CCCLXV.—*The Condensation of* o-*Aminothiophenol with αβ-Unsaturated Acids.*

By WILLIAM HOBSON MILLS and JAMES BELL WHITWORTH.

IN the course of some experiments carried out with *o*-aminothiophenol with the view of synthesising a carbothiocyanine dye (J., 1922, **121**, 455), we found that this base reacted in an unexpected manner with glutaconic acid. The two substances interacted very readily when heated together, but the product of the reaction was not the anticipated benzthiazole derivative; it was a new compound formed by the condensation of one molecule of glutaconic acid and one molecule of aminothiophenol, with the elimination of one molecule of water, as shown in the equation

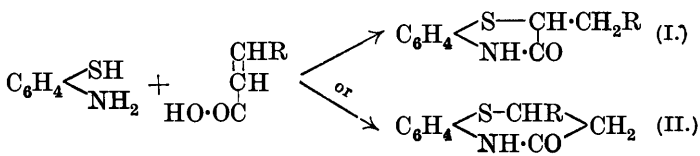
$$C_6H_7NS + C_5H_6O_4 = C_{11}H_{11}O_3NS + H_2O.$$

It was a monobasic acid and it showed none of the reactions characteristic either of the ethylenic linking, the thiol group, or the amino-group. In the interaction, therefore, both the thiol group and the amino-group of the aminothiophenol and the ethylenic linking and one of the carboxyl groups of the glutaconic acid are concerned. That addition of some group to the ethylenic linking had occurred was further indicated by the fact that the new compound was resolvable into antimeric optically active forms, for it would seem that the only way in which an asymmetric carbon atom could be produced in its molecule would be through addition to this linking.

The behaviour of the following αβ-unsaturated acids towards *o*-aminothiophenol was then examined: acrylic, crotonic, and cinnamic acids, and they were all found to react with it similarly to glutaconic acid.

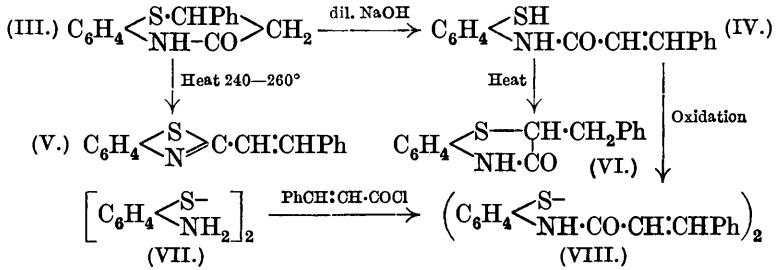
There are four ways in which the observed condensations might occur:

In the first place, *addition of the thiol group* of the aminothiophenol to the ethylenic linking of the acid might take place, accompanied by condensation between the amino- and carboxyl groups. This would give two possible formulæ, according as the sulphur was attached (1) to the α-carbon atom (formation of a ketodihydro-1 : 4-benzthiazine derivative, I), or (2) to the β-carbon atom (formation of a ketotetrahydro-1 : 5-heptabenzthiazine derivative, II).



Alternatively, *addition of the amino-group* of the aminothiophenol to the ethylenic linking of the acid might occur, with condensation between the carboxyl and thiol groups. This would give two further possible constitutions—(3) and (4)—according to whether the nitrogen was attached to the α- or the β-carbon atom.

We found that actually condensation of the amino-group of the aminothiophenol with the carboxyl group of the acid had occurred and that therefore addition of the thiol group to the ethylenic linking had taken place. This was established by examining the compound obtained from cinnamic acid and aminothiophenol. The resulting compound was an indifferent substance, but on being heated with dilute alkalis it dissolved gradually, forming a yellow solution from which carbon dioxide precipitated an isomeric compound, which could be proved to have the constitution (IV); for it had all the properties of a thiophenol, being soluble in alkalis, giving a mercuric derivative with mercuric chloride, and being converted by atmospheric oxygen and various other oxidising agents—iodine, ferric chloride, or hydrogen peroxide—with loss of one atom of hydrogen into a compound insoluble in alkalis, which was shown to be the disulphide (VIII), since it could be synthesised by introducing a cinnamoyl group into each of the two amino-groups of *oo'*-diaminodiphenyl disulphide (VII), by treatment with cinnamoyl chloride.

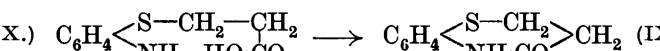


These observations limit the possible formulæ for the compound to (I), the ketodihydrobenzthiazine, or (II), the ketotetrahydroheptabenzthiazine (R = Ph). The behaviour towards alkalis, however, is different from that recorded for the ketodihydrobenzthiazines, which, according to Unger and Graff (*Ber.*, 1897, **30**, 2387), undergo, on boiling with potash, fission of the heterocyclic ring between the -NH- and -CO- groups. Further, the compound could be shown definitely not to be a ketodihydrobenzthiazine, since it was different from the *keto*-2-*benzyldihydrobenzthiazine* (VI) we obtained, according to the general method described by Unger and Graff (*loc. cit.*) for preparing these compounds, by heating *o*-aminothiophenol with α-bromo-β-phenylpropionic acid.

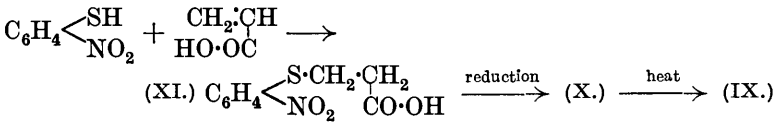
Similarly, our products from acrylic acid and crotonic acid and aminothiophenol are different from the keto-2-methyldihydrobenzthiazine and the keto-2-ethyldihydrobenzthiazine obtained by Unger and Graff from α-bromopropionic acid and α-bromobutyric acid and aminothiophenol; also we found that α-bromoglutaric acid (employed in the form of its ester) gave a different product from that obtained with glutaconic acid.

The compounds in question are therefore ketotetrahydroheptabenzthiazines of the general formula (II).

A final confirmation of the correctness of this conclusion was secured by showing that the compound got by heating aminothiophenol with acrylic acid is identical with the ε-lactam (IX) obtained by Mayer and Horst (*Ber.*, 1923, **56**, 1415) by heating β-2-aminophenylthiolpropionic acid (X), and further by the synthesis of this

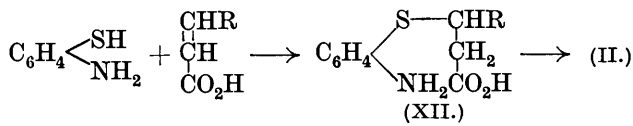


compound from *o*-nitrothiophenol and acrylic acid, as follows, the initial condensation evidently consisting in β-addition of the thiol group of the nitrothiophenol to the ethylenic linkage of the acrylic acid:



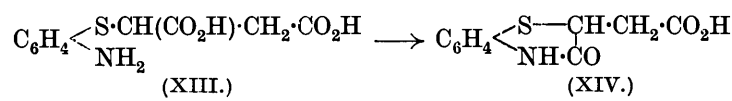
When *cinnamamidothiophenol* (IV) (see scheme on p. 2739) is heated, it is not converted into 1-styrylbenzthiazole (V) as perhaps might have been expected, but ring closure takes place through addition of the thiol group to the ethylenic linkage. The product is, however, not the original ε-lactam (III) (*keto-2-phenyltetrahydroheptabenzthiazine*), but the isomeric δ-lactam (VI) (keto-2-benzyldihydrobenzthiazine), the sulphur becoming attached to the α-carbon atom of the ethylenic linking. The tendency to the formation of a six- rather than of a seven-membered ring thus over-rides the natural tendency of the sulphur atom of the thiol group to attach itself to the β-carbon atom of the ethylenic linking (Posner, *Ber.*, 1907, **40**, 4788). It follows from this fact that, in the interaction of the αβ-unsaturated acids with *o*-aminothiophenol, of the various reactions possible that which takes place with the greatest velocity (excluding of course salt formation between the acid and base) is the addition of the thiol group to the ethylenic linking, the sulphur becoming attached to the β-carbon atom, the resulting aminophenyl-

thiolpropionic acid (XII) passing, at the temperature employed, with loss of water into its ε-lactam :



(XII.)

To test this conclusion, the interactions of *o*-aminothiophenol with maleic acid and with monobromosuccinic acid were studied. In all the other cases investigated, we have seen that a different product was obtained according as *o*-aminothiophenol was heated with a given αβ-unsaturated acid or with the corresponding α-bromo-saturated acid. In this one case, however, identical products should be formed, since in the intermediate product (XIII) arising from maleic acid there is, besides the carboxyl group to which, as in the other cases, the amino-group is in the ε-position, a second carboxyl group to which it is in the δ-position and with which it can consequently react, producing a normal six-membered ring :



(XIII.) (XIV.)

The result was as expected, the same product (*3-ketodihydrobenzthiazine-2-acetic acid*, XIV) being obtained by heating either maleic acid or monobromosuccinic acid with *o*-aminothiophenol.

If the ε-lactam (keto-2-phenyltetrahydroheptabenzthiazine, III obtained by heating *o*-aminothiophenol with cinnamic acid is heated to 240—260°, water is eliminated and there is formed, although not very smoothly, 1-styrylbenzthiazole (V). This explains why Hofmann (*Ber.*, 1880, **13**, 1235) had obtained from *o*-aminothiophenol and cinnamic acid this benzthiazole derivative, whilst we had found the product of the reaction to be the ε-lactam; we had worked at 160—170°, whereas Hofmann had heated the mixture on a sand-bath. Hofmann's procedure does not, however, provide an advantageous method for preparing the benzthiazole base : it can be much more readily prepared by treating *o*-aminothiophenol (or, better, its sodium salt) with cinnamoyl chloride in the cold On the other hand, we found that the corresponding saturated acid, β-phenylpropionic acid, reacted readily with *o*-aminothiophenol to give phenylethylbenzthiazole.

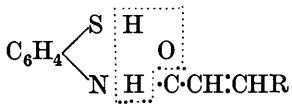
If *o*-aminothiophenol is heated with ethyl cinnamate instead of with cinnamic acid, a higher temperature has to be employed to bring about reaction, and the product is then the δ-lactam (keto-2-benzyldihydrobenzthiazine, VI).

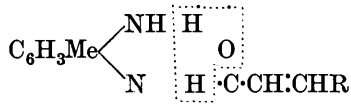
Thus, according as *o*-aminothiophenol is heated with cinnamic

acid, its ester, or its chloride, three different heterocyclic compounds are obtained.

o-Aminothiophenol —(cinnamic acid)→ Ketophenyltetrahydroheptabenzthiazine (III).
o-Aminothiophenol —(ethyl cinnamate)→ Ketobenzyldihydrobenzthiazine (VI).
o-Aminothiophenol —(cinnamoyl chloride)→ Styrylbenzthiazole (V).

The non-formation of a benzthiazole base when *o*-cinnamamidothiophenol (IV) is heated, or when ethyl cinnamate is heated with *o*-aminothiophenol, shows that the attachment of a $-CH{:}CHR$ group, instead of a saturated system, to the carbon of the $-CO{\cdot}NH-$ group in *N*-acyl derivatives of *o*-aminothiophenol makes the elimination of water in the manner shown more difficult.





The corresponding phenomenon was observed by Fichter (*J. pr. Chem.*, 1906, **74**, 316) with the crotonyl and dimethylacrylyl derivatives of 1 : 3 : 4-tolylenediamine.

The ketotetrahydroheptabenzthiazines are readily acetylated when boiled with acetic anhydride. This was also observed by Mayer and Horst, who found (*loc. cit.*) that their ε-lactam reacted easily with acetic anhydride. However, they assigned to the product the formula (XV), which is at variance with the composition we find for it and for the two corresponding derivatives which we have obtained from our analogous ε-lactams; the molecule is actually less by the elements of a molecule of water than this formula indicates. It is also at variance with the chemical character of the compounds: they are neutral and unaffected by cold

(XV.) $C_6H_4\langle^{S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}_{NHAc}$ $C_6H_4\langle^{S--CHR}_{NAc{\cdot}CO}\rangle CH_2$ (XVI.)

$C_6H_4\langle^{S{\cdot}CH_3}_{NH{\cdot}CO}\rangle CH_3$ (XVII.)

sodium carbonate solution. Since, moreover, the acetyl group is readily eliminated on warming with dilute hydrochloric acid or sodium carbonate with regeneration of the original lactam, the constitution of these acetyl derivatives is clearly that represented by (XVI). Their ready formation is in accordance with the fact observed by Ulffers and von Janson (*Ber.*, 1894, **27**, 93) and by Sudborough (J., 1901, **79**, 533) that diacetylation of a primary aromatic amine is particularly easy when there is another substituent group in the ortho-position to the amino-group. These ε-lactams are closely related in constitution to *o*-acetamidothio-

anisole (XVII) (linking of the two methyl groups in which, with removal of two atoms of hydrogen, would yield the ε-lactam of Mayer and Horst), and Mr. G. E. Watts, working in this laboratory, found that *o*-aminothioanisole is readily converted into a diacetyl derivative when heated with acetic anhydride.

An interesting alternation in properties exists between the γ-, δ-, and ε-lactams, benzthiazolone (XVIII), ketodihydrobenzthiazine (XIX), and ketotetrahydroheptabenzthiazine (IX), with respect to

(XVIII.) $C_6H_4\langle{}^{S-}_{NH}\rangle CO$ $\qquad\qquad$ $C_6H_4\langle{}^{S—CH_2}_{NH\cdot CO}$ (XIX.)

acetylation. Benzthiazolone (for which a new method of preparation is described in the experimental part) and, as has been stated, the ε-lactam (IX) are readily acetylated when boiled with acetic anhydride, whilst ketodihydrobenzthiazine is not (Unger and Graff, *loc. cit.*).

EXPERIMENTAL.

I. *Glutaconic Acid and* o-*Aminothiophenol.*

4-Ketotetrahydro-1 : 5-heptabenzthiazine-2-acetic Acid (II; R = $CH_2\cdot CO_2H$).—A mixture of glutaconic acid (2·5 g.) and *o*-aminothiophenol (2·5 g.; 1 mol.) was heated in an atmosphere of carbon dioxide at 120—130° for 20 minutes. A vigorous reaction occurred and after a few minutes the whole had set to a crystalline mass, which, recrystallised from dilute alcohol or water, yielded the pure product as thin, colourless, silky needles, m. p. 235—236° (decomp.). Yield, 4 g. (84·4%) (Found : C, 55·5; H, 4·6. $C_{11}H_{11}O_3NS$ requires C, 55·7; H, 4·6%).

The compound dissolves readily in dilute aqueous sodium carbonate and can be sharply titrated against sodium hydroxide and phenolphthalein [0·2607 g. required 11·1 c.c. *N*/10-NaOH. Found : *M*, 234·8 (monobasic). $C_{11}H_{11}O_3NS$ requires *M*, 237]. It has no marked basic properties, dissolving in hot, concentrated hydrochloric acid and crystallising unchanged on cooling. It is soluble in acetone or glacial acetic acid, sparingly soluble in ether, and practically insoluble in benzene, ligroin, or chloroform.

The *ethyl* ester was prepared by keeping the acid (1 g.) in excess of cold, absolute alcohol, containing dry hydrogen chloride, for 24 hours; when the resulting solution was diluted, and neutralised with sodium carbonate, the *ester* separated in small, lustrous, colourless needles (0·8 g.), which, after recrystallisation from benzene–ligroin, melted at 139—140° (Found : C, 58·7; H, 5·7. $C_{13}H_{15}O_3NS$ requires C, 58·9; H, 5·7%). It is readily soluble in alcohol, ether, or benzene, and sparingly soluble in ligroin.

The ester was also obtained directly from ethyl glutaconate: A mixture of ethyl glutaconate (1 mol.) and *o*-aminothiophenol (1 mol.) was heated under reflux, in an atmosphere of carbon dioxide, at 160—180° for 3 hours; a brown gum was then obtained, from which some crystals separated on standing. The crystalline product was extracted from the gum with hot ligroin, from which it separated on cooling in small, colourless, glistening needles, m. p. 138—140°. A mixture with the ester prepared as described above melted at 139—140°.

Resolution of 4-*Ketotetrahydro*-1 : 5-*heptabenzthiazine*-2-*acetic Acid into Optically Active Components.*—d-4-*Ketotetrahydro*-1 : 5-*heptabenzthiazine*-2-*acetic acid.* From a solution of the *dl*-acid (4·7 g.) and anhydrous brucine (7·9 g.) in warm alcohol (60 c.c.) the brucine salt was rapidly deposited in small, soft, colourless needles. After cooling, the salt was collected and recrystallised three times from alcohol; its specific rotation then became constant. The l-*brucine* d-4-*ketotetrahydro*-1 : 5-*heptabenzthiazine*-2-*acetate* so obtained gave m. p. 164—165° (softening at 155°) and $[\alpha]^{20°}_{5461}$ +154·7° in aqueous solution ($l = 2$; $c = 0{\cdot}527$). On decomposition of this salt with cold, dilute hydrochloric acid, the d-*acid* was deposited in fine, colourless needles, which on recrystallisation from alcohol gave the pure *d*-acid (1 g.), m. p. 230° and $[\alpha]^{20°}_{5780}$ +436·9°, $[\alpha]^{20°}_{5461}$ +506°, $[\alpha]^{20°}_{4359}$ +981° in absolute ethyl alcohol ($l = 2$; $c = 0{\cdot}6008$) (Found: C, 56·0; H, 4·7. $C_{11}H_{11}O_3NS$ requires C, 55·7; H, 4·6%).

Ethyl d-4-*ketotetrahydro*-1 : 5-*heptabenzthiazine*-2-*acetate* was obtained by treating the pure *d*-acid with cold alcoholic hydrogen chloride. It separated from benzene–ligroin in short, thin, colourless needles, m. p. 145—146° and $[\alpha]^{20°}_{5780}$ +424·5°, $[\alpha]^{20°}_{5461}$ +491·7°, $[\alpha]^{20°}_{4359}$ +948·8° in absolute alcohol ($l = 2$; $c = 0{\cdot}5512$).

1-4-*Ketotetrahydro*-1 : 5-*heptabenzthiazine*-2-*acetic acid.* The crude *l*-acid (1·7 g.), recovered from the mother-liquor of the above described brucine salt, and cinchonine (2·2 g.), were dissolved in alcohol (12 c.c.). After the addition of ether, the cinchonine salt gradually separated in small, colourless prisms, which were recrystallised twice from aqueous alcohol; m. p. 193—195° (softening at 175—180°). This salt, decomposed with cold, dilute hydrochloric acid, gave the pure l-*acid* (0·5 g.) in microscopic, colourless needles, m. p. 229—230° and $[\alpha]^{20°}_{5780}$ −435·5°, $[\alpha]^{20°}_{5461}$ −505°, $[\alpha]^{20°}_{4359}$ −976° in absolute ethyl alcohol ($l = 2$; $c = 0{\cdot}6004$).

Ethyl 3-*Keto*-2 : 3-*dihydro*-1 : 4-*benzthiazine*-2-*propionate* (I; R = $CH_2{\cdot}CO_2Et$).—This compound was synthesised for comparison with the compound obtained from *o*-aminothiophenol and glutaconic acid. It melts at 91°, whilst the isomeric ethyl ketotetrahydro-1 : 5-heptabenzthiazine-2-acetate melts at 139—140°.

o-Aminothiophenol (3·4 g.; 2 mols.) and ethyl α-bromoglutarate (3·2 g.) were heated together under reflux, in an atmosphere of carbon dioxide, at 120—130° for an hour; a brisk reaction then occurred with elimination of alcohol and formation of a crystalline material (hydrobromide). The crude product was extracted with hot ligroin, from which *ethyl* 3-*keto*-2 : 3-*dihydro*-1 : 4-*benzthiazine*-2-*propionate* separated in small, colourless, silky needles; these, after recrystallisation from ligroin, melted at 91° (Found: C, 58·8; H, 5·6. $C_{13}H_{15}O_3NS$ requires C, 58·9; H, 5·7%). The residue remaining after the extraction of the ester consisted of the hydrobromide of *oo'*-diaminodiphenyl disulphide. On hydrolysis of the ester, 3-keto-2 : 3-dihydro-1 : 4-benzthiazine-2-propionic acid was obtained in colourless needles, m. p. 174—175°.

II. *Cinnamic Acid and o-Aminothiophenol.*

4-*Keto*-2-*phenyltetrahydro*-1 : 5-*heptabenzthiazine* (III).—A mixture of *o*-aminothiophenol (8 g.) and cinnamic acid (10 g.) was heated for 2 hours under reflux, in an atmosphere of carbon dioxide, at 160—170°; a vigorous reaction then set in with elimination of water. On cooling, the product set to a hard, reddish-brown mass which, on crystallisation from alcohol, yielded 4-*keto*-2-*phenyltetrahydro*-1 : 5-*heptabenzthiazine* in short, colourless, silky needles, m. p. 177°. Yield 11 g. (Found: C, 70·5; H, 5·0. $C_{15}H_{13}ONS$ requires C, 70·6; H, 5·1%).

The compound is soluble in chloroform, acetone, or glacial acetic acid, sparingly soluble in ether or benzene, and insoluble in water. It dissolves in hot concentrated hydrochloric acid and separates from the solution unchanged on cooling.

The *acetyl* derivative (XVI; R = Ph) was obtained by boiling the substance with excess of acetic anhydride for 15 minutes. It crystallised from alcohol in short, glistening, colourless needles, m. p. 155—156° (Found: C, 68·2; H, 5·0. $C_{17}H_{15}O_2NS$ requires C, 68·7; H, 5·0%). It is readily hydrolysed by warming on the water-bath with dilute hydrochloric acid, giving the original material.

The Sulphoxide, $C_6H_4<^{SO\cdot CHPh}_{NH—CO}>CH_2$.—To a solution of the heptabenzthiazine (0·6 g.) in warm acetone (15 c.c.), a 4% solution of potassium permanganate in aqueous acetone was added until in slight excess, together with a little dilute sulphuric acid. The mixture was then boiled and filtered hot and the residue was extracted with hot acetone. The almost pure *sulphoxide* separated from the filtrate and was collected after dilution with water and cooling. It separated from acetone–alcohol or from dilute acetic

acid in clusters of thin, silky needles, m. p. 210° (Found: C, 66·4; H, 4·8. $C_{15}H_{13}O_2NS$ requires C, 66·4; H, 4·8%).

The sulphoxide is soluble in glacial acetic acid, sparingly soluble in alcohol or ether, and insoluble in water. It can also be obtained, in an almost pure condition, by treating the heptabenzthiazine with hydrogen peroxide (30%) in cold glacial acetic acid solution and diluting the mixture with water after several hours.

The Sulphone.—To a solution of the heptabenzthiazine (0·7 g.) in glacial acetic acid (10 c.c.), excess of 5% aqueous potassium permanganate (20 c.c.) was slowly added at room temperature, with stirring. The *sulphone* soon began to separate from the solution and after an hour the product was collected and recrystallised from dilute acetic acid, the solution being decolorised by charcoal. It was thus obtained in short, colourless, glistening needles, m. p. 234—235° (Found: C, 62·6; H, 4·6. $C_{15}H_{13}O_3NS$ requires C, 62·7; H, 4·5%).

The sulphone is moderately easily soluble in glacial acetic acid, sparingly soluble in alcohol or benzene, and insoluble in light petroleum, chloroform, or water. It is also formed when the heptabenzthiazine is oxidised by chromic acid in boiling glacial acetic acid solution.

Action of Alkali on 4-*Keto*-2-*phenyltetrahydro*-1 : 5-*heptabenzthiazine*: *Formation of* o-*Cinnamamidothiophenol* (IV).—When the heptabenzthiazine is heated for some time with excess of dilute caustic alkali solution, complete hydrolysis takes place into cinnamic acid and *o*-aminothiophenol. When, however, it is carefully heated with a small excess of caustic alkali, the product is o-*cinnamamidothiophenol.*

4-Keto-2-phenyltetrahydro-1 : 5-heptabenzthiazine (4 g.) was heated with 10% caustic potash solution (40 c.c.) and a little alcohol (8 c.c.) under reflux for 20—30 minutes, a deep yellow solution being obtained. After cooling, this was diluted with water and treated with carbon dioxide; *o*-cinnamamidothiophenol was then precipitated as a faintly yellowish-white, pasty mass. It crystallised from alcohol in clusters of small, almost colourless needles, m. p. 147—148°. Yield, 2 g. (Found: C, 70·6; H, 5·2. $C_{15}H_{13}ONS$ requires C, 70·6; H, 5·1%).

o-Cinnamamidothiophenol is readily soluble in acetone, chloroform, or benzene, and moderately easily soluble in ether or ligroin. It dissolves in caustic soda and slowly in sodium carbonate, giving yellow solutions, from which it is precipitated on acidification. It is readily oxidised to the corresponding disulphide by means of iodine, hydrogen peroxide or ferric chloride, or by exposure to the air.

The *mercurichloride* is precipitated when an alcoholic solution of the cinnamamidothiophenol is treated with aqueous mercuric chloride. It crystallises from alcohol, in which it is only sparingly soluble, in fine, colourless needles, m. p. 211—212°.

Conversion of o-*Cinnamamidothiophenol into* 3-*Keto*-2-*benzyl*-2 : 3-*dihydro*-1 : 4-*benzthiazine* (VI).—*o*-Cinnamamidothiophenol was heated in an atmosphere of dry carbon dioxide at 165—170° for 4—6 hours. The resulting dark, viscous liquid set, on cooling, to a hard, glassy mass, which was powdered and extracted with ether. The colourless, crystalline residue separated from alcohol in clusters of small, yellowish-white, silky needles. It proved to be 3-keto-2-benzyldihydro-1 : 4-benzthiazine and melted, alone or mixed with a specimen synthesised from α-bromo-β-phenylpropionic acid and *o*-aminothiophenol (see below), at 159—160°.

oo′-*Dicinnamamidodiphenyl Disulphide* (VIII).—(a) *From* o-*cinnamamidothiophenol.* From a solution of *o*-cinnamamidothiophenol (1 g.) in cold acetone (30 c.c.) to which excess of 30% hydrogen peroxide (2—3 c.c.) had been added, the *disulphide* soon separated as a mass of colourless, silky needles, which, after recrystallisation from acetone or glacial acetic acid, and when mixed with the pure disulphide synthesised as described below, melted at 163—164° (Found: C, 70·9; H, 4·8. $C_{30}H_{24}O_2N_2S_2$ requires C, 70·9; H, 4·7%).

(b) *From* oo′-*diaminodiphenyl disulphide* (VII). A solution of cinnamoyl chloride (2·6 g.) in dry benzene was gradually added to a solution of *oo′*-diaminodiphenyl disulphide (3·9 g.) in the same solvent. After 30 minutes, the pasty product was collected and treated with warm alcohol to remove the hydrochloride of the diaminodiphenyl disulphide, and the residue was crystallised from glacial acetic acid; pure *oo′*-dicinnamamidodiphenyl disulphide then separated in colourless, silky needles, m. p. 163—164° (Found: C, 71·0; H, 4·8%).

The disulphide is readily soluble in chloroform or hot benzene, sparingly soluble in alcohol, and insoluble in light petroleum.

Bromo-derivative. To a solution of *oo′*-dicinnamamidodiphenyl disulphide (0·5 g.) in dry chloroform (12 c.c.), a 10% solution of bromine in dry chloroform (6 c.c.) was gradually added; a colourless, pasty solid was then precipitated. After being washed with chloroform, this crystallised from acetone in small, glistening, colourless plates (0·4 g.), which darkened at 205° and melted at 213° (decomp.) (Found: C, 54·2; H, 3·6; Br, 23·8.

$C_{30}H_{24}O_2N_2Br_2S_2$

requires C, 53·9; H, 3·6; Br, 24·0%).

3-*Keto*-2-*benzyl*-2 : 3-*dihydro*-1 : 4-*benzthiazine* (VI).—(a) *From* α-*bromo*-β-*phenylpropionic acid.* A mixture of α-bromo-β-phenyl-

propionic acid (2·5 g.) and *o*-aminothiophenol (2 g.) was heated in an atmosphere of carbon dioxide at 125—130°; a vigorous reaction then set in and was complete after about 20 minutes. The crude product was crystallised twice from alcohol, pure 3-*keto*-2-*benzyl*-2 : 3-*dihydro*-1 : 4-*benzthiazine* being obtained in short, colourless, silky needles, m. p. 159—160° (1·6 g.) (Found: C, 70·3; H, 5·1. $C_{13}H_{15}ONS$ requires C, 70·6; H, 5·1%). This substance is readily soluble in acetone, chloroform, benzene, or glacial acetic acid and moderately easily soluble in ligroin or ether. It is insoluble in concentrated hydrochloric acid and in dilute caustic soda solution, but it dissolves in cold, concentrated sulphuric acid to a yellow solution, from which it is precipitated unchanged by water. It does not form an acetyl derivative.

(b) *From ethyl cinnamate.* A mixture of ethyl cinnamate (3 g.) and *o*-aminothiophenol (2 g.) was heated under reflux in an atmosphere of carbon dioxide at 230—240° for 4—5 hours. The crude product was a deep red, oily liquid, which, on treatment with ether, yielded a pale yellow, crystalline solid. Recrystallised from alcohol, this separated in small, faintly yellow, silky needles, m. p. and "mixed m. p." with pure 3-keto-2-benzyldihydro-1 : 4-benzthiazine synthesised as above, 159—160° (Found: C, 70·5; H, 5·0%).

1-*Styrylbenzthiazole* (V).—(a) *From cinnamoyl chloride.* The condensation of cinnamoyl chloride with *o*-aminothiophenol takes place readily in cold benzene solution, but the following method, using the sodium salt of the aminothiophenol, is more satisfactory.

To a solution of *o*-aminothiophenol (1·3 g.) and sodium (0·23 g.) in absolute alcohol (12 c.c.), cinnamoyl chloride (1·6 g.) was gradually added, the mixture warmed on the water-bath for a few minutes, and the solution filtered from the precipitated sodium chloride and concentrated. On cooling, 1-*styrylbenzthiazole* was deposited from the solution and on recrystallisation from alcohol it separated in short, thick, colourless prisms (1 g.), m. p. 112—113° (Found: C, 75·7; H, 4·8. $C_{15}H_{11}NS$ requires C, 75·9; H, 4·6%).

The *picrate* crystallised from alcohol, in which it is only sparingly soluble, in bright yellow platelets, m. p. 195—196°.

(b) *From* 4-*keto*-2-*phenyltetrahydro*-1 : 5-*heptabenzthiazine.* The thiazine was heated at 240—260° for about an hour; water was evolved and the fused mass changed to a dark brown gum, which set to a hard solid. This was crystallised twice from alcohol (charcoal) and 1-styrylbenzthiazole was then obtained in short, colourless prisms. These, alone or mixed with the pure base obtained by method (a), melted at 112—113°. The yield was poor.

(c) *From cinnamic acid* (compare Hofmann, *Ber.*, 1880, **13**, 1235).

Cinnamic acid (2 g.) and *o*-aminothiophenol (1·8 g.) were heated together at 210—220° for about 2 hours; a dark-coloured gum was obtained which was difficult to purify. On treatment with picric acid in alcoholic solution, however, the picrate of the benzthiazole base was precipitated, and after crystallisation from alcohol (charcoal), this was obtained in bright yellow platelets (1 g.), m. p. 195—196° (Found: C, 54·3; H, 2·9. $C_{21}H_{14}O_7N_4S$ requires C, 54·1; H, 3·0%).

The base was also obtained in small yield by heating together cinnamic acid and aminothiophenol at a higher temperature and treating the crude product with alkali, according to Hofmann's method. Its formation did not readily take place below about 220°.

β-*Phenylpropionic Acid and* o-*Aminothiophenol:* 1-β-*Phenylethylbenzthiazole.*—A mixture of β-phenylpropionic acid (1 mol.) and *o*-aminothiophenol (1 mol.) was heated under reflux in an atmosphere of carbon dioxide at 160—170° for 2 hours. The crude product was heated for a short time on the water-bath with 10% caustic soda solution; the yellow oil obtained solidified on cooling, and on crystallisation from dilute alcohol it yielded 1-β-*phenylethylbenzthiazole* in lustrous, colourless platelets, m. p. 60—61° (Found: C, 75·4; H, 5·5. $C_{15}H_{13}NS$ requires C, 75·3; H, 5·4%). The base is moderately easily soluble in cold alcohol and readily soluble in ether.

The *picrate* separates from alcohol in small, bright yellow plates, m. p. 132—133°.

III. *Crotonic Acid and* o-*Aminothiophenol.*

4-*Keto*-2-*methyltetrahydro*-1 : 5-*heptabenzthiazine* (II; R = Me).—A mixture of crotonic acid (1·3 g.) and *o*-aminothiophenol (1·8 g.) was heated in an atmosphere of carbon dioxide at 165—170° for 20 minutes. A vigorous reaction then occurred and the whole set to a crystalline mass, which, recrystallised from alcohol, yielded pure 4-*keto*-2-*methyltetrahydro*-1 : 5-*heptabenzthiazine* in small, granular, colourless plates (2 g.), m. p. 205—206° (Found: C, 61·9; H, 5·6. $C_{10}H_{11}ONS$ requires C, 62·2; H, 5·7%).

The compound is soluble in glacial acetic acid, benzene, or ligroin, and sparingly soluble in ether. It crystallises from chloroform in thin needles.

The *acetyl* derivative (XVI; R = Me) was obtained by boiling the substance with excess of acetic anhydride for 10 minutes, and separated from dilute alcohol in thin, colourless, glistening needles, m. p. 93° (Found: C, 60·9; H, 5·5. $C_{12}H_{13}O_2NS$ requires C, 61·3; H, 5·5%). It is readily hydrolysed by warming on the water-bath with dilute hydrochloric acid or sodium carbonate for a short time,

giving the original material (m. p. 205—206°). It is moderately easily soluble in alcohol and readily soluble in ether.

IV. *Acrylic Acid and* o-*Aminothiophenol.*

4-*Ketotetrahydro*-1 : 5-*heptabenzthiazine* (IX).—Acrylic acid (2 g.) and *o*-aminothiophenol (3·5 g.) were heated together in an atmosphere of carbon dioxide at 125—130° for about an hour. The crystalline product was washed with ether and recrystallised from dilute alcohol, from which 4-*ketotetrahydro*-1 : 5-*heptabenzthiazine* separated in small, lustrous, colourless needles (1·3 g.), m. p. 215—216° (Found: C, 60·5; H, 5·1. C_9H_9ONS requires C, 60·3; H, 5·0%). The compound is readily soluble in acetone or glacial acetic acid, sparingly soluble in benzene, and practically insoluble in ether, chloroform, or light petroleum.

The *acetyl* derivative (XVI; R = H) was obtained by boiling the compound with excess of acetic anhydride for 15 minutes. It crystallised from alcohol in small, colourless needles, m. p. 96—97° (Found: C, 59·8; H, 5·0; N, 6·3; S, 14·4. $C_{11}H_{11}O_2NS$ requires C, 59·7; H, 5·0; N, 6·3; S, 14·5%). It is hydrolysed by warm dilute hydrochloric acid, yielding the original material.

Synthesis of 4-*Ketotetrahydro*-1 : 5-*heptabenzthiazine* (IX) *from Acrylic Acid and* o-*Nitrothiophenol.*—The *o*-nitrothiophenol was obtained by reduction of *oo'*-dinitrodiphenyl disulphide by means of sodium sulphide (Claasz, *Ber.*, 1912, **45**, 747) and isolated from the solution by means of dilute acetic acid. It crystallised from light petroleum in pale yellow needles, m. p. 61°.

Addition of o-*nitrothiophenol to acrylic acid:* o-*Nitrophenylthiolpropionic acid* (XI). *o*-Nitrothiophenol (5·2 g.) and acrylic acid (2·4 g.) were together dissolved in dry benzene (25 c.c.) with the addition of 2—3 drops of piperidine, and the solution kept for 48 hours (compare Ruhemann, J., 1905, **87**, 17); o-*nitrophenylthiolpropionic acid* gradually separated in yellow crystals. Recrystallised from glacial acetic acid, it formed short, yellow needles (4 g.), m. p. 148—149° (Found: C, 47·7; H, 4·0. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0%).

o-*Aminophenylthiolpropionic acid* (X). A mixture of *o*-nitrophenylthiolpropionic acid (4·5 g.), concentrated hydrochloric acid (15 g.), and tin (7·1 g.) was heated on the water-bath until the reduction was complete. The solution was then largely diluted with water, treated with hydrogen sulphide to precipitate the tin, and concentrated by evaporation in a vacuum. On cooling, the hydrochloride of *o*-aminophenylthiolpropionic acid separated in short, colourless needles, m. p. 173—174°, which soon became coloured on standing.

On treating the hydrochloride (1·2 g.) in concentrated aqueous solution with *N*-sodium hydroxide (5 c.c.), the *amino-acid* was obtained in colourless crystals (0·8 g.), which separated from dilute alcohol in short, thick needles, m. p. 87—88° (Found: C, 54·8; H, 5·7. $C_9H_{11}O_2NS$ requires C, 54·8; H, 5·6%) (compare Mayer and Horst, *loc. cit.*).

4-*Ketotetrahydro*-1 : 5-*heptabenzthiazine.* The hydrochloride of *o*-aminophenylthiolpropionic acid (1·5 g.) was heated at 180—190° for ½ hour, hydrogen chloride and water being eliminated. On cooling, the product set to a reddish-brown solid, which, crystallised from alcohol, yielded pure ketotetrahydro-1 : 5-heptabenzthiazine (0·2 g.) in lustrous, colourless needles, m. p. and "mixed m. p." with the lactam synthesised from acrylic acid and *o*-aminothiophenol, 215—216°.

The acetyl derivative of the lactam was obtained on heating the above hydrochloride with excess of acetic anhydride for 30 minutes.

V. *Maleic Acid and* o-*Aminothiophenol.*

3-*Keto*-2 : 3-*dihydro*-1 : 4-*benzthiazine*-2-*acetic Acid* (XIV).—Maleic acid (3·5 g.) and *o*-aminothiophenol (3 g.), when mixed, reacted readily with considerable development of heat and the whole soon set to a hard mass. After being heated for a few minutes at 100—110°, the product was crystallised from dilute alcohol, from which it separated in small, colourless needles, melting at 195—196°, and at the same temperature after mixture with pure 3-*keto*-2 : 3-*dihydro*-1 : 4-*benzthiazine*-2-*acetic acid* synthesised from *o*-aminothiophenol and monobromosuccinic acid (see below). Yield 5 g. (93·5%) (Found: C, 53·6; H, 4·0. $C_{10}H_9O_3NS$ requires C, 53·8; H, 4·0%).

The compound is soluble in alcohol, sparingly soluble in ether, and practically insoluble in benzene, chloroform, or ligroin. It crystallises from water in thin, silky needles. It dissolves readily in cold, dilute sodium carbonate solution and is precipitated on acidification. After boiling for some time with 10% caustic potash solution it was precipitated unchanged on acidification.

The same product was obtained from fumaric acid and *o*-aminothiophenol. In this case no reaction appeared to take place in the cold, but the compound was readily formed on heating the two substances together at 150—160° for 15 minutes.

3-*Keto*-2 : 3-*dihydro*-1 : 4-*benzthiazine*-2-*acetic Acid from Monobromosuccinic Acid.*—Monobromosuccinic acid (1 g.) and *o*-aminothiophenol (0·6 g.) were heated together in an atmosphere of carbon dioxide at 120—125° for 15 minutes; a vigorous reaction then occurred and the mixture soon set to a solid mass. The product

was crystallised twice from dilute alcohol (charcoal) and pure keto-dihydrobenzthiazineacetic acid was thus obtained in small, colourless needles (0·6 g.), m. p. 195—196° (Found : C, 54·2; H, 4·0%).

The following work was kindly carried out by Mr. G. E. WATTS :

Diacetyl Derivative of o-*Aminothioanisole.*—*o*-Aminothioanisole (10 g.) was boiled with acetic anhydride (30 g.; 4 mols.) for an hour. The resulting solution was distilled in a vacuum to remove acetic acid and anhydride, and the residual gum crystallised from alcohol, from which the *diacetyl* derivative separated in colourless, transparent prisms, m. p. 69—70°. Yield, 13 g. (82%) (Found : C, 59·1; H, 5·9; N, 6·1. $C_{11}H_{13}O_2NS$ requires C, 59·2; H, 5·8; N, 6·3%).

Preparation of Benzthiazolone (XVIII).—*Ethyl* o-*nitrophenylthiolformate*, $NO_2 \cdot C_6H_4 \cdot S \cdot CO_2Et$. To a solution (deep red) of *o*-nitrothiophenol (31 g.) in alcoholic sodium hydroxide (8 g. of NaOH in 30 c.c. of alcohol) a solution of ethyl chloroformate (21·7 g.) in alcohol (20 c.c.) was added, with shaking; the red colour of the nitrothiophenol soon disappeared, considerable heat was evolved, and sodium chloride was precipitated. The mixture was poured into water (500 c.c.) and the ethyl nitrophenylthiolformate, which separated as a yellow oil, was extracted with ether. It decomposed when heated in a vacuum.

Ethyl o-*aminophenylthiolformate.* Crude ethyl nitrophenylthiolformate (35 g.), mixed with alcohol (20 c.c.), was shaken with a solution of stannous chloride (115 g.) in concentrated hydrochloric acid (50 c.c.) for an hour, the mixture being cooled in ice from time to time. The solution was diluted, freed from tin by means of hydrogen sulphide, made alkaline with sodium bicarbonate, and extracted with ether. On removal of the ether the amino-ester remained as a colourless oil. Yield, 20 g. (67%).

The *hydrochloride* of the amino-ester was prepared by treating an alcoholic solution of the ester with hydrogen chloride and precipitated by the addition of ether. It crystallised from alcohol–ether in fine, colourless needles, m. p. 120—122° (Found : Cl, 15·2. $C_9H_{12}O_2NClS$ requires Cl, 15·2%).

Benzthiazolone. Ethyl *o*-aminophenylthiolformate, mixed with a little of its hydrochloride, was heated at 115° for 2 hours; it then changed to a crystalline mass. This, recrystallised from aqueous alcohol, gave colourless needles of benzthiazolone; they melted at 128° and were readily soluble in strong alkalis and in strong mineral acids (compare Claasz, *Ber.*, 1912, **45**, 1029).

The acetyl derivative was obtained by boiling the substance with excess of acetic anhydride for 15 minutes. It separated from aqueous alcohol in fine, colourless needles, m. p. 50° (compare Claasz,

loc. cit.), and was readily hydrolysed by warm 10% sodium hydroxide solution, giving the original material.

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