The Disproportionation of Di-[2-(N-2′-aminobenzylformamido)propenyl] Disulphide.

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A 2-aminobenzyl analogue of thiamine disulphide has been prepared and its disproportionation in heated hydroxylic solvents studied. Its breakdown exactly parallels that of thiamine disulphide, yielding a thiochrome analogue and a thiamine thiazol-2-one (Sykes and Todd, *J.*, 1951, 534) analogue; both of these have been synthesised.

In previous papers (Sykes and Todd, *J.*, 1951, 534; Sykes, *Angew. Chem.*, 1954, **66**, 452), a mechanism was suggested for the disproportionation of thiamine disulphide, in hot, high-boiling hydroxylic solvents, to thiochrome and thiamine thiazol-2-one, and evidence has been adduced in its support. Thiamine disulphide was the only case in which such a disproportionation had been observed and, as much of the evidence turned on the resistance to breakdown exhibited by suitably substituted disulphides (Nesbitt and Sykes, *J.*, 1954, 4581), further confirmation was sought by studying another disulphide, di-[2-(*N*-2′-aminobenzylformamido)propenyl] disulphide (II), in which groups believed to be essential for the ready occurrence of disproportionation were present.

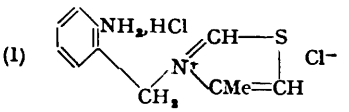
3-2′-Aminobenzyl-4-methylthiazolium chloride hydrochloride (I) was converted into the disulphide (II) by oxidation in alkaline solution with iodine or hydrogen peroxide, though the latter leads to some simultaneous attack on the benzene nucleus. This compound, like several other disulphides derived from thiazolium derivatives, retains a wide variety of solvents of crystallisation most tenaciously.

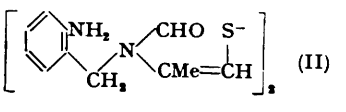
When a solution of the disulphide (II) was refluxed in *iso*butanol, the colour darkened and decomposition took place. It proved impossible to separate the fragments by fractional crystallisation, so the mixture was treated with phenyl *iso*cyanate to render neutral any product still containing an amino-group. Separation with hydrochloric acid then led to the isolation of 3′ : 4′-dihydro-4-methylquinazolino(2′ : 3′-2 : 3)thiazole (III) (the analogue of thiochrome) and 3-2′-phenylureidobenzyl-4-methylthiazol-2-one (IV; R = NH·CO·NHPh, X = O) (the phenyl *iso*cyanate derivative of the analogue of thiamine thiazol-2-one). For comparison both of these compounds were synthesised.

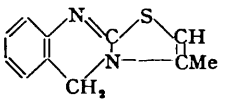
A suitable starting material for the thiazolone (IV) was 2-cyanocarbanilide (V; R = CN) which was to be converted into the amine (V; R = CH_2·NH_2) and thence into the thiazol-2-one (cf. Sykes, *J.*, 1951, 2507). Hydrogenation of a very dilute solution of the cyanide in propan-2-ol (cf. Nesbitt and Sykes, *J.*, 1954, 3057) in the presence of Raney nickel led only to the corresponding secondary amine, and there was no uptake of hydrogen in the presence of platinum or palladium–charcoal catalysts in glacial acetic acid, alone or containing acetic anhydride. Attempted hydrogenation in the presence of anhydrous ammonia yielded the cyclised product (VI; R = Ph, R′ = NH, X = O), there being no reduction. This ring-closure takes place extremely rapidly in the cold in the presence of

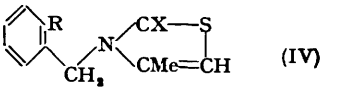
a trace of basic catalyst. Attempted reduction with acid reducing agents yielded only the quinazoline-dione (VI; R = Ph, R' = X = O), presumably through initial hydrolysis of the cyano-group.

It is not possible to carry out the desired series of reactions with 2-aminobenzylamine owing to the preferential formation of tetrahydroquinazoline derivatives. Reaction of



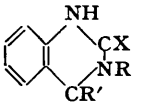






2-nitrobenzylamine, however, with carbon oxysulphide in the presence of one equivalent of alkali, followed by shaking with chloroacetone, led to the separation, apparently, of the thiolcarbamate (VII; R = NO_2, R' = CH_2Ac, X = O) (a small amount of di-2-nitrobenzylurea is obtained as a by-product in the first stage). Replacement of carbon oxysulphide by carbon disulphide apparently yielded the corresponding dithiocarbamate (VII; R = NO_2, R' = CH_2Ac, X = S). Both these compounds exhibited no ketonic properties,

(V)



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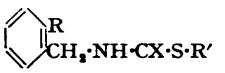
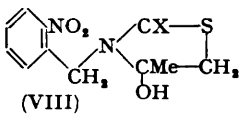


(VII)



(VIII)

however, and the infrared spectrum of the supposed dithiocarbamate showed no carbonyl absorption; it did, however, exhibit a hydroxyl band. The infrared spectrum of the supposed thiolcarbamate did show a carbonyl band at 6·03 μ but this is more characteristic of a substituted amide than of a simple ketonic group, as is confirmed by the similar absorption at 6·09 μ of the thiolcarbamate of unequivocal structure (VII; R = H, R' = $CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, X = O) prepared for comparison. The slight shift of the band is not unexpected in that the carbon atom adjacent to nitrogen in the structure (VIII; X = O) is electronegative, making the nitrogen atom less basic than in the model (VII) and resulting in electron transfer to the adjacent CO group, thereby increasing the contribution made by the $>C^+-O^-$ structure, which would be expected to lead to a slight shift in the observed direction. Thus the two supposed thiocarbamates have, not the expected structure (VII; R = NO_2, R' = CH_2Ac, X = O or S), but the cyclic formula (VIII; X = O or S) (cf. Yoshida, *Pharm. Bull.*, 1954, **2**, 249). Attempts to form a derivative from the tertiary hydroxyl group of the thiazolid-2-thione with phenyl *iso*cyanate were unsuccessful, while attempted benzoylation caused dehydration, yielding the thiazol-2-thione (IV; R = NO_2, X = S). It is probable that this dehydration proceeds *via* an unstable *O*-benzoyl derivative, as the starting material is stable in the presence of alkali or pyridine alone; dehydration is promoted only by acid catalysis or by heating the compound above its m. p. This behaviour is in marked contrast to that of the simpler dithiocarbamate (VII) which yielded a stable benzoyl derivative. The compounds (VIII) are also unaffected by hydrogen peroxide in alkaline solution while the model compounds (VII) yielded di-4-nitrobenzyl disulphide.

Aqueous-ethanolic hydrogen chloride converted the compounds (VIII) very readily into the thiazol-2-ones (IV; R = NO_2, X = O and S, respectively). Reduction with titanous chloride yielded the corresponding amino-derivatives (IV; R = NH_2, X = O and S, respectively); the infrared spectrum of the aminothiazol-2-one disclosed considerable hydrogen bonding between the amino- and the carbonyl group. Reaction of the aminothiazol-2-one with phenyl *iso*cyanate then yielded the desired thiazolone moiety (IV; R = NH·CO·NHPh, X = O).

The thiochrome analogue (III) might be expected to be obtained by potassium ferricyanide oxidation of an alkaline solution of the salt (I), analogous to the formation of thiochrome from thiamine. The initial attack of a one-electron oxidising agent is on the activated benzene nucleus, however, and only dark polymers were obtained, just as with, *e.g.*, aniline. The desired compound was, however, formed on condensation of 1 : 2 : 3 : 4-tetrahydro-2-thioquinazoline (VI; R = H, R′ = H_2, X = S) (Busch, *J. prakt. Chem.*, 1895, **51**, 128) with chloroacetone, to yield the hydrochloride of the base (III); this with alkali yielded a pseudo-base which was not dehydrated to the anhydro-base so readily as with thiochrome itself.

The thermal stability of the amino-thiazolone and -thiazol-2-thione (IV; R = NO_2, X = O and S, respectively) is considerable and neither cyclises, except under extreme conditions, to yield the tricyclic compound (III). They are, in fact, quite as stable as thiamine thiazol-2-one and -2-thione (Sykes and Todd, *loc. cit.*) in this respect despite the greater basicity of their amino-groups.

Experimental

Di-[2-(N-2′-*aminobenzylformamido*)*propenyl*] *Disulphide* (II).—3-2′-Aminobenzyl-4-methylthiazolium chloride hydrochloride (I) (Livermore and Sealock, *J. Biol. Chem.*, 1947, **167**, 699) (0·82 g.) in water (5 ml.) was treated with 1·065N-sodium hydroxide (8·35 ml., 3 equiv.), and hydrogen peroxide (20-vol.; 0·84 ml., 0·5 equiv.) was then added dropwise to the yellow solution. The separated, sticky solid was set aside for 1 hr., then collected and washed with water. The *disulphide* crystallised from ethanol–acetone as pale yellow needles (0·22 g., 35%), m. p. 136° (decomp.) (Found: C, 59·7; H, 6·0; N, 12·6. $C_{22}H_{26}O_2N_4S_2$ requires C, 59·7; H, 5·9; N, 12·7%).

Heating of Di-[2-(N-2′-*aminobenzylformamido*)*propenyl*] *Disulphide* (II) *in* iso*Butanol.*—The foregoing disulphide (2·2 g.) in dry *iso*butanol (75 ml.) was refluxed under nitrogen for 4 hr.; some darkening took place. The solvent was removed at room temperature/10^{-4} mm., the residue taken up in dry toluene and again evaporated under reduced pressure to remove the last traces of *iso*butanol. The residue was taken up in dry benzene and heated with phenyl *iso*cyanate (0·6 g.) at 50° for 1 hr. Evaporation at room temperature/10^{-4} mm. yielded an orange gum. This was dissolved in ether (150 ml.), and the ethereal solution extracted several times with 3N-hydrochloric acid. The ethereal extract was washed with water, dried (Na_2CO_3), and evaporated under reduced pressure, yielding a yellow oil. Crystallisation from ethanol (charcoal) yielded 3-2′-phenylureidobenzyl-4-methylthiazol-2-one (IV; R = NH·CO·NHPh, X = O) as colourless needles, m. p. and mixed m. p. 165° (Found: C, 63·7, H, 4·8; N, 12·6. Calc. for $C_{18}H_{17}O_2N_3S$: C, 63·6; H, 5·0; N, 12·4%).

The hydrochloric acid extract was washed with ether and made alkaline with 3N-sodium hydroxide, and the separated oil then extracted with ether. The ethereal extract was dried (Na_2CO_3) and a slow stream of dry hydrogen chloride passed through it, a crystalline hydrochloride separating. Recrystallisation from *n*-butanol yielded 3′ : 4′-dihydro-4-methylquinazolino(2′ : 3′-2 : 3)thiazole hydrochloride as colourless plates, m. p. and mixed m. p. 282° (decomp.) (Found: C, 55·0; H, 4·8; N, 11·4. Calc. for $C_{11}H_{10}N_2S$,HCl: C, 55·1; H, 4·6; N, 11·7%).

Reduction of 2-Cyanocarbanilide (V; R = CN).—(*a*) A solution of 2-cyanocarbanilide (1 g.) in *iso*propanol (200 ml.) was hydrogenated at room temperature and atmospheric pressure with freshly prepared W-7 Raney nickel (3 g.), the theoretical volume of hydrogen being absorbed in 45 min. The mixture was then filtered through "Hyflo Supercel" and evaporated to dryness under reduced pressure yielding a pink gum. Trituration with ether and N-hydrochloric acid induced crystallisation. Recrystallisation from ethanol yielded *di-*(2-*phenylureidobenzyl*)*amine hydrochloride* as needles, m. p. 177° (Found: C, 67·2; H, 5·7; N, 14·1. $C_{28}H_{27}O_2N_5$,HCl requires C, 67·8; H, 5·6; N, 14·0%). Hydrogenation did not occur in the presence of acetic or hydrochloric acids with platinum or palladium catalysts.

(*b*) The above reduction was repeated with propan-2-ol saturated with dry ammonia at 0° as solvent, at room temperature/75 atm. for 11 hr. Removal of the catalyst and evaporation of the solution yielded 1 : 2 : 3 : 4-*tetrahydro*-4-*imino*-2-*oxo*-3-*phenylquinazoline* (VI; R = Ph, R′ = NH, X = O) which crystallised from aqueous alcohol as prisms, m. p. 224° (Found: C, 70·7; H, 4·9; N, 17·9. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·6; N, 17·7%), insoluble in water, soluble in dilute hydrochloric acid [hydrochloride, m. p. 250° (decomp.)] from which it is precipitated unchanged by aqueous ammonia or potassium carbonate but not by sodium hydroxide.

The isomerisation of 2-cyanocarbanilide may also be effected very rapidly with aqueous ammonia or sodium hydroxide.

(*c*) A solution of 2-cyanocarbanilide (1 g.) in ethanol (100 ml.) was diluted with 3N-hydrochloric acid (30 ml.), and granulated zinc (2·5 g.) added. The mixture was warmed slightly and then kept at room temperature for 24 hr. Evaporation under reduced pressure led to the separation of colourless crystals of 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-3-phenylquinazoline (VI; R = Ph, R' = X = O) (Paal, *Ber.*, 1894, **27**, 978), needles, m. p. 272° (from ethanol) (Found : C, 70·3; H, 4·0; N, 11·6. Calc. for $C_{14}H_{10}O_2N_2$: C, 70·5; H, 4·2; N, 11·8%).

4-Hydroxy-4-methyl-3-2'-nitrobenzylthiazolid-2-one (VIII; X = O).—2-Nitrobenzylamine hydrochloride (Ing and Manske, *J.*, 1926, 2350) (4·7 g.) was dissolved in water (150 ml.) and treated with N-sodium hydroxide (50 ml., 2 equiv.), and a rapid stream of pure carbon oxysulphide then passed through the solution for 45 min. The pale yellow solution (pH now 7·5) was filtered to remove a trace of di-2-nitrobenzylurea, chloroacetone (2·6 g., 1·1 equiv.) added, and the mixture shaken for 10 min. The crystals which separated were filtered off and washed with water. Recrystallisation from ethanol yielded the *thiazolid-2-one* (4·2 g., 63%) as colourless needles, m. p. 140° (decomp.) (Found : C, 49·3; H, 4·4; N, 10·6. $C_{11}H_{12}O_4N_2S$ requires C, 49·3; H, 4·5; N, 10·5%).

Similar reaction of the amine with carbon disulphide and alkali, followed by chloroacetone, yielded *4-hydroxy-4-methyl-3-2'-nitrobenzylthiazolid-2-thione* (VIII; X = S), which crystallised from ethanol (charcoal) as prisms (84%), m. p. 159° (decomp.) (Found : C, 46·8; H, 4·1; N, 10·0. $C_{11}H_{12}O_3N_2S_2$ requires C, 46·5; H, 4·2; N, 9·9%).

In attempted reactions with phenyl *iso*cyanate in benzene and with an alkaline solution of hydrogen peroxide in aqueous acetone unchanged starting material was recovered. Attempted benzoylation of the thione (VIII; X = S) under Schotten–Baumann conditions or in pyridine caused dehydration to the thiazol-2-thione (IV; X = S).

S-*4-Nitrobenzyl* N-*Benzylthiolcarbamate* (VII; R = H, R' = 4-CH_2·C_6H_4·NO_2, X = O).—Benzylamine (10·7 g.) in ethanol (200 ml.) was treated with a stream of carbon oxysulphide until no more solid separated. Ethanol (100 ml.) was then added and the mixture warmed till all the solid had dissolved. 4-Nitrobenzyl bromide (10 g., 1 equiv.) was added and the solution set aside to crystallise; a further crop was obtained by warming the mother-liquors and diluting them slightly with water. The crystals were collected and washed with ethanol. Recrystallisation from ethanol yielded the *thiolcarbamate* (10 g., 67%) as leaflets, m. p. 137° (Found : C, 59·8; H, 4·8; N, 9·2. $C_{15}H_{14}O_3N_2S$ requires C, 59·6; H, 4·6; N, 9·3%).

Similar reaction of the amine with carbon disulphide and 4-nitrobenzyl bromide yielded *4-nitrobenzyl* N-*benzyldithiocarbamate* (VII; R = H, R' = 4-CH_2·C_6H_4·NO_2, X = S), needles (70%) (from aqueous ethanol), m. p. 91° (Found : C, 56·8; H, 4·5; N, 8·8. $C_{15}H_{14}O_2N_2S_2$ requires C, 56·6; H, 4·4; N, 8·8%).

The dithiocarbamate (1 g.) in ethanolic acetone was treated with an excess of hydrogen peroxide (20-vol.) and an excess of N-sodium hydroxide. The solution immediately became dark red but subsequently lightened a little. After 5 min., water was added and the flocculent precipitate was collected and washed with water. Recrystallisation from ethanol yielded needles of di-4-nitrobenzyl disulphide (Price and Twiss, *J.*, 1909, **95**, 1728), m. p. and mixed m. p. 126° (Found : C, 50·3; H, 3·9; N, 8·0. Calc. for $C_{14}H_{12}O_4N_2S_2$: C, 50·0; H, 3·6; N, 8·3%).

The dithiocarbamate (1 g.) in dry pyridine (5 ml.) was treated with benzoyl chloride (0·45 g., 1 equiv.). After 4 hr. at room temperature the solution was poured into warm water with stirring. The aqueous phase was decanted and the sticky gum stirred with a further portion of water; it then began to crystallise on scratching. The crystals were collected and washed with water. Recrystallisation from ethanol–acetone (charcoal) yielded yellow needles of the *benzoyl derivative*, m. p. 114° (Found : C, 63·0; H, 4·3; N, 6·6. $C_{22}H_{18}O_3N_2S_2$ requires C, 62·6; H, 4·3; N, 6·6%).

4-Methyl-3-2'-nitrobenzylthiazol-2-one (IV; R = NO_2, X = O).—The foregoing thiazolid-2-one (0·75 g.) was dissolved in ethanol (50 ml.), 3N-hydrochloric acid (10 ml.) was added (cf. Sykes, *J.*, 1951, 2507), and the solution brought just to the b. p. After 5 min. it was again heated to the b. p., diluted with water, and allowed to cool. The crystals which separated were filtered off and washed with ethanol. Recrystallisation from ethanol yielded the *thiazol-2-one* (0·49 g., 70%) as colourless needles, m. p. 163° (Found : C, 53·0; H, 4·2; N, 11·1. $C_{11}H_{10}O_3N_2S$ requires C, 52·8; H, 4·0; N, 11·2%).

Similar treatment of the above thiazolid-2-thione yielded *4-methyl-3-2'-nitrobenzylthiazol-2-thione* (IV; R = NO_2, X = S), which crystallised from ethanol (charcoal) as colourless needles (56%), m. p. 129° (Found : C, 49·8; H, 4·0; N, 10·5. $C_{11}H_{10}O_2N_2S_2$ requires C, 49·6; H,

3·8; N, 10·5%). Ring closure was also effected (71%) by heating the dithiocarbamate above its m. p. till gas evolution had ceased (cf. Sykes and Todd, *J.*, 1951, 534).

3-2′-*Aminobenzyl*-4-*methylthiazol*-2-*one* (IV; R = NH_2, X = O).—The foregoing thiazol-2-one (1 g.) in ethanol (65 ml.) was heated to 70° and acid titanous chloride solution [15%; 25 ml., to which 3N-hydrochloric acid (20 ml.) has been added] was added dropwise. The solution was evaporated under reduced pressure to remove ethanol and treated with solid sodium carbonate till faintly cloudy and an excess of saturated aqueous picric acid then run into the stirred solution. The separated picrate was collected after 48 hr., washed with water, then shaken repeatedly with portions of ether and aqueous sodium hydroxide (10%). The combined ethereal extracts were filtered, washed with water, and extracted twice with 3N-hydrochloric acid and finally with water. The combined aqueous extract was treated with solid sodium carbonate until no more solid separated. Recrystallisation from ethanol yielded the *aminothiazol*-2-*one* as colourless needles (0·4 g., 45%), m. p. 104° (Found: C, 59·7; H, 5·3; N, 13·0. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·5; N, 12·7%).

Similar reduction of the above thiazol-2-thione (the decomposition of the picrate was less satisfactory, however) yielded 3-2′-*aminobenzyl*-4-*methylthiazol*-2-*thione* (IV; R = NH_2, X = S), prisms (29%) (from ethanol), m. p. 136° (Found: C, 56·2; H, 5·0; N, 12·1. $C_{11}H_{12}N_2S_2$ requires C, 56·0; H, 5·1; N, 11·9%).

4-*Methyl*-3-2′-*phenylureidobenzylthiazol*-2-*one* (IV; R = NH·CO·NHPh, X = O).—The foregoing aminothiazol-2-one (0·3 g.) in dry benzene (10 ml.) was treated with phenyl *iso*cyanate (0·17 g., 1 equiv.) in benzene (1·5 ml.) and the solution refluxed for 5 hr. Removal of the benzene yielded a gum which crystallised on trituration with ethanol. Recrystallisation from ethanol yielded the *phenylureidothiazol*-2-*one* as needles (0·35 g., 74%), m. p. 165° (Found: C, 63·8; H, 4·9; N, 12·5. $C_{18}H_{17}O_2N_3S$ requires C, 63·6; H, 5·0; N, 12·4%).

3′ : 4′-*Dihydro*-4-*methylquinazolino*(2′ : 3′-2 : 3)*thiazole* (III).—A solution of 1 : 2 : 3 : 4-tetrahydro-2-thioquinazoline (VI; R = H, R′ = H_2, X = S) (Busch, *J. prakt. Chem.*, 1895, **51**, 128) (1 g.) in dry acetone (50 ml.) was refluxed with redistilled chloroacetone (3 g.) for 4 hr. The separated crystals were then collected and washed with acetone. Recrystallisation from *n*-butanol yielded the *quinazolinothiazole hydrochloride* as colourless plates (0·7 g., 48%), m. p. 282° (decomp.) (Found: C, 54·9; H, 4·8; N, 11·5. $C_{11}H_{10}N_2S$,HCl requires C, 55·1; H, 4·6; N, 11·7%).

Treating a solution of the hydrochloride in aqueous ethanol with ammonia, collecting of the product, and recrystallising it from *n*-butanol yielded the *base* as colourless needles, m. p. 174° (decomp.) (Found: C, 60·2; H, 5·4; N, 12·6. $C_{11}H_{10}N_2S$,H_2O requires C, 60·0; H 5·5; N, 12·7%).

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