

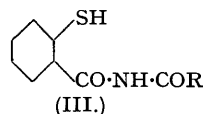
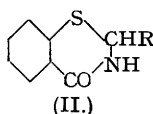
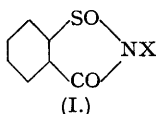
146. *The Formation of Some Benz-1 : 3-thiazine Derivatives by the Reduction of Benzisothiazolones.*

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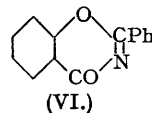
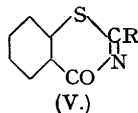
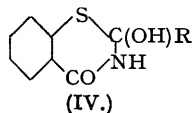
2-Methyl-, 2-ethyl-, and 2-benzyl-dihydro-1 : 3-benzthiazine-4-ones are formed when the *N*-acetyl-, -propionyl, and -phenylacetyl derivatives respectively of dihydrobenzisothiazolone or their *S*-oxides are reduced with zinc and acid, the change involving an expansion of the hetero-ring. The corresponding 2-phenyl compound is not obtainable by the similar reduction of the *N*-benzoyldihydrobenzisothiazolone but it is readily produced by condensation of benzaldehyde with 2 : 2'-dithiobenzamide. The properties and reactions of these substances have been examined.

IN the course of a study of some derivatives of benzisothiazolone (Hart, McClelland, and Fowkes, *J.*, 1938, 2214; Bartlett, Hart, and McClelland, *J.*, 1939, 760) the observation was made by Hart that *N*-acetylbenzisothiazolone *S*-oxide (I; X = COMe) was converted on reduction into the benz-*m*-thiazine derivative (II). The present paper records a further examination of such reactions and the substances which result.

The reduction products of the isothiazole oxides of type (I) vary according to the nature of the *N*-substituent, X. Thus the benzenesulphonyl and the benzoyl derivative (I;



X = SO₂Ph or C₆H₅) yield the corresponding disulphides (–S·C₆H₄·CO·NHX)₂, together with 2 : 2'-dithiobenzamide in the latter case. When, however, the *N*-substituent is an acyl group (X = COR, where R = Me, Et, CH₂Ph) ring expansion takes place with formation of the corresponding dihydrothiazine (II). The formation of the thiazines is evidently by way of the thiazolones, since the latter also give the thiazines on reduction under similar conditions. Reduction of the thiazolone presumably first yields the mercaptoamide (III), which passes into



the final product by the reduction of either the internal self-addition compound (IV) or the condensation product (V). The intermediate (V), which has not in fact been isolated, would be closely analogous to Titherley's 2-phenyl-1 : 3-benzoxazine-4-one (VI) (*J.*, 1910, 97, 200).

Although reduction of the *N*-benzoylbenzisothiazolone (I, X = C₆H₅) yielded none of the expected phenyldihydro-1 : 3-benzthiazine-4-one, this substance was readily obtained by condensation of 2 : 2'-dithiobenzamide with benzaldehyde, no additional reduction being found necessary. No corresponding reaction was found using acetaldehyde in place of benzaldehyde.

The behaviour of these dihydrobenz-1 : 3-thiazine derivatives has been studied. In view of the close structural relationship between the benzisothiazolones and the benz-1 : 3-thiazine-4-ones into which they are converted, it was of interest to find whether they would show analogous reactions. The former substances are transformed by heating with potassium acetate and acetic anhydride into thionaphthen derivatives, the group NX being eliminated (McClelland, *J.*, 1929, 1588; McClelland and D'Silva, *J.*, 1931, 2972; 1932, 2883; Bartlett and McClelland, *J.*, 1934, 818), and on the other hand they are readily oxidised to substances of the saccharin type. The benzthiazine-4-ones, however, are merely acetylated by acetic anhydride and potassium acetate and no rupture of the ring occurs. Oxidation by hydrogen peroxide yields a soluble acidic substance which is probably *o*-sulphobenzoic acid, but only on one occasion was there any indication of the production of a trace of a saccharin. When the *N*-acyl derivatives are oxidised the *S*-dioxide of the parent thiazine is obtained, but attempts to convert this into a saccharin by heating with pyridine or alkali were unsuccessful.

EXPERIMENTAL.

Preparation of the Acyldihydrobenzisothiazolone S-Oxides.—The method used by Hart, McClelland, and Fowkes (*loc. cit.*) to prepare the 1-acetyl compound, applied to propionamide yielded 2-*keto*-1-propionyl-1 : 2-dihydrobenzisothiazole *S*-oxide, crystallising in colourless needles, m. p. 136°, from alcohol (charcoal)

(Found: C, 53.6; H, 4.1; S, 14.2. $C_{10}H_9O_3NS$ requires C, 53.8; H, 4.0; S, 14.4%). Similarly, phenylacetamide gave 2-keto-1-phenylacetyl-1:2-dihydrobenzisothiazole S-oxide, crystallising in colourless prisms, m. p. 162° (Found: C, 63.0; H, 3.9; S, 11.4. $C_{14}H_{11}O_3NS$ requires C, 63.2; H, 3.9; S, 11.2%), and benzamide yielded 2-keto-1-benzoyl-1:2-dihydrobenzisothiazole S-oxide as fine colourless needles from benzene, m. p. 150° (Found: C, 62.4; H, 3.6; N, 5.1. $C_{14}H_9O_3NS$ requires C, 62.0; H, 3.3; N, 5.2%).

Reduction of 2-Keto-1-benzoyl-1:2-dihydrobenzisothiazole S-Oxide.—The benzisothiazolone oxide (2 g.) was boiled for 4 hrs. in glacial acetic acid (40 c.c.) with hydrochloric acid (3 c.c.) and zinc dust (2 g.). The filtered solution gave, on dilution with water, a white precipitate having a thiophenolic odour and giving a transient green colour with ferric chloride. It was soluble in alkali and was oxidised by iodine in alcohol to *NN'*-dibenzoyl-2:2'-dithiobenzamide, m. p. 189° (compare Reissert and Manus, *Ber.*, 1928, 61, 1308).

Reduction of 2-Keto-1-acetyl-1:2-dihydrobenzisothiazole S-Oxide.—This substance was not affected by sulphur dioxide in boiling alcohol, but was readily reduced by zinc dust as follows: the benzisothiazolone S-oxide (20 g.) was boiled in glacial acetic acid (275 c.c.) with concentrated hydrochloric acid (30 c.c.) and zinc dust (30 g.) for 4 hours with stirring. The solution, filtered from excess of zinc, was poured into water (800 c.c.). The precipitate was collected and further quantities were obtained by alternately concentrating and diluting the mother-liquor several times. The product was recrystallised from alcohol (yield 13.5 g.). 2-Methyl-dihydro-1:3-benzthiazine-4-one was thus obtained as colourless needles, m. p. 175° (Found: C, 60.0, 60.4; H, 5.0, 5.3; S, 17.9. C_9H_9ONS requires C, 60.3; H, 5.0; S, 17.9%). When larger quantities of hydrochloric acid were used the yield was much less and 2:2'-dithiobenzamide, m. p. 250°, and 2:2'-dithiobenzoic acid, m. p. 289°, were also produced. The *N-acetyl* derivative formed colourless needles from alcohol, m. p. 70° (Found: C, 60.0; H, 5.2; S, 16.6. $C_{11}H_{11}O_2NS$ requires C, 59.7; H, 5.0; S, 16.5%). This substance was volatile in steam, and was hydrolysed by boiling dilute hydrochloric acid to the parent compound. The *N-benzoyl* derivative, prepared by benzylation in pyridine, formed colourless needles, m. p. 127° (Found: C, 67.9; H, 4.9. $C_{18}H_{15}O_2NS$ requires C, 67.9; H, 4.6%).

When the methyl-dihydrobenzthiazinone was distilled with dilute aqueous sodium hydroxide, acetaldehyde was found in quantity in the distillate, and addition of ferric chloride to the acidified reaction mixture yielded 2:2'-dithiobenzoic acid. Oxidation of the methylbenzthiazinone with hydrogen peroxide in glacial acetic acid at 100° gave a water-soluble, hygroscopic, yellow, strongly acidic substance and a sweet taste was sometimes detected.

Oxidation of the acetyl or the benzoyl derivative by hydrogen peroxide in aqueous suspension at 100° yielded the *S-dioxide* of the parent substance, crystallising from water (charcoal) in colourless needles, m. p. 163° (Found: C, 51.0; H, 4.1; S, 15.1. $C_9H_9O_3NS$ requires C, 51.2; H, 4.3; S, 15.2%), together with hygroscopic material as produced in the previous oxidation.

Attempts at direct methylation of the methyl-dihydrobenzthiazinone with methyl iodide, methyl sulphate, or diazomethane were unsuccessful. When the substance was heated in a sealed tube at 120–130° with methyl iodide, methyl alcohol, and potassium carbonate, gas was evolved, a smell of iodoform was observed, and 2-methylthiobenzamide, m. p. 150°, was produced (compare McClelland and Warren, *J.*, 1929, 2625).

Preparation of 2-Ethyl- and 2-Benzyl-dihydro-1:3-benzthiazine-4-ones.—Reduction in the same way converted the 1-propionyl- and 1-phenylacetyl-2-ketodihydrobenzisothiazole S-oxides into 2-ethyl-dihydro-1:3-benzthiazine-4-one, colourless needles from alcohol, m. p. 112° (Found: C, 62.1; H, 5.5; S, 16.9. $C_{10}H_{11}ONS$ requires C, 62.2; H, 5.7; S, 16.6%), giving the acetyl derivative as an oil, and 2-benzyl-dihydro-1:3-benzthiazine-4-one, colourless needles from alcohol, m. p. 149.5° (Found: C, 70.7; H, 4.8; S, 12.5. $C_{16}H_{15}ONS$ requires C, 70.6; H, 5.1; S, 12.2%). These substances are insoluble in alkali and give no reaction with ferric chloride.

Reduction of the Benzisothiazolones.—When the acyl and benzoyl thiazolones were reduced instead of their S-oxides the products were respectively the same.

Preparation of 2-Phenyldihydro-1:3-benzthiazine-4-one.—2:2'-Dithiobenzamide (5 g.) was heated with benzaldehyde (10 c.c.) and potassium acetate (fused, 8 g.) at 160° for 3 hours. The pale yellow mass when cold was ground up, and the excess of benzaldehyde removed in a current of steam or by washing with aqueous alcohol. The residue, crystallised from alcohol in colourless needles, m. p. 176° (yield 4.5 g.), was 2-phenyldihydro-1:3-benzthiazine-4-one (Found: C, 69.6; H, 4.6; S, 6.1; *M*, in benzene, 247. $C_{14}H_{11}ONS$ requires C, 69.7; H, 4.6; S, 5.8%; *M*, 241). It is sparingly soluble in water, insoluble in alkali, and gives no reaction for a disulphide and no colouration with ferric chloride.