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REACTIONS OF N-THIOBENZOYL-α-AMINO-ACIDS AND RELATED N-SUBSTITUTED THIOBENZAMIDES WITH TRIFLUOROACETIC ANHYDRIDE

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Abstract—5-(2'-Benzamidoacyloxy)thiazoles are formed by the reaction of N-thiobenzoyl-α-amino-acids with trifluoroacetic anhydride. Corresponding esters on similar treatment undergo isosteric S–O exchange, giving N-benzoyl-α-amino-acid esters. While these are further examples of the differences shown in the reactions of N-(2-carboxyalkyl)thiobenzamides compared with their benzamide analogues, N$^{\alpha}$-thiobenzoyl-α-amino-acid amides are found to undergo cyclisation in trifluoroacetic anhydride to give 5-trifluoroacetamido-thiazoles, following the same reaction path as their N-benzoyl analogues. Terminal N-thiobenzoyl dipeptides give 5-(N-2-carboxyalkyl)trifluoroacetamido-thiazoles on treatment with trifluoroacetic anhydride, and it is established that trifluoroacetic anhydride fails to cleave the amide group of terminal N-thioacyl dipeptides, and is therefore not a suitable reagent for Edman-type sequence analysis of polypeptides.

The present work completes a project establishing routes from α-amino-acids to thiazoles carrying a hetero-atom (O, N or S) at the 5-position.

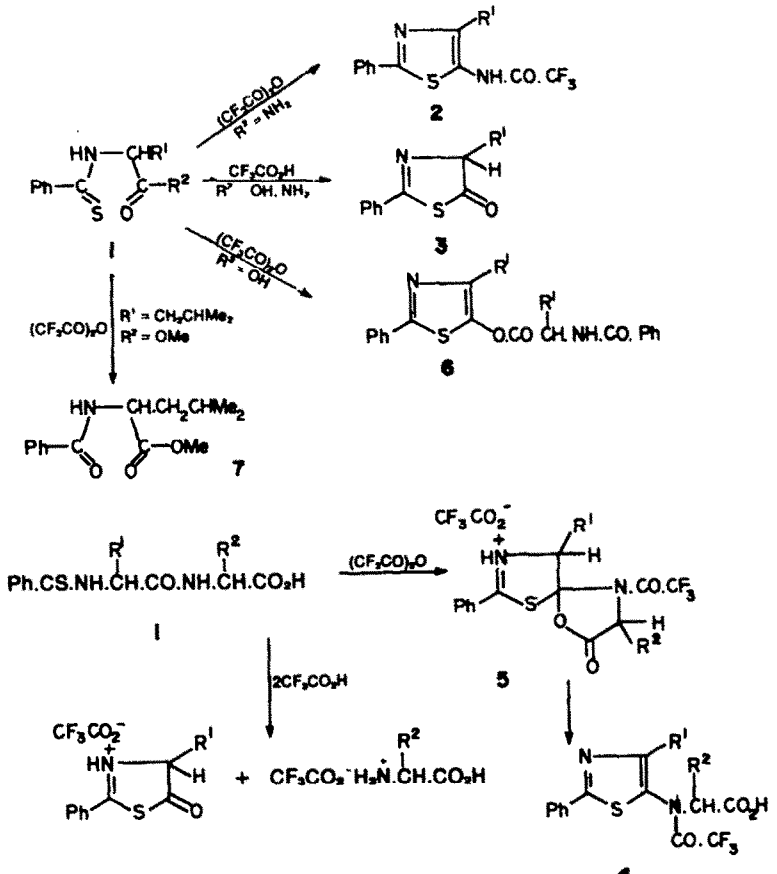
Trifluoroacetic anhydride has been used for the cyclisation of N-benzoyl-α-amino-acid amides to 5-trifluoroacetamido-oxazoles,[1] and has been claimed[2] to be effective for the cyclisation with concomitant cleavage of terminal N-phenylthiocarbamoyl peptides (i.e. the second step in a cycle of the Edman sequence analysis of polypeptides). Since we have established routes to 5-acetoxy-[3] and 5-(S-acetylmercapto)-[4] thiazoles from α-amino-acids via N-thiobenzoyl derivatives, and demonstrated a peptide sequencing procedure[5] related to the Edman method, employing terminal N-thiobenzoyl peptides (1; $R^2 = NH{\cdot}CHR^3{\cdot}CH.....$) in which the possibility of using trifluoroacetic anhydride as cleavage reagent appeared attractive, the reactions of representative N-thiobenzoyl-α-amino-acids and their esters and amides, N-thiobenzoyl peptides, and other thiobenzamides, with trifluoroacetic anhydride have been studied.

Reactions of N$^{\alpha}$-thiobenzoyl-L-α-amino-acid amides with trifluoroacetic anhydride

N$^{\alpha}$-Thiobenzoyl-L-leucinamide[6] (1; $R^1 = CH_2CHMe_2$, $R^2 = NH_2$) dissolved rapidly in excess trifluoroacetic anhydride, with the formation of a transient wine-red colour, to give the corresponding 5-trifluoroacetamido-thiazole (2; $R^1 = CH_2CHMe_2$) after evaporation of the reaction mixture and trituration of the resulting crystalline residue with aqueous sodium hydrogen carbonate. The corresponding L-phenylalanine derivative (1; $R^1 = PhCH_2$, $R^2 = NH_2$) dissolved more slowly in trifluoroacetic anhydride, but gave the analogous 5-trifluoroacetamido-thiazole (2; $R^1 = PhCH_2$).

The course of this reaction is as expected by analogy with the formation of 5-trifluoroacetamido-oxazoles from N-benzoyl-α-amino-acid amides by treatment with trifluoroacetic anhydride.[1,7] In principle, oxazoles (2; O in place of S) might have been formed by heterocyclisation of the thiobenzoylamino-acid amides, based on Fleury's mechanism,[7] but these were not found in reaction mixtures. Formation of 5-amino-thiazoles, rather than oxazoles, has been reported for the heterocyclisation of isomeric thioamides $R{\cdot}CO{\cdot}NH{\cdot}CHR^1{\cdot}CS{\cdot}NH_2$ in hot polyphosphoric acid,[8] and the formation of a 5-ethoxythiazole[9] by the reaction of the N$^{\alpha}$-acetyl amino-acid amide $MeCO{\cdot}NH{\cdot}CH(CO_2Et)CO{\cdot}NH_2$ with P_4S_{10} (suggested[9] to proceed via the thioacetamide) also indicates preferential formation of thiazoles in reaction of these general types.

The report[2] that N-phenylthiohydantoins are formed, via 2-anilinothiazol-5(4H)-ones (3; PhNH in place of Ph), by treatment of N-phenylthiocarbamoylpeptides (1; PhNH in place of Ph, $R^2 = NH{\cdot}CHR^3{\cdot}CO.....$) with trifluoroacetic anhydride, implies that a different course for the heterocyclisation reaction in this case is determined by the different thioacyl substituent. We have already shown[5] that N$^{\alpha}$-thiobenzoyl-α-amino-acid amides (1; $R^2 = NH_2$) and terminal N-thiobenzoyl peptides (1; $R^2 = NH{\cdot}CHR^3{\cdot}CO.....$) are cleaved in quantitative yields by trifluoroacetic acid to give 2-phenylthiazol-5(4H)-ones by –CO–NH– cleavage, and it was expected that trifluoroacetic acid produced by the reaction of these compounds with trifluoroacetic anhydride would react to give thiazolones as secondary products (1→2+3). The results reported[2] for the use of trifluoroacetic anhydride in an Edman polypeptide sequence analysis might therefore be accounted for on the basis of the reaction of trifluoroacetic acid with the N-phenylthiocarbamoyl peptide, which is the usual reagent for the cleavage step in the Edman method.[10] However, N-thiobenzoyl dipeptides[11,12] were found to give 5-(N-2-carboxyalkyl)trifluoroacetamido-thiazoles 4 by dissolution in trifluoroacetic anhydride, evaporation, and trituration with water, and therefore this reagent is unsuitable for the cleavage step in the stepwise degradation of polypeptides via terminal N-thiobenzoyl derivatives. Control experiments in which an N-thiobenzoyl dipeptide was dissolved in trifluoroacetic acid, and the solution was evaporated after a few minutes at room temperature, followed by trituration with water, gave the thiazolone 3 and an aqueous solution, shown by TLC to contain the C-terminal amino-acid, while the same pro-



Scheme 1.

cedure using trifluoroacetic anhydride gave an aqueous solution containing *no trace* of amino-acid. Evidently, N-trifluoroacetylation occurs rapidly and protects the substrate against cleavage by trifluoroacetic acid present in the reaction mixture.

N-Thiobenzoyl-glycyl-L-valine[11] gave racemic 5 - (N - 3' - methyl - 2' - carboxybutyl)trifluoroacetamido - 2 - phenylthiazole on treatment with trifluoroacetic anhydride; an intermediate was isolated in this case with analytical data close to those required by the salt (**5**; $R^1 = H$, $R^2 = iPr$) which showed IR absorption at frequencies characteristic of oxazol-5(4H)-ones and oxazolidin-5-ones, thus accounting for the racemisation of the C-terminal amino-acid residue. This intermediate was readily converted into the ultimate product by treatment with water.

A representative Edman N-terminal analysis, in which N-phenylthiocarbamoyl-DL-alanyl-DL-phenylalanine was treated with trifluoroacetic anhydride and worked up as above, gave no trace of phenylalanine, while a control experiment using trifluoroacetic acid gave 5-methyl-3-phenylthiohydantoin together with DL-phenylalanine. It must be presumed that the technique used in the procedure for polypeptide sequencing using trifluoroacetic anhydride[2] in which the phenylthiocarbamoylated peptide is placed on a paper strip, then treated with the anhydride, in fact involves trifluoroacetic acid as the effective reagent, which is liberated by reaction of the anhydride with cellulose and adsorbed water.

Further studies of the reactions of terminal N-thioacylated peptides with trifluoroacetic anhydride are being pursued.

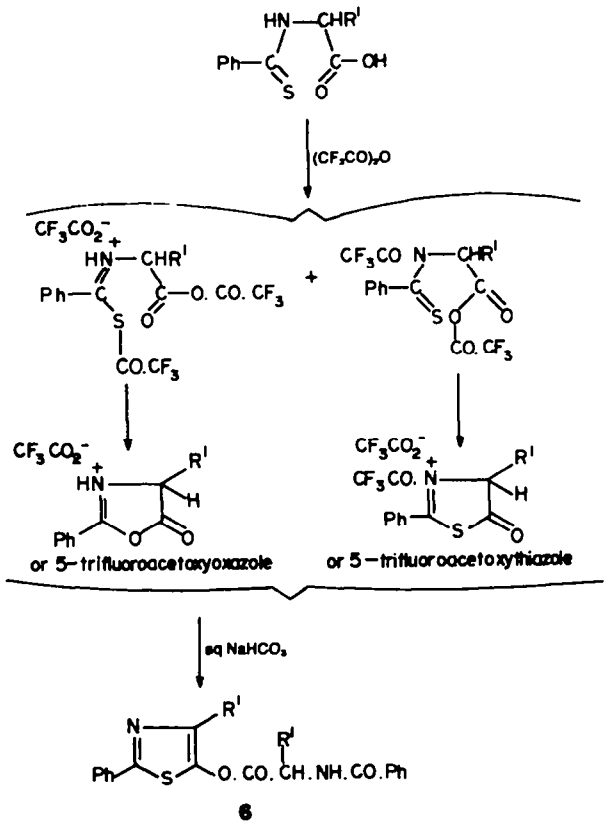
Reactions of N-thiobenzoyl-α-amino-acids with trifluoroacetic anhydride

Although no study has been made of the reaction of N-benzoyl-α-amino-acids with trifluoroacetic anhydride, they should be expected to behave like N-trifluoroacetyl-α-amino-acids (which give 2-trifluoromethyloxazol-5(4H)-ones[13]).

N-Thiobenzoyl-α-amino-acids[3,6] were included in the present study since in the most general application of our Edman-type polypeptide degradation (i.e. performed on a peptide with an unknown number of amino-acid residues), the C-terminal amino-acid would be encountered as an N-thiobenzoyl derivative. Unexpectedly, 5-(2'-benzamidoacyloxy)thiazoles **6** were formed in high yield when N-thiobenzoyl-α-amino-acids (**1**; $R^2 = OH$) were dissolved in trifluoroacetic anhydride. Spectroscopic data readily distinguished between the structure assigned (**6**) and the isomeric 5-(2'-thiobenzamidoacyloxy)oxazole formulation; in particular, the ultraviolet absorption feature of the products (λ_{max} 308 nm) is closely similar to that of 5-acetoxythiazoles,[3] and differs from the absorption features of the thiobenzamide chromophore ($\lambda\lambda_{max}$ *ca.* 240, 280, 380 nm)[9,11] which would be shown in spectra of the isomeric structure.

The course of the conversion of an N-thiobenzoyl-α-amino-acid (**1**; $R^2 = OH$) into a 5-(2'-benzamidoacyloxy)thiazole **6** can be explained by the concurrent formation of thiazolone and oxazolone precursors resulting from the competitive trifluoroacetylation of N and S atoms of the thioamide, as shown in Scheme 2.

Good analogy for this mechanism is provided by



Scheme 2.

recent studies of the reactions of ^{18}O-labelled aroylamino-acid amides (1; O in place of S) with trifluoroacetic anhydride.[7] Depending on the structure of the aroyl substituent, either carbonyl oxygen atom can appear as the ring oxygen in the resulting 5-trifluoroacetamidooxazole.[7] Evidence for trifluoroacetylation of a thioamide grouping, resulting in loss of sulphur by replacement by oxygen, has been obtained in the present work, and is discussed later in this paper in the section dealing with the reaction of trifluoroacetic anhydride with N-thiobenzoyl-α-amino-acid esters; the remaining step in Scheme 2 for which no precedent exists is the formation of the 5-(2'-benzamidoacyloxy)thiazole **6** from an oxazolone and a thiazolone. This reaction has been shown to be very easily achieved by bringing together the reactants in solution at room temperature,[14,15] and therefore can occur either before or after work-up with aqueous sodium hydrogen carbonate.

An alternative reaction scheme can be considered in which the thiobenzoyl amino-acid is converted into a thiazol-5(4H)-one by reaction with trifluoroacetic anhydride, and thence into a 5-(2'-thiobenzamidoacyloxy)thiazole (**6**; PhCS in place of PhCO), followed by isosteric S–O exchange as demonstrated for other N-thiobenzoyl-α-amino-acid esters (*vide infra*). We have suggested[14] that the relatively rapid racemisation of thiazol-5(4H)-ones in solution, and its marked acceleration by carboxylic acids, can be accounted for on the basis of an equilibrium involving two molecules of the thiazolone, and (**6**; PhCS in place of PhCO). Against this background of feasible processes, some further incidental support is provided by the fact that many 2-phenylthiazol-5(4H)-ones **3** are not stable on prolonged storage, in contrast with corresponding oxazolones (which may, however, slowly revert to their parent N-benzoyl-α-amino-acids in moist air). Our earlier reference[3] to the instability of 4 - isopropyl - 2 - phenylthiazol - 5(4H) - one (**3**; $R^1 = CHMe_2$) can now be understood in terms of a tendency to undergo desulphurisation by this route; the colourless crystalline material which separates from samples of freshly-prepared material is now shown to be identical with a sample of 5 - (2' - benzamido - 3' - methylbutanoyloxy) - 4 - isopropyl - 2 - phenylthiazole (**6**; $R^1 = CHMe_2$) prepared from N-thiobenzoyl-DL-valine and trifluoroacetic anhydride. Aged samples of the 4-methylthiazolone (**3**; $R^1 = Me$), which in contrast to the isopropyl analogue exists in the solid state and in the hydroxythiazole tautomeric form, are substantially pure after 1 month but on longer storage can be shown to contain elementary sulphur. Although no desulphurisation product (**6**; $R^1 = Me$) could be isolated, and these samples were better than 70% pure after 3 months as shown by acetylation (Ac_2O/pyridine) and extraction of the stable 5 - acetoxy - 4 - methyl - 2 - phenylthiazole,[3] the same slow accumulation of 5 - (2' - benzamidopropanoyloxy) - 4 - methyl - 2 - phenylthiazole (**6**; $R^1 = Me$) can be considered to be the main cause of deterioration.

The alternative reaction scheme just described, however, seems to be ruled out by the fact that 2-phenylthiazol-5(4H)-ones do not react with trifluoroacetic anhydride to give 5-benzamidoacyloxythiazoles **6**. Although by analogy with their reaction with acetic anhydride,[3] thiazol-5(4H)-ones are converted into 5-trifluoroacetoxythiazoles in trifluoroacetic anhydride,

these derivatives are converted back into starting materials on hydrolytic work-up.

A further basis on which this alternative mechanism may be ruled out is the failure of reaction mixtures containing an N-thiobenzoyl-α-amino-acid and trifluoroacetic anhydride to develop the intense wine-red colour which, as described in the next section, is a characteristic feature of solutions of N-thiobenzoyl-α-amino-acid esters in trifluoroacetic anhydride.

N-Thiobenzoyl-L-α-amino-acids gave racemic 5-(2'-benzamidoacyloxy)-thiazoles **6** by reaction with trifluoroacetic anhydride. This fact is consistent with both mechanistic schemes discussed above; oxazol-5-ones, and especially thiazol-5-ones,[14,15] are readily racemised by carboxylic acids (rapidly by trifluoroacetic acid[14]), and the product **6**, and the intermediate (**6**; PhCS in place of PhCO) involved in the alternative mechanism, are "active esters" of N-benzoyl-α-amino-acids and N-thiobenzoyl-α-amino-acids, respectively, and therefore especially prone to racemisation.[16,17]

N-Trifluoroacetylation of amides was not considered by Fleury *et al.*[7] when presenting their mechanism to account for the distribution of the label following cyclisation of ^{18}O-labelled aroylamino-acid amides. Our results support Fleury's mechanism, but also involve an N-trifluoroacetyl-thioamide intermediate (Scheme 2), as well as accepting the general assumption that amides are trifluoroacetylated on nitrogen.[18,19] In addition to the role of electron-release from the aryl substituent, stated by Fleury *et al.*[7] to account for the distribution of the label in the heterocyclisation products, the differences in electron-release properties to be expected for an N-trifluoroacetylated primary amide compared with a corresponding secondary amide should be considered to contribute to the observed cyclisation pathways for N-benzoyl-α-amino-acid amides.

Reactions of N-thiobenzoyl-α-amino-acid esters (**1**; R^2 = O-*alkyl*) *and other thiobenzamides with trifluoroacetic anhydride*

N-Thiobenzoyl-L-leucine methyl ester (**1**; R^1 = $CH_2{\cdot}CHMe_2$, R^2 = OMe) dissolved readily in excess cold trifluoroacetic anhydride to give a wine-red solution. Unlike the reaction mixture resulting from dissolution of the corresponding amide in trifluoroacetic anhydride, in which the colour persisted for only a few seconds, the colour faded slowly during 90 min by which time the absorption maximum at 495 nm had disappeared. Evaporation and trituration of the residual oil with aqueous sodium hydrogen carbonate gave N-benzoyl-L-leucine methyl ester **7** in good yield. N-Thiobenzoyl-α-amino-acid esters have been shown[12] to yield corresponding 2-phenylthiazol-5(4H)ones **3** by prolonged reaction with trifluoroacetic acid, but this reaction pathway was not followed with trifluoroacetic anhydride as reagent since the crude product showed no absorption features beyond 280 nm.

Thiobenzamide itself, and N-(2-carboxyethyl)thiobenzamide, were also readily soluble in trifluoroacetic anhydride to give wine-red solutions, but were recovered unchanged after evaporation. Since the colour in these cases persisted for as long as the solutions were stored, the relatively short-lived intermediate involved in the conversion of an N-thiobenzoyl-α-amino-acid ester into its benzoyl analogue with trifluoroacetic anhydride must receive assistance from the ester grouping when reacting further with trifluoroacetic anhydride (or trifluoroacetic acid or its anion) to bring about the S–O exchange. The intermediate involved in these reactions shows absorption some 100 nm to longer wavelengths relative to that shown by the thiobenzamides, and a likely structure for the intermediate is the N-trifluoroacetyl derivative; it is known[18] that N-acetylation of simple thioamides causes shifts to longer wavelengths of up to 80 nm, providing reasonable support for this conclusion. Since the present work provides examples of S–O exchange, evidence for both N- and S-trifluoroacetylation of thiobenzamides has been obtained.

EXPERIMENTAL

Microanalyses were by Mr S. Bance and Staff, May & Baker Ltd., Dagenham, Essex. Circular dichroism data were determined using a Roussel-Jouan Dichrographe Model II at the Department of Biochemistry, University of Oxford. Optical rotations were determined using a Perkin-Elmer polarimeter model 241.

Preparation of N-thiobenzoyl-α-amino-acid derivatives and related thiobenzamides

Thiobenzoylation of α-amino-acids and their esters and amides was carried out in neutral aqueous solutions using carboxymethyl dithiobenzoate.[3,6] The following procedure is typical: a soln of L-phenylalanine amide (0.463 g) and carboxymethyl dithiobenzoate (0.598 g) in N-sodium hydroxide (2.8 ml) was set aside at room temp. during 6 h. N-Thiobenzoyl-L-phenylalanine amide (0.72 g; 90%) separated during this time as yellow rhombs, m.p. 184–5° from EtOAc. Found: C, 67.6; H, 5.6; N, 9.7; S, 11.3. $C_{16}H_{16}N_2OS$ requires: C, 67.6; H, 5.65; N, 9.85; S, 11.3%. Kjaer[6] records m.p. 156–157° for the DL-compound, prepared by ammonolysis of N-thiobenzoyl-DL-phenylalanine ethyl ester. Other N-substituted thiobenzamides used in the present work were known compounds,[3,6,20,23] the N-thiobenzoyl dipeptides being prepared either from the dipeptides through the procedure above,[11] (glycyl-leucine, glycyl-valine) or by acylation of an amino-acid by a 4-substituted 2-phenylthiazol-5(4H)-one (leucyl-glycine).[12]

Reaction of N-thiobenzoyl-L-leucinamide with trifluoroacetic anhydride

A soln of N-thiobenzoyl-L-leucinamide[6] (0.94 g; 0.0038 mole) in trifluoroacetic anhydride (7 ml) became colourless within a few seconds, having passed from a pale yellow to a wine-red colour. After 10 min, evaporation and trituration of the crystalline residue with 3% aq $NaHCO_3$ gave 5-trifluoroacetamido-4-isobutyl-2-phenylthiazole (2; R^1 = CH_2CHMe_2), 0.72 g (58%), m.p. 128–129° from hexane. Found: C, 54.8; H, 4.5; N, 8.3; S, 9.6. $C_{15}H_{15}N_2OSF_3$ requires: C, 54.85; H, 4.6; N, 8.55; S, 9.75%. ν_{max} (Nujol): 3300, 1700, 1170 cm^{-1}. λ_{max} (Et_2O): 308 nm (ε 12,000).

Reaction of N-thiobenzoyl-L-phenylalanine amide with trifluoroacetic anhydride

N-Thiobenzoyl-L-phenylalanine amide (0.465 g; 0.0016 mole) dissolved in trifluoroacetic anhydride (2 ml) within 1 min to give a pink emulsion, which became colourless within 2 min. Work-up as for the leucine analogue (preceding paragraph) gave 5-trifluoroacetamido-4-benzyl-2-phenylthiazole (2; R^1 = CH_2Ph), 0.38 g (64%), m.p. 112° after chromatography on silica gel, elution with 5% Et_2O in hexane, and crystallisation from hexane. Found: C, 59.4; H, 3.6; N, 7.8; S, 8.8. $C_{18}H_{13}N_2OSF_3$ requires: C, 59.65; H, 3.6; N, 7.75; S, 8.85%. ν_{max} (Nujol): 3340, 1700, 1170 cm^{-1}.

Reaction of N-thiobenzoylglycyl-L-valine with trifluoroacetic anhydride

A soln of N-thiobenzoylglycyl-L-valine[11] (0.433 g; 1.5 mmol) in trifluoroacetic anhydride (3 ml) was evaporated after 5 min, and the residual oil was triturated with water to give 5 - (N - 2' - carboxy - 3' - methyl butyl)trifluoroacetamido - 2 - phenyl - thiazole (4; R^1 = H, R^2 = ^{i}Pr), 0.32 g (57%), m.p. 148–149° from aq MeOH. Found: C, 51.3; H, 4.05; N, 6.95; S, 8.4. $C_{16}H_{15}N_2O_3SF_3$

requires: C, 51.6; H, 4.05; N, 7.5; S, 8.6%. ν_{max} (Nujol): 3400, 3180, 1725, 1150 cm^{-1}.

Slow evaporation *in vacuo* of an identical reaction mixture gave crystals of the spiro-compound (5; R^1 = H, R^2 = ^{i}Pr), m.p. 61° from trifluoroacetic anhydride, 0.38 g (52%), $[\alpha]_D$ 0.000°, λ_{max}(Et_2O) 292 nm (ε 8000), ν_{max} (Nujol): 2700, 2550, 2470, 1820 cm^{-1}. Found: C, 45.6, 43.1; H, 3.44, 3.09; N, 5.76, 5.73; S, 6.97. $C_{18}H_{16}N_2O_5SF_6$ requires: C, 44.45; H, 3.3; N, 5.75; S, 6.6%. Further weak absorption features in the IR spectrum corresponding to those shown by 5 - (N - 2' - carboxy - 3' - methylbutyl)trifluoroacetamido - 2 - phenyl - thiazole (4; R^1 = H, R^2 = ^{i}Pr) suggested that 5 was readily converted into 4 by atmospheric moisture, and the m.p. of the sample of 5 rose to 81° and 106–107° during 3 and 5 days, respectively. The sample was readily converted into (4; R^1 = H, R^2 = ^{i}Pr) by rubbing with water, giving a sample m.p. and mixed m.p. 148–149°.

The aqueous soln obtained when 0.053 g N-thiobenzoylglycyl-L-valine was treated as above with trifluoroacetic anhydride, followed by evaporation and trituration with water, contained no trace of valine, as shown by TLC on silica gel using *n*-butanol:acetic acid:water = 6:2:2 for development. An identical experiment using trifluoroacetic acid showed that quantitative cleavage into valine had occurred (TLC) and 2-phenylthiazol-5(4H)-one.[3]

Reaction of N-thiobenzoyl-DL- and L-leucylglycine with trifluoroacetic anhydride

Treatment of N-thiobenzoyl-DL-leucylglycine[11] with trifluoroacetic anhydride and work-up as described from the reaction with N-thiobenzoylglycyl-L-valine gave 5 - (N - 2' - carboxy - 4' - methylpentyl)trifluoroacetamido - 2 - phenylthiazole (4; R^2 = H, R^1 = ^{i}Bu), 65%, m.p. 187–188° from aq MeOH. Found: C, 52.1; H, 4.3; N, 7.3; S, 8.6. $C_{17}H_{17}N_2O_5SF_3$ requires: C, 52.8; H, 4.45; N, 7.25; S, 8.3%. The N-thiobenzoyl-L-peptide gave the same product, $[\alpha]_D$ 0.000° (CH_2Cl_2), with superimposable IR spectra, m.p. and mixed m.p. 187–188°.

Reaction of other N-thiobenzoyl-peptides with trifluoroacetic anhydride

Small-scale experiments monitored by TLC, as described for N-thiobenzoylglycyl-L-valine, performed with N-thiobenzoyl derivatives of DL-leucylglycyl-glycine, glycyl-L-proline, and DL-methionylglycine, similarly proved that no peptide bond cleavage occurred in reactions with trifluoroacetic anhydride.

N-Phenylthiocarbamoyl-DL-alanyl-DL-phenylalanine

The derivative was prepared from the dipeptide and phenyl isothiocyanate according to Edman's method.[21] It had m.p. 159–160° from aq. EtOH. Found: C, 61.1; H, 5.65; N, 11.2; S, 8.8. $C_{19}H_{21}N_3O_3S$ requires: C, 61.45; H, 5.7; N, 11.3; S, 8.65%.

Reaction of N-phenyl thiocarbamoyl-DL-alanyl-DL-phenylalanine with trifluoroacetic anhydride

Reaction with trifluoroacetic anhydride and work-up as described above for N-thiobenzoylglycyl-L-valine gave an aqueous soln containing no phenylalanine. Trifluoroacetylated reaction product, obtained in solid form but with variable m.p. near 94–96°, gave erratic analytical data approximately consistent with the condensation of the N-phenylthiocarbamoylpeptide with two moles CF_3CO_2H. Found: C, 51.3; H, 3.55; N, 8.2; S, 7.1. $C_{23}H_{18}N_3O_5SF_6$ requires: C, 49.1; H, 3.2; N, 7.45; S, 5.7%.

Reaction of N-thiobenzoyl-α-amino-acids with trifluoroacetic anhydride

N-Thiobenzoyl-DL-leucine[3] (1; R^1 = CH_2CHMe_2, R^2 = OH), 0.43 g (1.7 mmol) dissolved rapidly, with evolution of heat, in trifluoroacetic anhydride (4 ml). Evaporation *in vacuo*, and trituration with 3% aq. $NaHCO_3$, gave 5 - (2' - benzamido - 4' - methylpentanoyloxy) - 4 - isobutyl - 2 - phenylthiazole (6; R^1 = CH_2CHMe_2), 0.32 g (83%), m.p. 116–117° from Et_2O-hexane. Found: C, 69.15; H, 6.75; N, 6.65; S, 7.35. $C_{26}H_{30}N_2O_3S$ requires: C, 69.3; H, 6.7; N, 6.2; S, 7.1%. ν_{max} (Nujol): 3380, 1720, 1630 cm^{-1}. λ_{max}(Et_2O) 307 nm (ε 11,900).

N-Thiobenzoyl-L-leucine, treated in the same way, gave the identical product, $[\alpha]_D$ 0.000° (CH_2Cl_2).

N-Thiobenzoyl-DL-alanine[3] (1; R^1 = Me), 2.31 g (10.5 mmol) treated in the same way, gave 5 - (2' - benzamidopropanoyloxy) - 4 - methyl - 2 - phenylthiazole (6; R^1 = Me), 1.72 g (86%), m.p. 150–151° from Et_2O-hexane. Found: C, 65.8; H, 4.8; N, 7.6; S, 8.5. $C_{20}H_{18}N_2O_3S$ requires: C, 65.55; H, 4.95; N, 7.65; S, 8.75%.

N-Thiobenzoyl-DL-butyrine[22] (1; R^1 = Et), 1.114 g (4.8 mmol) treated in the same way, gave 5 - (2' - benzamidobutanoyloxy) - 4 - ethyl - 2 - phenylthiazole (6; R^1 = Et), 0.87 g (66%), m.p. 116–117° from acetone–hexane. Found: C, 66.9; H, 5.65; N, 6.9; S, 8.0. $C_{22}H_{22}N_2O_3S$ requires: C, 66.95; H, 5.6; N, 7.1; S, 8.15%.

N-Thiobenzoyl-DL-valine[3] (1; R^1 = ^{i}Pr), 0.73 g (2.9 mmol) treated in the same way, gave 5 - (2' - benzamido - 3' - methylbutanoyloxy) - 4 - isopropyl - 2 - phenyl - thiazole (6; R^1 = ^{i}Pr), 0.53 g (85%), m.p. 107–108° from CH_2Cl_2-hexane. Found: C, 68.2; H, 6.55; N, 6.65; S, 7.5. $C_{24}H_{26}N_2O_3S$ requires: C, 68.2; H, 6.2; N, 6.65; S, 7.6%. λ_{max} (MeOH) 304 nm (ε 11,000). NMR (C^2HCl_3): τ 8.92 ($CHMe_2$, 12H, two superimposed quartets), 7.60 (m, 1H, $CHMe_2$), 6.80 (m, 1H, $CHMe_2$), 4.95 (m, 1H, $CH{\cdot}CHMe_2$), 3.30 (d, 1H, NH), 2.50 (m, 6H, C_6H_5), 2.10 (m, 4H, C_6H_5). This compound was identical with a compound which separated on standing from 4 - isopropyl - 2 - phenylthiazol - 5(4H) - one[3,23] prepared by cyclisation of N-thiobenzoyl-DL-valine with dicyclohexylcarbodi-imide[12] and distillation *in vacuo*.

Reaction of 4 - isobutyl - 2 - phenylthiazol - 5(4H) - one with trifluoroacetic anhydride

The thiazolone[3] (1.2 g) dissolved in the anhydride to give a colourless soln, without evolution of heat. Evaporation gave a colourless oil, from which a pale yellow solid m.p. 118–119° was obtained on trituration with 3% aq. $NaHCO_3$, which had m.p. 119–121° on crystallisation from Et_2O, IR similar to that of the starting material.

Reaction of N-thiobenzoyl-L-leucine methyl ester with trifluoroacetic anhydride

A soln of N-thiobenzoyl-L-leucine methyl ester,[20] $[\alpha]_D$ + 58.6° (c 0.432, CH_2Cl_2) (0.934 g; 3.5 mmol) in trifluoroacetic anhydride (5 ml) slowly lost its wine-red colour during 1 h at room temp. The circular dichroism of the soln, $\Delta\varepsilon$ − 0.41, at λ_{max} 495 nm, slowly decreased to zero during *ca.* 90 min. Evaporation *in vacuo* after 2 h gave an oil which on trituration with 3% aq. $NaHCO_3$ gave N-benzoyl-L-leucine methyl ester (0.553 g; 63%), m.p. 103–105° from hexane (lit.[24] m.p. 100–102°). Found: C, 67.7; H, 7.65; N, 5.4. Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.7; N, 5.6%.

Reaction of other N-substituted thiobenzamides with trifluoroacetic anhydride

Evaporation of solns of thiobenzamide, or N-(2-carboxyethyl)thiobenzamide,[25] in trifluoroacetic anhydride, and trituration of the residue with water, gave back the starting materials in quantitative yields.

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