480. *Degradative Studies on Peptides and Proteins. Part IV.* The Formation of Salts of 2-Acylaminothiazol-5-ones by Acid-catalysed Degradation of N-Acylthiocarbamoylpeptides and their Behaviour towards Nucleophilic Reagents.*

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N-Acylthiocarbamoylpeptides and their esters, under suitable conditions of acid catalysis, afford salts of 2-acylaminothiazol-5-ones. Nucleophilic reagents such as water, alcohols, and primary amines open the heterocyclic ring to give *N*-acylthiocarbamoylamino-acid derivatives, which have in most cases been identified by comparison with samples prepared by unambiguous routes. 2-Benzamidothiazol-5-one hydrochloride is converted into 1-benzoylthiocarbamoyl-2-thiohydantoin by reaction with ammonium thiocyanate.

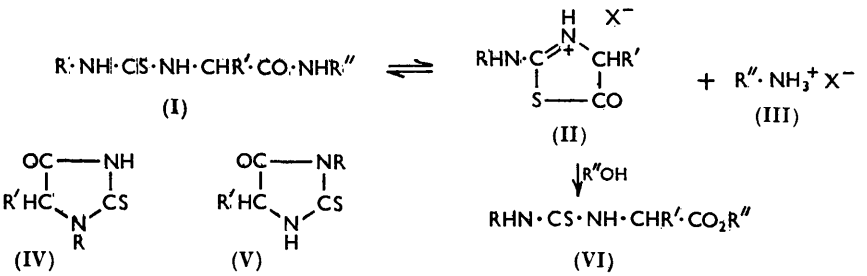
Recently, a new method of stepwise degradation of peptides was reported,[1] in which *N*-acylthiocarbamoylpeptides were subjected to mild acid treatment. The *N*-terminal amino-acid of the original peptide was recovered and identified as a 2-thiohydantoin. It was briefly mentioned that, if anhydrous acid catalysts were used, 3-acyl-2-thiohydantoins (V; R = Ac or Bz) were formed initially. Later work, however, has revealed that these products are in fact salts (II) of 2-acylaminothiazol-5-ones. Such compounds were prepared by Aubert, Knott, and Williams [2] by treatment of *N*-acylthiocarbamoylamino-acids with phosphorus tribromide in a mixture of dioxan and ether. These authors considered the alternative structure (IV), but rejected it because the latter would be expected to be stable, whereas their products were unstable in moist air and aqueous sodium acetate. In fact, the only reasonable structure not involving an acyl migration would be a 3-acyl-2-thiohydantoin (V). Such compounds, which may be regarded as *NN*-diacylthioamides, would almost certainly be attacked by nucleophilic reagents. Hence, the lability to bases of the compounds isolated by Aubert *et al.*[2] is no criterion of their structure. It is exceedingly unlikely, however, that 3-acyl-2-thiohydantoins (V) would be basic, since neither 2-thiohydantoins nor their 1-acyl derivatives are. On the other hand, thiazol-5-ones, like oxazol-5-ones, would be expected to be weak bases. Moreover, as Aubert *et al.*[2] indicated, electronic considerations suggest that nucleophilic attack by the sulphur atom at the electrophilic carbonyl-carbon atom giving 2-acylaminothiazol-5-ones is the more likely event. A similar mechanism is envisaged for the acid-catalysed degradation of *N*-acylthiocarbamoyl peptides, since protonation of the peptide linkage would increase the electrophilic character of the carbonyl-carbon atom. Very recently, Edman [3] has demonstrated that 2-anilinothiazol-5-ones (II; R = Ph) are the first products resulting from the acid-catalysed degradation of *N*-phenylthiocarbamoylpeptides (I; R = Ph). Kenner and Khorana [4] had earlier suggested that degradation of *N*-thioncarbalkoxypeptides in nitromethane saturated with dry hydrogen chloride afforded thiazolid-2 : 5-diones, although the instability of the latter unfortunately precluded rigid proof of structure. These observations corroborate our present view of the mechanism of acid-catalysed degradation of *N*-acylthiocarbamoylpeptides, but we decided to obtain definitive proof if possible.

Since acid-catalysed degradation of *N*-acylthiocarbamoylpeptides produces two salts (II and III), which frequently have similar solubilities, the isolation of the unstable 2-acylaminothiazol-5-one salts (II) in an analytically pure state has been difficult. Nevertheless, we successfully isolated 2-benzamidothiazol-5-one hydrochloride (II; R = Bz, R′ = H,

* Part III, *J.*, 1956, 192.

[1] Elmore and Toseland, *J.*, 1954, 4533.
[2] Aubert, Knott, and Williams, *J.*, 1951, 2185.
[3] Edman, *Nature*, 1956, **177**, 667; *Acta Chem. Scand.*, 1956, **10**, 761.
[4] Kenner and Khorana, *J.*, 1952, 2076.

X = Cl) after treatment of *N*-benzoylthiocarbamoylglycylglycine ethyl ester (I; R = Bz, R′ = H, R″ = CH_2·CO_2Et) with dry hydrogen chloride in nitromethane. Elementary analysis and comparison of its ultraviolet and infrared spectra with those of the corresponding hydrobromide made by the method of Aubert *et al.*[2] confirmed its structure. In addition, the hydrochloride was also obtained from *N*-benzoylthiocarbamoylglycine by the action of phosphorus trichloride in dioxan–ether and it had an identical infrared spectrum. In some cases it was possible to precipitate pure 2-acylamidothiazol-5-one salts from reaction mixtures of the *p*-toluidides of *N*-acylthiocarbamoylamino-acids (I; R″ = *p*-Me·C_6H_4) in acetic acid saturated with dry hydrogen chloride by careful addition of ether. By this method, the thiazol-5-one hydrochlorides (II; R = Ac, R′ = H and Me, X = Cl; and R = Bz, R′ = Me, X = Cl) were obtained. *N*-Benzoylthiocarbamoyl-DL-norleucine *p*-toluidide and -DL-phenylalanine *p*-toluidide (I; R = Bz,



R′ = Bu^n and Ph·CH_2, R″ = *p*-Me·C_6H_4), however, were rather resistant to degradation, probably as a result of steric hindrance, and the corresponding thiazol-5-ones could not be prepared from these compounds. Finally, *N*-acetyl- and *N*-2 : 4-dichlorobenzoylthiocarbamoylglycylglycine ethyl ester (I; R = Ac and $C_6H_3Cl_2$·CO, R′ = H, R″ = CH_2·CO_2Et) in trifluoroacetic acid afforded what are believed to be the 2-acylaminothiazol-5-one trifluoroacetates (II; R = Ac and $C_6H_3Cl_2$·CO, R′ = H, X = CF_3·CO_2) as amorphous powders. These could not be crystallised and did not give satisfactory analyses, but their reactions leave little doubt of their constitution.

Thiazol-5-ones would be expected to undergo ring-opening by nucleophilic reagents more readily than oxazol-5-ones, since the $+M$ effect of –SR is less than that of –OR. For example, Cook, Harris, Heilbron, and Shaw [5] found that 2-benzylthiothiazol-5-one hydrobromide afforded *N*-dithiobenzyloxycarbonylglycine benzylamide with benzylamine in the cold, and Jepson, Lawson, and Lawton [6] showed that 2-arylthiazol-5-ones were cleaved by a variety of bases. We have found that 2-acylaminothiazol-5-ones readily undergo ring-scission with a variety of nucleophilic reagents. Water and alcohols at elevated temperatures rapidly gave rise to *N*-acylthiocarbamoylamino-acids (VI; R″ = H) and their esters respectively, while amines reacted in the cold or on brief warming to give the corresponding amide derivative (I). Although Jepson *et al.*[6] reported that 2-arylthiazol-5-ones were unaffected by ammonium thiocyanate, we found that 2-benzamidothiazol-5-one hydrochloride (II; R = Bz, R′ = H, X = Cl) reacted smoothly to give a product, which is believed to be 1-benzoylthiocarbamoyl-2-thiohydantoin (IV; R = Bz·NH·CS, R′ = H), although we have not confirmed this by independent synthesis. Presumably, the thiazol-5-one ring was cleaved initially to give benzoylthioureidoacetyl *iso*thiocyanate, which then cyclised in the usual manner.[7] In view of the ease with which the thiazol-5-one ring can be opened, it is remarkable that Takahashi, Nishigaki, and Sakomoto [8] have reported that 2-acetamido-5-amino-4-propenylthiazole is converted into 2-acetamido-4-propenylthiazol-5-one by recrystallisation from ethanol.

[5] Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1056.
[6] Jepson, Lawson, and Lawton, *J.*, 1955, 1791.
[7] Johnson and Scott, *J. Amer. Chem. Soc.*, 1913, **35**, 1136.
[8] Takahashi, Nishigaki, and Sakomoto, *J. Pharm. Soc. Japan*, 1953, **73**, 1076; *Chem. Abs.*, 1954, **48**, 12082 h.

In conclusion, it is worth recording that the method of peptide synthesis due to Anderson, Blodinger, and Welcher [9] has proved very suitable for converting *N*-acylthiocarbamoylamino-acids into amide derivatives.

Experimental

Infrared spectra were measured in pressed discs of potassium bromide with a Grubb-Parsons double-beam spectrometer and a rock-salt prism.

N-*Benzyloxycarbonylglycine* p-*Toluidide*.—This *compound* (57%) was prepared by using the mixed acid anhydride procedure of Vaughan *et al.*[10] Recrystallised from chloroform–light petroleum (b. p. 40—60°), it had m. p. 153—154° (Found: C, 67·9; H, 6·1; N, 9·4. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1; N, 9·4%).

Glycine p-*Toluidide Hydrobromide*.—Treatment of *N*-benzyloxycarbonylglycine *p*-toluidide with hydrogen bromide in acetic acid [11] afforded this *salt* in almost quantitative yield. After two recrystallisations from ethanol–ether, it softened and decomposed above 200° (Found: C, 43·5; H, 5·3; N, 11·3. $C_9H_{13}ON_2Br$ requires C, 44·1; H, 5·4; N, 11·4%).

N-*Benzyloxycarbonyl*-DL-*alanine* p-*Toluidide*.—This *compound* was prepared through mixed acid anhydrides by using ethyl chloroformate [10] (58%) or tetraethyl pyrophosphite [9] (96%). Crystallised from chloroform–light petroleum (b. p. 60—90°), it had m. p. 153·0—153·5° (Found: C, 69·3; H, 6·6; N, 8·9. $C_{18}H_{20}O_3N_2$ requires C, 69·2; H, 6·5; N, 9·0%).

DL-*Alanine* p-*toluidide hydrobromide* was prepared from the *N*-benzyloxycarbonyl derivative by treatment with hydrogen bromide in acetic acid.[11] The *product* (87%), after recrystallisation from ethanol, had m. p. 203—204° (Found: C, 46·1; H, 5·5; N, 10·6. $C_{10}H_{15}ON_2Br$ requires C, 46·3; H, 5·8; N, 10·8%).

N-*Benzyloxycarbonyl*-DL-*phenylalanine* p-*toluidide* was obtained in excellent yield by the pyrophosphite procedure of Anderson *et al.*[9] After recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) and then from chloroform, it had m. p. 157° (Found: C, 74·4; H, 6·4; N, 7·4. $C_{24}H_{24}O_3N_2$ requires C, 74·2; H, 6·2; N, 7·2%).

DL-*Phenylalanine* p-*toluidide hydrobromide* was obtained in almost theoretical yield by treatment of the foregoing compound with hydrogen bromide in acetic acid.[11] Three recrystallisations from ethanol–ether afforded the salt as a monohydrate, m. p. 210·0—210·5°, after previously melting at 119—121° and resolidifying above this temperature (Found: C, 54·4; H, 6·0; N, 7·9. $C_{16}H_{19}ON_2Br,H_2O$ requires C, 54·4; H, 6·0; N, 7·9%).

N-*Benzyloxycarbonyl*-DL-*norleucine* p-*Toluidide*.—The method of Anderson *et al.*[9] gave this compound in theoretical yield, m. p. 149·5—150·5° after recrystallisation from ethyl acetate–light petroleum (b. p. 60—90°) (Found: C, 71·1; H, 7·3; N, 7·8. $C_{21}H_{26}O_3N_2$ requires C, 71·2; H, 7·4; N, 7·9%).

DL-*Norleucine* p-*Toluidide*.—*N*-Benzyloxycarbonyl-DL-norleucine *p*-toluidide, in methanol containing a few drops of acetic acid, was hydrogenolysed over palladous oxide. After filtration and evaporation, the residue was partitioned between ethyl acetate and dilute hydrochloric acid. The aqueous layer was basified and extracted with ethyl acetate. DL-*Norleucine* p-*toluidide* (72%) crystallised from the dried extract after evaporation and addition of light petroleum (b. p. 40—60°); it had m. p. 63·5—64·0° (Found: C, 70·6; H, 9·1; N, 12·6. $C_{13}H_{20}ON_2$ requires C, 70·9; H, 9·1; N, 12·7%).

N-*Benzyloxycarbonylglycine* p-*Benzyloxycarbonylanilide*.—Reaction of *N*-benzyloxycarbonylglycine, benzyl *p*-aminobenzoate, and tetraethyl pyrophosphite in diethyl hydrogen phosphite at 95—100° for 1 hr.[9] afforded this *compound* in almost quantitative yield. After two recrystallisations from ethyl acetate–light petroleum (b. p. 40—60°), it had m. p. 144—145° (Found: C, 68·8; H, 5·5; N, 7·1. $C_{24}H_{22}O_5N_2$ requires C, 68·9; H, 5·3; N, 6·7%).

Glycine p-*Carboxyanilide*.—The foregoing compound (5·8 g.) was hydrogenolysed in methanol (150 c.c.) and dioxan (30 c.c.) over palladous oxide. The solution was filtered and the precipitate was leached with boiling water. The cooled extract deposited glycine *p*-carboxyanilide (2·2 g.), m. p. 240° (decomp.). A paper chromatogram of the product irrigated with butan-1-ol–acetic acid–water (4 : 1 : 5) revealed a single yellow spot when sprayed with 0·2% ninhydrin

[9] Anderson, Blodinger, and Welcher, *J. Amer. Chem. Soc.*, 1952, **74**, 5309.
[10] Vaughan and Osato, *ibid.*, p. 676.
[11] Ben-Ishai, *J. Org. Chem.*, 1954, **19**, 62.

in butan-1-ol (Found: C, 50·3; H, 5·7; N, 12·9. Calc. for $C_9H_{10}O_3N_2,H_2O$: C, 50·9; H, 5·7; N, 13·2%). King, Clark-Lewis, Kidd, and Smith [12] report m. p. 300° (decomp.) but Tropp [13] reports m. p. 229° (decomp.) for the monohydrate.

2-Benzamidothiazol-5-one Hydrochloride (II; R = Bz, R′ = H, X = Cl).—(*a*) Dry hydrogen chloride was blown through a suspension of *N*-benzoylthiocarbamoylglycylglycine ethyl ester (4 g.; prepared as before [1] in almost quantitative yield; m. p. 161·0—161·5° after softening at 155°) in dry nitromethane at 0°. During 2 hr., the starting material dissolved and was replaced by a precipitate of *2-benzamidothiazol-5-one hydrochloride* (2·25 g.), which was collected and dried *in vacuo* over phosphoric oxide and sodium hydroxide and then had m. p. 192—193° (decomp.) (Found: C, 46·5; H, 3·8; N, 11·3. $C_{10}H_9O_2N_2SCl$ requires C, 46·8; H, 3·5; N, 10·9%). Light absorption in methylene chloride: $\lambda_{max.}$ 2440 (ε 17,800). The filtrate from 2-benzamidothiazol-5-one hydrochloride deposited glycine ethyl ester hydrochloride (1·3 g.), m. p. 138—139°.

(*b*) This compound was also prepared from *N*-benzoylthiocarbamoylglycine by treatment with phosphorus trichloride in ether–dioxan [2] and had m. p. 190—192° (decomp.).

2-Benzamidothiazol-5-one hydrobromide, prepared as described by Aubert *et al.*,[2] had m. p. 206—207° (decomp.) (Found: C, 39·6; H, 3·3; N, 9·2. Calc. for $C_{10}H_9O_2N_2SBr$: C, 39·9; H, 3·0; N, 9·3%). Light absorption in methylene chloride: $\lambda_{max.}$ 2460—2480 (ε 17,100). The infrared spectra of the two samples of hydrochloride and the hydrobromide were severally identical.

N-Benzoylthiocarbamoylglycine.—2-Benzamidothiazol-5-one hydrochloride (20 mg.) was heated in boiling water (4 c.c.) for 5 min. On cooling, *N*-benzoylthiocarbamoylglycine (14 mg.) separated, having m. p. 202—203° alone or on admixture with an authentic sample. The infrared spectra of the two samples were identical.

N-Benzoylthiocarbamoylglycine Methyl Ester (VI; R = Bz, R′ = H, R″ = Me).—(*a*) This *ester* (67%) was prepared by the general method of Douglass and Dains.[14] Recrystallised from methanol, it had m. p. 98° (Found: C, 52·4; H, 4·9; N, 11·0; S, 12·5. $C_{11}H_{12}O_3N_2S$ requires C, 52·4; H, 4·8; N, 11·1; S, 12·7%).

(*b*) 2-Benzamidothiazol-5-one hydrochloride (100 mg.) was heated in methanol (10 c.c.) on the steam-bath for 5 min. The product, which separated after the addition of ether (10 c.c.), had m. p. 98° alone or in admixture with the foregoing specimen.

N-Benzoylthiocarbamoylglycine Ethyl Ester.—Ring-scission of 2-benzamidothiazol-5-one hydrochloride with ethanol afforded this compound (85%), m. p. 129° from ethanol–light petroleum (b. p. 40—60°). Mixed m. p. with an authentic sample was not depressed, and infrared spectra of the two specimens were identical.

N-Benzoylthiocarbamoylglycine cyclo*Hexylamide* (I; R = Bz, R′ = H, R″ = C_6H_{11}).—(*a*) A mixture of *N*-benzoylthiocarbamoylglycine (476 mg.), *cyclo*hexylamine (198 mg.), and tetraethyl pyrophosphite (542 mg.) in diethyl hydrogen phosphite (2 c.c.) was kept at 90° for 1 hr. The cyclo*hexylamide* (478 mg.), precipitated by addition of water, was recrystallised from ethanol three times and had m. p. 204—205° (Found: C, 60·2; H, 6·3; N, 12·7. $C_{16}H_{21}O_2N_3S$ requires C, 60·2; H, 6·6; N, 13·2%).

(*b*) To a solution of *cyclo*hexylamine (165 mg.) in chloroform (10 c.c.) was added 2-benzamidothiazol-5-one hydrochloride (360 mg.). The solution immediately darkened and, after being warmed for a few minutes, was shaken with charcoal, filtered, and washed successively with dilute hydrochloric acid, water, saturated sodium hydrogen carbonate, and water. After the solution was evaporated to dryness, the product (118 mg.), crystallised from ethanol, had m. p. 203·5—204·0°, undepressed by admixture with the above sample. The infrared spectra were identical.

1-Benzoylthiocarbamoyl-2-thiohydantoin (IV; R = Bz·NH·CS, R′ = H).—A mixture of 2-benzamidothiazol-5-one hydrochloride (1·4 g.) and dry ammonium thiocyanate (1·5 g.) in glacial acetic acid (25 c.c.) was heated on the steam-bath until dissolution was complete and was then poured into water (300 c.c.). The precipitate, recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), afforded yellow *1-benzoylthiocarbamoyl-2-thiohydantoin* (0·92 g.), m. p. 189—192° (decomp.) (Found: C, 47·1; H, 3·7; N, 15·3; S, 22·9. $C_{11}H_9O_2N_3S_2$ requires C, 47·3; H, 3·3; N, 15·0; S, 23·0%).

[12] King, Clark-Lewis, Kidd, and Smith, *J.*, 1954, 1039.
[13] Tropp, *Ber.*, 1928, **61**, 1431.
[14] Douglass and Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 719.

2-Benzamido-4-methylthiazol-5-one Hydrochloride (II; R = Bz, R′ = Me, X = Cl).—A suspension of *N*-benzoylthiocarbamoyl-DL-alanine *p*-toluidide (300 mg.) (see below) in acetic acid (9 c.c.) saturated with dry hydrogen chloride was shaken for 1 hr. Dry ether (7 c.c.) was added to the clear solution; the precipitated *product* (150 mg.) had m. p. 187—189° (decomp.) (Found: C, 49·0; H, 4·3; N, 9·8. $C_{11}H_{11}O_2N_3SCl$ requires C, 48·8; H, 4·1; N, 10·4%).

N-*Benzoylthiocarbamoyl*-DL-*alanine* p-*Toluidide* (I; R = Bz, R′ = Me, R″ = *p*-C_6H_4Me).—(*a*) This *compound* was obtained from DL-alanine *p*-toluidide by reaction with either benzoyl *iso*thiocyanate in ether (92%) or methyl *N*-benzoyldithiocarbamate in ethanol–ether (89%). Recrystallised from ethanol, it had m. p. 207·0—207·5° (Found: C, 63·0; H, 5·7; N, 12·4. $C_{18}H_{19}O_2N_3S$ requires C, 63·3; H, 5·6; N, 12·3%).

(*b*) 2-Benzamido-4-methylthiazol-5-one hydrochloride (167 mg.) and *p*-toluidine (66 mg.) in warm chloroform (5 c.c.) were allowed to react for a few minutes. Addition of light petroleum (b. p. 40—60°) to the cooled and filtered solution afforded *N*-benzoylthiocarbamoyl-DL-alanine *p*-toluidide (86 mg.), m. p. 207·5° after recrystallisation from ethanol and on admixture with the above product. Infrared spectra of the two specimens were identical.

N-*Benzoylthiocarbamoyl*-DL-*alanine* (VI; R = Bz, R′ = Me, R″ = H).—(*a*) Reaction of methyl *N*-benzoyldithiocarbamate with DL-alanine afforded N-*benzoylthiocarbamoyl*-DL-*alanine* (74%), which separated from ethanol with one molecule of solvent of crystallisation, then having 144° (Found: C, 52·7; H, 6·0; N, 9·4. $C_{11}H_{12}O_3N_2S,C_2H_5OH$ requires C, 52·3; H, 6·1; N, 9·4%). After drying at 120°/0·05 mm. for 6 hr., it had m. p. 157° (Found: C, 52·4; H, 4·5; N, 11·0. $C_{11}H_{12}O_3N_2S$ requires C, 52·4; H, 4·8; N, 11·1%).

(*b*) Dissolution of 2-benzamido-4-methylthiazol-5-one hydrochloride in boiling water followed by cooling afforded the above compound (92%), m. p. 155—157°. This specimen did not depress the m. p. of that prepared as above and had an identical infrared spectrum.

N-*Benzoylthiocarbamoyl*-DL-*alanine Ethyl Ester* (VI; R = Bz, R′ = Me, R″ = Et).—This ester (77%), which resulted from the action of hot ethanol on 2-benzamido-4-methylthiazol-5-one hydrochloride, had m. p. 121°, undepressed on admixture with an authentic sample.[1] Comparison of infrared spectra confirmed their identity (Found: C, 55·8; H, 5·7; N, 10·2; S, 11·9. Calc. for $C_{13}H_{16}O_3N_2S$: C, 55·7; H, 5·8; N, 10·0; S, 11·4%).

N-2 : 4-*Dichlorobenzoylthiocarbamoylglycylglycine Ethyl Ester* (I; R = $C_6H_3Cl_2$·CO, R′ = H, R″ = CH_2·CO_2Et).—Reaction of methyl *N*-2 : 4-dichlorobenzoyldithiocarbamate [15] with glycyl-glycine ethyl ester in chloroform at room temperature during 2 days afforded this *ester* (77%), m. p. 206·5—207·0° (decomp.) after recrystallisation from propan-1-ol (Found: C, 43·0; H, 4·2; N, 10·3; S, 7·8. $C_{14}H_{15}O_4N_3SCl_2$ requires C, 42·9; H, 3·9; N, 10·7; S, 8·2%).

2-(2 : 4-*Dichlorobenzamido*)*thiazol-5-one Trifluoroacetate* (II; R = $C_6H_3Cl_2$·CO, R′ = H, X = CF_3·CO_2).—*N*-2 : 4-Dichlorobenzoylthiocarbamoylglycylglycine ethyl ester (1 g.) was left in trifluoroacetic acid (5 c.c.) for 4 hr. at room temperature. The solution was poured into dry ether (200 c.c.) and left for 15 min. at 0°. A crystalline precipitate (presumably glycine ethyl ester trifluoroacetate, although satisfactory analyses could not be obtained), m. p. 136·0—137·5°, was removed and the filtrate was evaporated under reduced pressure to 50 c.c. Addition of light petroleum (b. p. 40—60°) precipitated, after 15 min. at 0°, the thiazol-5-one salt as a light brown, amorphous solid, which was used for the reactions described below.

N-2 : 4-*Dichlorobenzoylthiocarbamoylglycine Ethyl Ester* (VI; R = $C_6H_3Cl_2$·CO, R′ = H, R″ = Et).—(*a*) Reaction of methyl *N*-2 : 4-dichlorobenzoyldithiocarbamate with glycine ethyl ester in chloroform produced N-2 : 4-*dichlorobenzoylthiocarbamoylglycine ethyl ester* (50%), m. p. 145·5—146·5° after recrystallisation from carbon tetrachloride (Found: C, 43·1; H, 3·9; N, 8·1; Cl, 21·5. $C_{12}H_{12}O_3N_2SCl_2$ requires C, 43·0; H, 3·6; N, 8·4; Cl, 21·2%).

(*b*) 2-(2 : 4-Dichlorobenzamido)thiazol-5-one trifluoroacetate in refluxing ethanol afforded the above ester (45%), m. p. 142·5—143·5° after recrystallisation. The infrared spectra of the two samples were identical.

N-2 : 4-*Dichlorobenzoylthiocarbamoylglycine* (VI; R = $C_6H_3Cl_2$·CO, R′ = R″ = H).—(*a*) Reaction of methyl *N*-2 : 4-dichlorobenzoyldithiocarbamate with glycine in 67% aqueous dioxan at pH 8·8 and 37° during 5·25 hr., followed by isolation in the usual way,[1] afforded the desired *compound* (91%), m. p. 197·5—199·0° (decomp.) after recrystallisation from ethanol–light petroleum (b. p. 40—60°) (Found: C, 39·0; H, 2·8; S, 10·7. $C_{10}H_8O_3N_2SCl_2$ requires C, 39·1; H, 2·6; S, 10·4%).

[15] Elmore, Ogle, Fletcher, and Toseland, *J.*, 1956, 4458.

(*b*) A solution of 2-(2 : 4-dichlorobenzamido)thiazol-5-one trifluoroacetate in refluxing 25% aqueous dioxan gave, after decantation from tar, the same compound (37%), m. p. 193—195° (decomp.), raised after recrystallisation to 197·0—197·5° (decomp.) alone or on admixture with the above sample. Infrared spectra of the two specimens were identical.

N-2 : 4-*Dichlorobenzoylthiocarbamoylglycine* p-*Carboxyanilide* (I; R = $C_6H_3Cl_2$·CO, R′ = H, R″ = *p*-C_6H_4·CO_2H).—Brief warming of a mixture of 2-(2 : 4-dichlorobenzamido)thiazol-5-one trifluoroacetate and *p*-aminobenzoic acid in chloroform–dioxan (2 : 1) gave the desired *product* (82%). After recrystallisation from aqueous dioxan then from pyridine–benzene, it had m. p. 260—261° (decomp.) (Found: C, 48·1; H, 3·1; N, 10·3. $C_{17}H_{13}O_4N_3SCl_2$ requires C, 47·9; H, 3·1; N, 9·9%).

2-*Acetamidothiazol-5-one Hydrochloride* (II; R = Ac, R′ = H, X = Cl).—(*a*) *N*-Acetylthiocarbamoylglycine *p*-toluidide (265 mg.) was degraded in acetic acid (10 c.c.) saturated with hydrogen chloride. Addition of dry ether (8 c.c.) precipitated the *product* (94 mg.), m. p. 176° (decomp.) after darkening from about 160° (Found: C, 31·1; H, 4·0; N, 14·0. $C_5H_7O_2N_2SCl$ requires C, 30·8; N, 3·6; N, 14·4%).

(*b*) Treatment of *N*-acetylthiocarbamoylglycine in ether–dioxan with phosphorus trichloride also afforded the desired compound (84%), m. p. 178—183° (decomp.) after darkening from about 160°. Infrared spectra of the two specimens were identical. This compound was very unstable; after storage in a desiccator for 3 weeks, infrared spectroscopy showed that it had completely reverted to *N*-acetylthiocarbamoylglycine.

2-*Acetamidothiazol-5-one Trifluoroacetate* (II; R = Ac, R′ = H, X = CF_3·CO_2).—*N*-Acetylthiocarbamoylglycylglycine ethyl ester (the m. p. of this compound is 166°, not 112° as reported earlier [1]), degraded in trifluoroacetic acid as described for the *N*-2 : 4-dichlorobenzamido-analogue, afforded 2-acetamidothiazol-5-one trifluoroacetate, m. p. 105—106°. Satisfactory analytical results could not be obtained on this substance, probably because of rapid loss of trifluoroacetic acid (cf. Aubert *et al.*[2]). In consequence, the yields of products derived through ring-opening reactions are not significant and are not given. Treatment with hot water and hot ethanol respectively afforded *N*-acetylthiocarbamoylglycine, m. p. 200—202°, and its ethyl ester, m. p. 105°. Comparison of infrared spectra with those of authentic specimens confirmed their identities.

N-*Acetylthiocarbamoylglycine* p-*Toluidide* (I; R = Ac, R′ = H, R″ = *p*-C_6H_4Me).—(*a*) A mixture of *N*-acetylthiocarbamoylglycine (220 mg.), *p*-toluidine (107 mg.), and tetraethyl pyrophosphite (300 mg.) in diethyl hydrogen phosphite (6 c.c.) was kept at 90° for 30 min. and then poured into water.[9] The precipitated *product* (280 mg.), after recrystallisation from ethanol, had m. p. 237—239° (decomp.) (Found: C, 54·5; H, 5·7; N, 15·8. $C_{12}H_{15}O_2N_3S$ requires C, 54·3; H, 5·7; N, 15·8%).

(*b*) Reaction of 2-acetamidothiazol-5-one trifluoroacetate with *p*-toluidine in warm chloroform also afforded this compound, m. p. 237—239° (decomp.), undepressed by admixture with the above sample. Infrared spectra were identical.

N-*Acetylthiocarbamoylglycine* p-*Ethoxycarbonylanilide* (I; R = Ac, R′ = H, R″ = *p*-C_6H_4·CO_2Et).—(*a*) A mixture of *N*-acetylthiocarbamoylglycine (350 mg.), ethyl *p*-aminobenzoate (330 mg.), and tetraethyl pyrophosphite (520 mg.) in diethyl hydrogen phosphite (3 c.c.) was kept at 100—110° for 1 hr.[9] Addition of water to the cooled mixture furnished the *product* (550 mg.), m. p. 226—227° (decomp.), unaltered by recrystallisation from ethanol–chloroform–light petroleum (b. p. 60—90°) (Found: C, 51·5; H, 5·5; N, 13·0; S, 10·1. $C_{14}H_{17}O_4N_3S$ requires C, 52·0; H, 5·3; N, 13·0; S, 9·9%).

(*b*) The above compound was also obtained on reaction between 2-acetamidothiazol-5-one trifluoroacetate and ethyl *p*-aminobenzoate in chloroform. The recrystallised sample had m. p. 226° (decomp.), undepressed on admixture with the above specimen, and had an identical infrared spectrum.

N-*Acetylthiocarbamoyl* p-*Carboxyanilide* (I; R = Ac, R′ = H, R″ = *p*-C_6H_4·CO_2H).—(*a*) Interaction of glycine *p*-carboxyanilide (640 mg.) and methyl *N*-acetyldithiocarbamate (895 mg.) in 67% aqueous dioxan at pH 9·0 and 37° furnished N-*acetylthiocarbamoylglycine* p-*carboxyanilide* (660 mg.), m. p. 260—262° (decomp.) after recrystallisation from pyridine–benzene (Found: C, 48·8; H, 4·4; N, 14·4. $C_{12}H_{13}O_4N_3S$ requires C, 48·8; H, 4·2; N, 14·2%).

(*b*) Reaction of 2-acetamidothiazol-5-one trifluoroacetate with *p*-aminobenzoic acid in dry dioxan at room temperature overnight also afforded this compound, m. p. 260° (decomp.) after recrystallisation. The two specimens had identical infrared spectra.

N-*Acetylthiocarbamoyl*-DL-*alanine* p-*Toluidide* (I; R = Ac, R′ = Me, R″ = *p*-C_6H_4Me).—Reaction of DL-alanine *p*-toluidide and methyl *N*-acetyldithiocarbamate in ethanol–ether (4 : 1) at room temperature gave this *compound* (93%), m. p. 218° after recrystallisation from ethanol (Found : C, 56·1; H, 5·9; N, 15·2; S, 11·4. $C_{13}H_{17}O_2N_3S$ requires C, 55·9; H, 6·1; N, 15·0; S, 11·5%).

2-*Acetamido*-4-*methylthiazol*-5-*one Hydrochloride* (II; R = Ac, R′ = Me, X = Cl.)—(*a*) *N*-Acetylthiocarbamoyl-DL-alanine *p*-toluidide (279 mg.) was degraded in acetic acid (10 c.c.) saturated with dry hydrogen chloride. After addition of ether (8 c.c.), the *product* (43 mg.) crystallised overnight at 0°, and had m. p. 144—148° (decomp.) (Found : 34·3; H, 4·3; N, 13·3. $C_6H_9O_2N_2SCl$ requires C, 34·5; H, 4·4; N, 13·4%).

(*b*) Reaction of *N*-acetylthiocarbamoyl-DL-alanine with phosphorus trichloride in ether–dioxan also furnished this compound (76%), m. p. 147—149° (decomp.) (Found : C, 34·2; H, 4·8; N, 13·1%). The two specimens had identical infrared spectra.

N-*Benzoylthiocarbamoyl*-DL-*phenylalanine* p-*Toluidide* (I; R = Bz, R′ = Ph·CH_2, R″ = *p*-C_6H_4Me).—Prolonged reaction of methyl *N*-benzoyldithiocarbamate and DL-phenylalanine *p*-toluidide in chloroform at room temperature gave only 58% of the theoretical yield of this *compound*. After recrystallisation from ethanol, it had m. p. 176·0—176·5° (Found : C, 68·9; H, 5·8; N, 10·1; S, 8·2. $C_{24}H_{23}O_2N_3S$ requires C, 69·0; H, 5·6; N, 10·1; S, 7·7%).

N-*Benzoylthiocarbamoyl*-DL-*norleucine* p-*Toluidide* (I; R = Bz, R′ = Bu^n, R″ = *p*-C_6H_4Me).—Prepared from DL-norleucine *p*-toluidide and methyl *N*-benzoyldithiocarbamate, this *compound* (85%) had m. p. 179·0—179·5° after recrystallisation from ethanol–light petroleum (b. p. 60—90°) (Found : C, 65·9; H, 6·9; N, 10·8. $C_{21}H_{25}O_2N_3S$ requires C, 65·8; H, 6·6; N, 11·0%).

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