NH_2	89[c,f]	185 (d.)	$C_{16}H_{16}O_2N_2S$	63.97

[a] Recrystallized from benzene-hexane. [b] DL-Configuration.
[c] Recrystallized from aqueous ethanol. [d] Form B. The dimorphous form A had m. p. 119°, but could not, on account of its ready transformation into B, be purified quite satisfactorily for analysis. Found: C, 55.31; H, 4.78; N, 14.02; S, 16.17. [e] Recrystallized from 96 % ethanol. [f] L-Configuration, $[\alpha]_D = +162.6°$ in 96 % ethanol (0.1412 g/5.00 ml, 1 dm, + 4.59°).



I	R = H	IV	R′ = CH_3
II	R = CH_3	V	R′ = C_6H_5
III	R′ = H	VI	R′ = *p*-$OHC_6H_4CH_2$

All attempts to thiobenzoylate ethyl α-amino-isobutyrate proved fruitless in spite of moderate heating and prolonged reaction time. This behaviour, which reflects a greatly diminished reactivity of the amino group, may be explained in terms of unfavorable sterical conditions.

Treating the esters (I) and (II) with methanolic ammonia yielded quantitatively the corresponding amides, (III) and (IV), identical with the products obtained upon direct thiobenzoylation of the amino amides. No difficulties were encountered in the isolation and purification of the reaction products, which are well crystallizing compounds, usually of an intensive yellow colour. Thiobenzoyl-L-tyrosineamide (VI), however, formed colourless crystals

of α-N-thiobenzoylamino acids.

bon, %	Hydrogen, %		Nitrogen, %		Sulphur, %	
Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
57.92	5.30	5.12	6.69	6.51	15.32	15.48
59.36	5.87	5.62	6.27	6.15	14.35	14.29
55.34	5.19	4.92	14.42	14.19	16.50	16.44
57.75	5.81	5.93	13.45	13.43	15.39	15.32
66.67	5.22	5.22	10.36	10.55	11.86	11.93
64.04	5.37	5.04	9.33	9.49	10.67	10.27

as did one of the dimorphous forms of thiohippuramide (III) *(vide infra)*. Both colourless compounds gave intensively yellow solutions in ethanol or water. The intense absorption of an ethanolic solution of (VI) in the visible produces an abnormally high rotation at the sodium D-line.

The occurence of dimorphism in this series was noticed by Holmberg [4] in the case of thiobenzhydrazide of which two different forms were isolated and mutually converted one into the other on seeding. In the course of the present work, thiohippuramide (III) was found to exist in two forms, A and B. A crystallized in nacreous, yellow plates, m. p. 119°, and B in colourless cubes with m. p. 136-7°. Upon rapid cooling of a hot solution of B in aqueous ethanol, A separated, but could be isolated only with great difficulty, owing to the readiness with which it changed into B. Seeding a supersaturated solution of B with A, however, did not result in the crystallization of A, unless rapid cooling was applied. Although the phenomenon appears to be a case of dimorphism, it cannot on basis of the experimental facts be definitely excluded that a dynamic isomerism is implied.

Studies in ring-closure reactions of thioacylated derivatives of α-amino acids are in progress in this laboratory.

EXPERIMENTAL *

Carboxymethyl dithiobenzoate

A Grignard-solution, prepared under nitrogen in the usual way from 16.5 g (0.68 m) of magnesium, 300 ml of dry ether and 101.6 g (0.65 m) of freshly distilled bromobenzene, is transferred under nitrogen pressure to a dropping funnel, inserted in a three-necked flask with ground joints. The flask is further provided with mechanical stirring and inlet and outlet tubes for nitrogen. In the flask is placed a solution of 76.5 g (1.01 m) of dry carbon disulphide in 150 ml of dry ether, kept cold throughout the reaction by

* All melting points are uncorrected. Microanalyses were carried out in this laboratory by Mr. A. Grossmann.

means of an ice-bath. In a stream of nitrogen, the Grignard-solution is added dropwise, in the course of one hour, to the vigorously stirred and well-cooled solution. The reaction mixture is allowed to come to room temperature overnight, then cooled again in an ice-bath. To the stirred solution is added 400 g of ice, a small amount of a brown precipitate is removed by filtration, and the deep-red aqueous layer separated and extracted once with a portion of fresh ether.

To the aqueous phase is added at once a solution of 64.2 g (0.68 m) of chloroacetic acid in 250 ml of water, neutralized with 38 g (0.36 m) of sodium carbonate. After standing for 48 hours at 5°, the mixture is acidified by slowly adding a solution of 45 ml (0.83 m) of conc. sulphuric acid in 50 ml of water. The dark-red precipitate is collected by suction, and a little oily material removed by pressing the filter cake. After being washed thoroughly with water, the crystals are dried *in vacuo* over calcium chloride. Yield 76.7 g (56 %), m. p. 126-7°. An analytically pure product is obtained after one recrystallization from 350 ml of benzene, yielding 70.4 g (51.5 %) of thin, beautifully red plates, melting at 127-8°.

The thiobenzoylation of α-amino amides and -esters

In general the reactions were performed in the following way. A solution of one mole of carboxymethyl dithiobenzoate in one equivalent of 2 *N* sodium hydroxide was added in one portion to another solution of one mole of α-amino-amide or -ester in water, containing one equivalent of sodium hydroxide in case the ester or amide hydrochlorides were used. After thorough shaking, the mixture deposited within a few minutes a yellow oil, crystallizing rapidly on cooling and scratching. The crystals were collected, dried and recrystallized from suitable solvents or solvent mixtures. Yields ranging from 70—90 % were obtained. The results are summarized in Table 1.

Ammonolysis of methyl α-thiobenzamidopropionate

In a glass-stoppered flask, a solution of 1.72 g of methyl α-thiobenzamidopropionate in 5 ml of methanolic ammonia, was shaken for four hours at room temperature, when yellow plates separated from the solution. After standing for 18 hours at room temperature 1.47 g (92 %) of N-thiobenzoyl-DL-alanineamide were collected. Recrystallized once from ethanol. M. p. 205° (dec.).

SUMMARY

An improved procedure for preparing carboxymethyl dithiobenzoate from bromobenzene, carbon disulphide and chloroacetic acid is described.

A series of thiobenzoylated esters and amides of α-amino acids is prepared, and a case of dimorphism, involving differently coloured forms, is noticed.

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Received September 2, 1950.