Reactions of Thioacetic Acid with Amino-acids

By G. C. BARRETT* and A. R. KHOKHAR
(*Department of Chemistry, West Ham College of Technology, Romford Road, London, E.*15)
and J. R. CHAPMAN
(*Consultant Laboratory, A.E.I. Scientific Apparatus Division, Urmston, Manchester*)

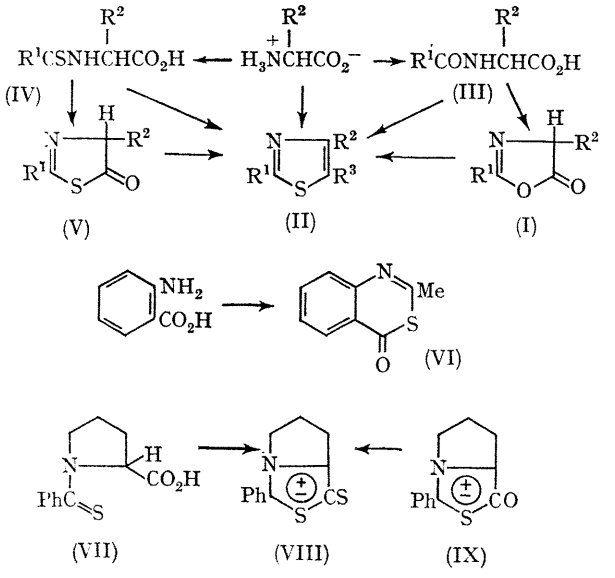
Summary Reactions of amino-acids, and of their *N*-acyl and *N*-thioacyl derivatives, with thioacetic acid, offer simple new routes to nitrogen–sulphur heterocyclic compounds.

CONDENSATION reactions of polyfunctional compounds with thioacetic acid have established new applications for this reagent in heterocyclic synthesis.[1] Its use as an acetylating agent, and its "sulphur–oxygen exchange" reactions,[2–4] are well-known; the latter property is exemplified in the conversion of azlactones (2-phenyl-4-benzylideneoxazolid-5-one[2,4] and its 4-isopropylidene analogue[4]) into corresponding thiazolidones. However, the claim[4] that a "saturated azlactone" (I; R^1 = Ph, R^2 = CH_2·Ph) reacts similarly has required re-investigation, since the product (m.p. 112°) differs from the thiazol-5(4*H*)-one (V; R^1 = Ph, R^2 = CH_2·Ph; m.p. 136°) obtained[5] by cyclisation of *N*-thiobenzoylphenylalanine.

In fact, we find that "saturated azlactones" [oxazol-5-(4*H*)-ones; (I)] react with thioacetic acid to yield 5-(*S*-acetylthio)thiazoles (II; R^3 = S·CO·Me). A simple synthesis of the 2-methylthiazoles (II; R^1 = Me, R^3 = S·CO·Me) involves the direct condensation of an α-amino-acid with an excess of thioacetic acid at 100° for 16 hr., though any one of a number of likely intermediates, *viz.* *N*-acyl- or *N*-thioacyl-amino-acids (III or IV), oxazol- or thiazol-5-(4*H*)-ones (I or V), or 5-acetoxythiazoles (II); R^3 = O·CO·Me) may be used in place of the α-amino-acid in this reaction. Reactions of amino-acids with thioacetic acid which have been described[6] have involved brief contact of the reactants, leading merely to *N*-acetyl derivatives. Data on representative thiazoles obtained

through routes displayed in the Scheme, are listed in the Table.

Anthranilic acid was converted nearly quantitatively into 2-methyl-4,5-benzo-6*H*-1,3-thiazin-6-one (VI) by reaction with an excess of thioacetic acid (100°/16 hr.); this compound has been obtained[7] *via* the corresponding 6-thione, which results in low yield from the reaction between methyl *N*-acetylanthranilate and phosphorus pentasulphide.[7] *N*-Thiobenzoylproline (VII) gave the mesoionic 2-phenylthiazole-5-thione (VIII) on treatment with an excess of warm thioacetic acid for 2 hr.; the same product was obtained by an easy cyclo-addition reaction of the corresponding thiazolone (IX)[5,8] and cold carbon disulphide.[9] Respectively, these observations provide a new synthesis, and a new interconversion procedure,[10] of sulphur analogues of mesoionic oxazolones.[9,11,12]



TABLE

Thiazoles from amino-acids, and from derivatives (I), (III—IV)*

Thiazole	R¹	R²	R³	M.p.
(IIa)	Me	CH_2·Ph	S·CO·Me	65—66°
(IIb)	Ph	CH_2·Ph	S·CO·Me	112
(IIc)	Ph	H	S·CO·Me	108—109
(IId)	Ph	Me	S·CO·Me	66
(IIe)†	Ph	CH_2·Ph	SH	142—144
(IIf)‡	Me	CH_2·Ph	SH	116—118
(VIII)	—	—	—	193

* Satisfactory analytical data and supporting mass spectra have been obtained for these compounds.

† As disulphide; obtained by treatment of (IIb) with cold piperidine.

‡ From (IIa) by treatment with cold piperidine.

The broad scope of these routes contrasts with that of an earlier study,[13] in which 2-acetylamino-5-(*S*-acetylthio)-thiazoles (II; R^1 = Me·CO·NH, R^3 = S·CO·Me) were shown to be formed from *N'*-acetylthiohydantoic acids (IV; R^1 = Me·CO·NH) or from corresponding thiazolones (V; R^1 = Me·CO·NH) by reaction with thioacetic acid, but that related compounds [*e.g.* (IV; R^1 = Ph·CH_2·S or Ph·NH)] did not react analogously.

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