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Thioacylamido Acid Amides and Their Reactions with Mercuric Acetate

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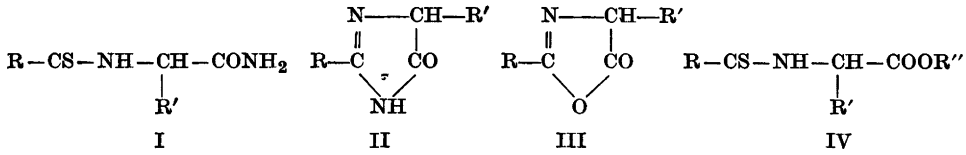
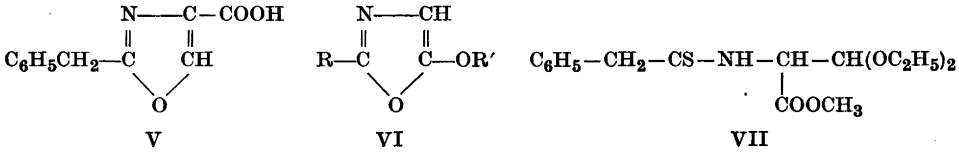
In previous papers [1,2] the preparation of various N-thioacylated amino acid amides was reported. The present communication describes some additional substances of a similar type and is concerned also with the action of mercuric acetate on these compounds (I), a study originally initiated with the prime objective of providing a new method of synthetising 5-imidazolones (II).



I II III IV

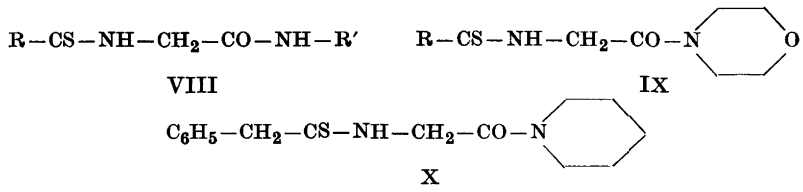
In recent years several syntheses of heterocyclic rings have been reported utilising the elimination of hydrogen sulphide from an acyclic thioamide function. For example, the important method of closing imidazole-rings developed by Todd *et al.*[3] and the successful synthesis of desthiobenzyldihydropenillamine by the Upjohn group [4] rest on this principle. The formation of 5-oxazolones (III) upon treatment of α-thioacylamido acids (IV,R″ = H) with silver salts [5] was discovered during the work on penicillin chemistry. This also contributed valuable new routes to 2-benzyloxazole-4-carboxylic acid [6] (V) and 5-alkoxy-oxazoles [7] (VI) by cyclisation of methyl thiobenzylpenaldate diethyl acetal (VII) and α-thioacylamido esters (IV, R″ = alkyl) respectively, under the influence of silver salts. Apparently, however, no attempts to extend this reaction to α-thioacylamido acid amides (I) have been recorded.



V VI VII

The requisite thioacylamides (I) were produced as previously described [1,2], the ammonolysis of the thioacylamido esters generally being preferred to the direct thioacylation of α-amino amides most of which are rather tedious to prepare. Thiohippuramide (I, R = C_6H_5, R′ = H) and thiophenaceturamide (I, R = $C_6H_5CH_2$,R′ = H) however, were conveniently obtained by the latter method [1,2] owing to the ready availability of glycinamide [8]. In performing the thioacylations of the amino esters, duplicate runs were made in pyridine solution with triethylamine, following the directions recently given by Crawhall and Elliott [9]. This modification, however, did not in the present cases constitute any improvement over the original method, neither with regard to time nor results. High yields of thiobenzoylalanine methyl ester (IV,R = C_6H_5,R′ = R″ = CH_3) and phenylthioacetylalanine methyl ester (IV,R = $C_6H_5CH_2$,R′ = R″ = CH_3), obtained upon treatment of the corresponding acids with diazomethane, demonstrated the uncomplicated reactions with this reagent. The ethyl esters of L-aspartic acid, L-glutamic acid, L-leucine, L-tyrosine, DL-methionine and DL-phenylalanine were submitted to thiobenzoylation, yielding oily reaction-products of which only the last two crystallised spontaneously. No efforts were made to induce crystallisation of the oily products which were aminolysed without further purification. N-Phenylthioacetyl-DL-alanine methyl ester was readily obtained as colourless crystals from reaction of the ester with carboxymethyl dithiophenylacetate [2] in aqueous solution.

During the ammonolysis experiments a rather striking difference in reactivity was noticed. Whereas all the esters studied reacted quantitatively at room temperature in the course of about twenty-four hours with a methanolic solution of dry ammonia, regardless of the nature of the alkyl in the ester grouping, the same substances were hardly affected under similar circumstances after treatment with ammonia dissolved in ethanol. This influence of the medium presents no novelty in the ammonolysis of esters (see *e.g.*[10]) but in the present case the effect appears to be extraordinarily pronounced. The resulting amides containing the thiobenzoyl-grouping (I,R = C_6H_5) are crystalline compounds with yellow colours of varying intensity (see Table 1). For the products derived from L-aspartic and L-glutamic esters, analysis indicates that both ester functions have been exchanged with ammonia producing the compounds (I,R = C_6H_5,R′ = CH_2CONH_2) and (I,R = C_6H_5,R′ = $CH_2CH_2CONH_2$) respectively. In cases where R in (I) is benzyl, the amides are colourless substances, melting considerably lower than the corresponding thiobenzoyl-derivatives.

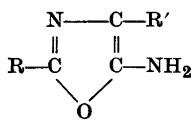


VIII IX

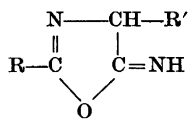
X

On submitting ethyl thiohippurate to reaction with ethylamine in methanol, N-ethyl-thiohippuramide (VIII, $R = C_6H_5$, $R' = C_2H_5$) was obtained as colourless crystals which showed signs of existing also in a yellow form as previously discussed in an analogous case [1]. Again, benzylamine yielded the intensely yellow N-benzylamide (VIII, $R = C_6H_5$, $R' = C_6H_5CH_2$) whereas with morpholine the yellow thiohippuromorpholide (IX, $R = C_6H_5$) was produced. Piperidine reacted abnormally with the ester, a small amount of the benzylamine salt of thiohippuric acid being the sole crystalline constituent which could be isolated from the complex reaction mixture. No reaction could be induced with aniline, even under forced conditions. Thiohippurylglycine (VIII, $R = C_6H_5$, $R' = CH_2COOH$) was produced for the first time following the directions previously given [1]. The corresponding ethyl thiophenaceturate yielded a crystalline N-benzylamide (VIII, $R = R' = C_6H_5CH_2$), morpholide (IX, $R = C_6H_5CH_2$) and piperidide (X). Again, aniline failed to react.

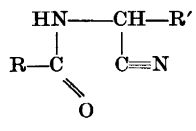
Attention was next turned to the reaction of the amides (I) with mercuric acetate. On mixing equimolecular amounts of the reactants dissolved in absolute ethanol an instantaneous reaction took place, indicated by the separation of a precipitate, ranging in colour from white to yellow — presumably a mercuric mercaptide — darkening within a few seconds and changing into precisely one molecular proportion of mercuric sulphide. The filtrates on evaporation deposited crystalline, colourless products, possessing elementary compositions indicating the loss of the elements of hydrogen sulphide, and devoid of notable basic properties. The formulation of the products as 5-imidazolones (II) was excluded by their low melting points, their insolubility in aqueous alkali, and also by direct comparison with an authentic specimen of the representative compound (II, $R = C_6H_5$, $R' = CH_3$), prepared according to Cornforth and Huang [11]. Alternative formulations as 5-aminoöxazoles (XI) or the tautomeric 5-iminoöxazolines (XII) were ruled out, partly because of the lack of basic properties (which may, however, be rather feeble in such structures) but mainly on account of the ultra-violet absorption spectra being incompatible with the oxazole-structure.



XI



XII



XIII

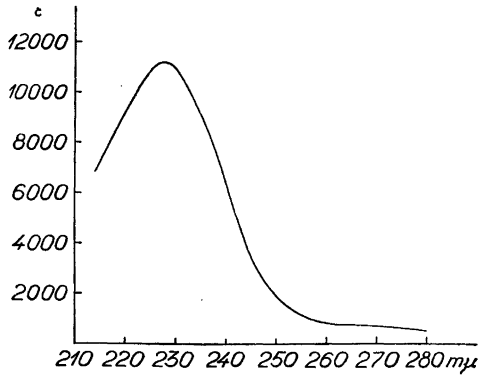


Fig. 1. Ultra-violet absorption spectrum in 95% ethanol of (XIII, R = C_6H_5, R′ = H), typical in its general form for all compounds listed in Table 2 with R = C_6H_5.

As inferred from the rather scant literature [12,13], strong absorption would be expected at *ca.* 300 mμ for the 5-aminoöxazoles (XI or XII, R = C_6H_5, R′ = alkyl). However, most reaction products listed in Table 2 showed typical benzamide-absorption [14] with a high peak at 228 mμ and a plateau at about 270 mμ as seen from Fig. 1, whereas the analogous compounds containing the benzyl grouping possessed absorption data (Fig. 2) agreeing with those of phenylacetamide [15]. Confirmatory evidence for the correctness of formulating the reaction products as acylated α-aminonitriles (XIII) was obtained by comparison of (XIII, R = C_6H_5 or $C_6H_5CH_2$, R′ = H) with authentic samples of hippuronitrile and phenaceturonitrile [16]. Furthermore, (XIII, R = C_6H_5, R′ = CH_3) agrees in melting point with the known α-benzamidopropionitrile [17].

Only a few acylated α-aminonitriles (XIII) are recorded in the literature, all prepared by acylation of the corresponding α-aminonitriles. The present reaction proceeds from α-amino acids and may be of some value in the synthesis of α-acylamidonitriles, especially those containing complicated side chains, particularly because it obviates the preparation of the often difficultly accessible aldehydes needed in the traditional Strecker-synthesis of the corresponding α-aminonitriles.

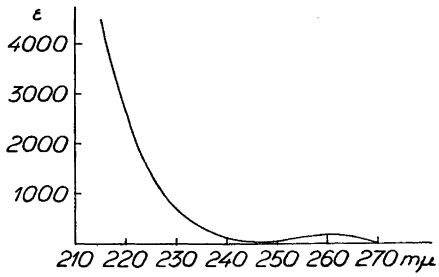
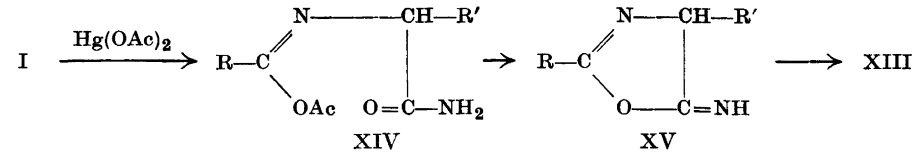


Fig. 2. Ultra-violet absorption spectrum in 95% ethanol of (XIII, R = $C_6H_5CH_2$, R′ = H or CH_3).

The reactions leading to the acylamidonitriles may be envisioned as proceeding through the following stages:



the postulation of (XIV) as an intermediate being purely hypothetical. The smooth interconversion of (XV) to (XIII) is conceivable, being paralleled in various analogous compounds [12,13]. This formulation is in accord with the observation made during the present study that N-substituted thioacylamides (VIII) undergo simple desulphurisation to the corresponding oxygen-analogues, the intermediates (XIV) or possibly (XV) suffering hydrolytic fission during the isolation procedure. Thus, on treatment with mercuric acetate, the compounds (VIII, R = C_6H_5, R′ = $C_6H_5CH_2$) and (VIII, R = R′ = $C_6H_5CH_2$) gave N-benzylhippuramide and N-benzylphenaceturamide respectively, both being produced in low yield and identified by comparison with synthetic specimens. Again, (X) similarly treated afforded phenaceturopiperidide, whose identity was proved by independent synthesis. In all other cases where N-substituted thioacylamides were submitted to treatment with mercuric acetate, exactly one molecular proportion of mercuric sulphide was formed, but only impure oily reaction products were obtained, indicating the complex nature of the reaction.

EXPERIMENTAL *

α-Thioacylamido esters (IV)

Prepared according to the procedure previously described [1] or by the method of Crawhall and Elliott [9]. Yields of the crude oily reaction products, which were used in the following step without further purification, amounted to 75—90 % regardless of which conditions were selected.

*N-Thiobenzoyl-*DL*-methionine ethyl ester* (IV, R = C_6H_5, R′ = $CH_3SCH_2CH_2$, R″ = C_2H_5). The crude reaction product crystallised spontaneously. Yellow, rhombic platelets from light petroleum, m.p. 82—83°.

$C_{14}H_{19}O_2NS_2$ (297.4)	Calc.	C 56.54	H 6.44	N 4.71	S 21.56
	Found	» 56.33	» 6.22	» 4.91	» 21.49

*N-Thiobenzoyl-*DL*-phenylalanine ethyl ester* (IV, R = C_6H_5, R′ = $C_6H_5CH_2$, R″ = C_2H_5). Separated as clusters of yellow prisms from light petroleum, m.p. 74—76°.

$C_{18}H_{19}O_2NS$ (313.4)	Calc.	C 68.98	H 6.11	N 4.47	S 10.23
	Found	» 69.01	» 6.07	» 4.69	» 10.41

* All melting points are uncorrected and have been determined in capillary tubes in an electrically heated block.

*N-Thiobenzoyl-*DL*-alanine methyl ester* (IV, R = C_6H_5, R′ = R″ = CH_3). Upon treatment of 2.07 g (0.01 mole) of N-thiobenzoyl-DL-alanine, dissolved in methanol, with an ethereal solution containing 0.025 mole of diazomethane, 1.72 g (77 %) of the crystalline ester was produced. Recrystallised from dilute methanol, m.p. 99—100°. (Ref.[1] 100—101°).

*N-Phenylthioacetyl-*DL*-alanine methyl ester* (IV, R = $C_6H_5CH_2$, R′ = R″ = CH_3). Obtained by methylation of the corresponding acid with diazomethane as described above, in 72 % yield after one recrystallisation from dilute methanol. An additional recrystallisation from chloroform-petroleum ether yielded an analytical sample as colourless leaflets, m.p. 71—73°.

$C_{12}H_{15}O_2NS$ (237.3) Calc. C 60.73 H 6.37 N 5.90 S 13.51
Found » 60.70 » 6.40 » 5.67 » 13.46

Phenylthioacetylation of DL-alanine methyl ester gave a 71 % yield of the ester, m.p. 70°.

α-Thioacylamido amides (I)

As a general procedure the thioacylated amino esters above were treated with 7—8 times their weight of dry methanol, saturated at 0° with dry ammonia. After standing at room temperature in tightly stoppered vessels for 24 hours, the solvent was removed and the remaining yellow solids were recrystallised from appropriate amounts of 95 % ethanol, if necessary diluted with water. The experimental data are presented in Table 1.

N-Substituted thioacylamido amides (VIII)

N-Ethyl-thiohippuramide (VIII, R = C_6H_5, R′ = C_2H_5). A mixture of 1.85 g of ethyl thiohippurate and 2.0 ml of anhydrous ethylamine in 5 ml of methanol was left at room temperature overnight. After removal of the solvent *in vacuo* the residue crystallised readily on scratching with dry ether. Recrystallised from 50 % ethanol as practically colourless prisms. Yield 1.36 g (74 %), m.p. 116—117°. An analytical sample was pro-

Table 1.

α-Thioacylamido Acid Amides

R—CS—NH—CH(R′)—CO—NH_2

	R′	Yield %	M.p.	Formula	Analyses: Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Sulphur Calc.	Sulphur Found
H_5	CH_2CONH_2 [a,b]	59	174—175	$C_{11}H_{13}O_2N_3S$	52.56	52.98	5.22	4.85	16.72	16.55	12.76	12.61
H_5	$CH_2CH_2CONH_2$ [a,c]	61	186—187	$C_{12}H_{15}O_2N_3S$	54.32	54.55	5.70	5.62	15.84	15.79	12.09	12.15
H_5	$CH_2CH(CH_3)_2$ [a,d]	63	163	$C_{13}H_{18}ON_2S$	62.37	62.24	7.25	7.02	11.20	11.21	12.81	12.77
H_5	$CH_2CH_2SCH_3$	88	151—152	$C_{12}H_{16}ON_2S_2$	53.69	53.59	6.01	6.25	10.44	10.42	23.88	23.96
H_5	$CH_2C_6H_5$	83	156—157	$C_{16}H_{16}ON_2S$	67.58	67.71	5.67	5.55	9.85	10.00	11.28	11.06
H_5CH_2	CH_3 [e]	77	144—145	$C_{11}H_{14}ON_2S$	59.41	59.21	6.35	6.59	12.60	12.50	14.42	14.22

a L-Configuration.
b $[\alpha]_D^{23}$ + 5.9° (*c* 0.51, dioxane).
c $[\alpha]_D^{23}$ + 6.0° (*c* 0.50, dioxane).
d $[\alpha]_D^{23}$ + 31.0° (*c* 2.55, ethanol).
e Colourless crystals.

duced by an additional crystallisation from aqueous ethanol, m.p. 117°. The solutions in various solvents were intensely yellow and once an apparently unstable yellow modification was brought to crystallisation.

$C_{11}H_{14}ON_2S$ (222.3)	Calc.	C	59.41	H	6.35	N	12.60	
	Found	»	59.57	»	6.27	»	12.69	

Attempts to determine the sulphur according to the Zimmermann-procedure [18], usually employed in this laboratory, led to violent explosions in the reaction with metallic potassium.

N-Benzyl-thiohippuramide (VIII, R = C_6H_5, R′ = $C_6H_5CH_2$). Prepared in 81 % yield from ethyl thiohippurate and benzylamine by the procedure just described. Thin, spear-shaped yellow plates were obtained by recrystallisation from 65 % ethanol, m.p. 123—124°.

$C_{16}H_{16}ON_2S$ (284.4)	Calc.	C	67.57	H	5.67	N	9.85	S 11.28
	Found	»	67.30	»	5.80	»	10.02	» 11.01

Thiohippuromorpholide (IX, R = C_6H_5). A solution of 1.98 g of ethyl thiohippurate and 2.0 ml of morpholine in 3 ml of methanol was heated for 3 hours on a steam bath, cooled and scratched after addition of dry ether. 1.07 g (46 %) of yellow crystalline material were obtained, sparingly soluble in ethanol. Recrystallisation from a large volume of ethanol afforded beautiful yellow prisms, m.p. 160°.

$C_{13}H_{16}O_2N_2S$ (264.3)	Calc.	C	59.07	H	6.10	N	10.60	S 12.13
	Found	»	59.23	»	6.07	»	10.76	» 11.97

N-Benzyl-thiophenaceturamide (VIII, R = R′ = $C_6H_5CH_2$). After heating a mixture of 2.02 g of oily ethyl thiophenaceturate, 2.0 ml of benzylamine and 2 ml of ethanol on the steam bath for 2 hours, addition of ether precipitated 1.94 g (76 %) of a pale yellow crystalline product, m.p. 130—132°. Very pale yellow needles were produced upon recrystallisation from dilute methanol, m.p. 132—133°.

$C_{17}H_{18}ON_2S$ (298.4)	Calc.	C	68.41	H	6.08	N	9.39	S 10.74
	Found	»	68.63	»	5.91	»	9.45	» 10.53

Thiophenaceturomorpholide (IX, R = $C_6H_5CH_2$). A poor yield (about 15 %) of the thiomorpholide was obtained employing the procedure just described. Clusters of flat, colourless prisms separated from 50 % ethanol, m.p. 120—121°.

$C_{14}H_{18}O_2N_2S$ (278.4)	Calc.	C	60.41	H	6.52	N	10.07	S 11.52
	Found	»	60.39	»	6.73	»	10.14	» 11.76

Thiophenaceturopiperidide (X). The conditions just described gave in poor yield (about 30 %) the crystalline piperidide, separating from 50 % ethanol in small, colourless needles, m.p. 119—120°.

$C_{15}H_{20}ON_2S$ (276.4)	Calc.	C	65.17	H	7.30	N	10.14	S 11.60
	Found	»	65.13	»	7.13	»	10.24	» 11.53

Thiohippurylglycine (VIII, R = C_6H_5, R′ = CH_2COOH). Following the directions given in previous papers [1,2] an 84 % yield of crude product was obtained. From water a colourless or a yellow form can be produced, apparently depending on the rate of cooling. Small, pale yellow needles separated from ethyl acetate-petroleum ether. M.p. 153° with decomposition, after preliminary sintering from about 146°.

$C_{11}H_{12}O_3N_2S$ (252.3)	Calc.	C	52.36	H	4.80	N	11.11	S 12.71
	Found	»	52.36	»	5.03	»	11.27	» 12.72

α-Acylamidonitriles (XIII)

The following general procedure was employed: equimolecular amounts of the thioacylamido amide and mercuric acetate were separately dissolved in the minimum amounts of lukewarm absolute ethanol. The two solutions were mixed at once and a white to yellow precipitate immediately formed. Within a few seconds this turned dark and, after standing at room temperature for 24 hours, the mercuric sulphide was filtered off on a tared glass filter. In numerous experiments conducted as just described the weight of mercuric sulphide formed never deviated more than 5% from the calculated amount. The yellow to orange filtrates were concentrated *in vacuo*, yielding crystalline residues often contaminated with oily by-products. Recrystallisation from dilute methanol, if necessary with addition of decolourising charcoal, followed by a crystallisation from appropriate solvents yielded the analytically pure and colourless products listed in Table 2.

Table 2.

α-Acylamidonitriles

$$R-CO-NH-\underset{\displaystyle R'}{\underset{|}{CH}}-C\equiv N$$

R	R′	Yield %	M.p.	Formula	Analyses Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found
C_6H_5	H	60[a]	142[b]	$C_9H_8ON_2$	67.48	67.56	5.04	4.98	17.50	17.44
C_6H_5	CH_3	80[a]	108–109[c]	$C_{10}H_{10}ON_2$	68.95	69.23	5.79	5.91	16.09	16.21
C_6H_5	$CH_2CH(CH_3)_2$	58[d]	96–97	$C_{13}H_{16}ON_2$	72.19	72.38	7.46	7.43	12.95	12.97
C_6H_5	$CH_2CH_2SCH_3$	71[d]	118–119	$C_{12}H_{14}ON_2S$[e]	61.50	61.65	6.02	5.92	11.96	11.95
C_6H_5	CH_2CONH_2	57[f]	203–204[g]	$C_{11}H_{11}O_2N_3$	60.81	61.06	5.11	5.23	19.35	19.39
C_6H_5	$CH_2CH_2CONH_2$	59[f]	170–171	$C_{12}H_{13}O_2N_3$	62.33	62.22	5.67	5.69	18.18	18.37
C_6H_5	$CH_2C_6H_5$	68[d]	150	$C_{16}H_{14}ON_2$	76.79	76.91	5.64	5.51	11.20	11.06
C_6H_5	(*p*)-$CH_2C_6H_4OH$	78[a]	200–202	$C_{16}H_{14}O_2N_2$	72.16	72.16	5.30	5.23	10.53	10.59
$C_6H_5CH_2$	H	68[f]	91[h]	$C_{10}H_{10}ON_2$	68.95	68.92	5.79	5.88	16.09	15.89
$C_6H_5CH_2$	CH_3	88[a]	87–88	$C_{11}H_{12}ON_2$	70.18	70.03	6.43	6.45	14.88	15.20

[a] Recrystallised from dilute ethanol.
[b] Ref.[16] 142°.
[c] Ref.[17] 108°.
[d] Recrystallised from chloroform-petroleum ether.
[e] Sulphur analysis: Calc. 13.68, Found 13.60.
[f] Recrystallised from water.
[g] Decomposition.
[h] Ref.[16] 90.5°.

Reactions between N-substituted thioacylamido amides (VIII)–(X) and mercuric acetate

N-Benzyl-hippuramide. When the general method above was applied to N-benzylthiohippuramide, an orange-coloured oil was obtained yielding, after addition of water and concentration *in vacuo*, a small amount of crystalline material. Two subsequent recrystallisations from benzene and dilute ethanol, yielded colourless leaflets, m.p. 160–161.5°.

$C_{16}H_{16}O_2N_2$ (268.3)	Calc.	C 71.63	H 6.01	N 10.45
	Found	» 71.39	» 6.23	» 10.43

An authentic sample of N-benzylhippuramide was produced from hippuric acid azlactone and benzylamine in the usual way. M.p. 161°, not depressed on admixture with the substance above.

Found C 71.69 H 6.20 N 10.39

The literature lists a non-analysed product with m.p. 162—162.5°[19].

N-Benzyl-phenaceturamide. On recrystallisation from methanol of the crude oily product, resulting from the reaction between (VIII, R = R′ = $C_6H_5CH_2$) and mercuric acetate, a small amount of crystalline material was isolated. After an additional crystallisation from ethanol, colourless, rhombic platelets were obtained, m.p. 176—177°.

$C_{17}H_{18}O_2N_2$ (264.3) Calc. C 72.33 H 6.43 N 9.92
Found » 72.64 » 5.99 » 9.92

For the purpose of identification, authentic N-benzyl-phenaceturamide was prepared from methyl phenaceturate and benzylamine. Colourless plates, m.p. 177—178°, unchanged on mixing with the preparation just described.

Found C 72.44 H 6.60 N 10.11

In the Penicillin Monograph two non-analysed preparations are reported with m.p. 178—179° and 175—176° respectively [20].

Phenaceturopiperidide. Reaction of (X) with mercuric acetate afforded a 20% yield of a crystalline substance which, after two recrystallisations from dilute ethanol, appeared as clusters of fine, colourless needles with m.p. 156—158°, not depressed on admixture with the authentic material described below.

$C_{15}H_{20}O_2N_2$ (260.3) Calc. C 69.20 H 7.75 N 10.76
Found » 69.46 » 7.89 » 10.60

An authentic specimen of phenaceturopiperidide was prepared from methyl phenaceturate and piperidine, m.p. 157°.

Found C 69.18 H 7.60 N 10.82

Again, a non-analysed preparation was reported previously [21] with m.p. 161—162°.

Upon treatment of the following thioacylamido amides with mercuric acetate under the usual conditions, the theoretical amount of mercuric sulphide rapidly separated but only yellow oily products were obtained from the filtrates, resisting all attempts to induce crystallisation: thiohippurylglycine (VIII, R = C_6H_5, R′ = CH_2COOH), N-ethyl-thiohippuramide (VIII, R = C_6H_5, R′ = C_2H_5), thiohippuromorpholide (IX, R = C_6H_5), thiophenaceturomorpholide (IX, R = $C_6H_5CH_2$) and N-phenylthioacetyl-L-asparagine [2] as a representative of the β-thioacylamido amides.

SUMMARY

A series of amides and substituted amides of thioacylated α-amino acids are described.

Reaction of the former with mercuric acetate in ethanol was shown to yield acylated α-aminonitriles, whereas the N-substituted amides were partly transformed into the corresponding acylated α-amino acid amides.

The microanalyses have been performed in this laboratory by Mr. A. Grossmann.

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